HYPNOTICS AND ANTIHISTAMINES
Effects on Cognitive Functions and Driving Performance

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Effects on Cognitive Functions and Driving Performance

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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Chapter 1

General introduction

Centrally acting or 'psychoactive' drugs are widely used in the treatment of psychological, psychiatric or neurological problems, such as anxiety, depression, schizophrenia, epilepsy and Parkinson's disease. Yet, like all medicinal drugs, these substances not only have therapeutic effects, but also a variety of side effects. In contrast to drugs that act only peripherally, however, centrally acting drugs may also have adverse effects on mental and behavioural functions. They may cause sedation and associated slowing of reactions and attentional deficits, memory disturbances, or emotional and motivational changes. In patients using these drugs such effects can have severe adverse effects on their quality of life and safety of activities of daily living. One of the most important daily activities in industrialized societies is car driving. Yet it is also one of the most hazardous, as shown by injury and mortality statistics. There is a growing awareness among pharmaceutical industries, health care professionals and regulatory authorities that driving under the influence of medicinal drugs might be a risk factor for traffic safety (Alvarez and Del Rio, 2002). It is of particular concern since the use of psychoactive medicinal drugs is widespread among ambulant patients who occasionally or regularly drive. Between 1993 and 1997 6.4% of the general population of France, Germany, Italy and the United Kingdom reported use of hypnotics, anxiolytics or antidepressants (Ohayon and Lader 2002). Although these drugs classes are among the most frequently used, several others exist that are commonly used and that may impair performance, e.g. sedating antihistamines, anticonvulsants, antipsychotics, and opiates. In 1995, De Gier reported that, according to conservative estimates, an average of 10% of the adult population in the Europe drives under the influence of medicinal drugs with twice the risk of becoming involved in a traffic accident. If so, these drugs caused 4,500 deaths, 135,000 injuries and 6.3 billion Euro in property damage and medical care per year (De Gier 1995).

With the current growth in the use of psychoactive medicinal drugs and increase in traffic the urge to lower the rate of drug-related accidents increases. There are essentially two ways to achieve this goal: restricting driving while using drugs and reducing the use of drugs that affect driving. Restricting the license to drive for patients who use performance impairing medicinal drugs can have severe consequences for their participation in society. Moreover, legal measures are only effective when they can be effectively reinforced. Currently, lack of screening devices and inability to determine legal limits for drug concentrations in blood prevent such reinforcement, however. Therefore, prevention is preferred. Reducing the use of drugs that affect driving can be achieved by stimulating the development, prescription and use of drugs that are unlikely to produce performance

impairment and thus safe for driving. The latter is possible since large differences exist between the effects of different drugs within the same therapeutic class.

Either way information is needed regarding the impairing effects of many different drugs and doses and on factors that may modulate these effects. The current dissertation addresses these issues. In order to clarify the objectives of the individual studies presented here, the next paragraphs will briefly describe some background information as well ass the general questions and methods to answer them.

Adverse effects of medicinal drugs on performance

One of the most notorious side effects, associated with the use of a large number drugs, is sedation. Since a wide range of neurotransmitters and peptides seem to play a role in the maintenance of alertness and sleep-wake regulation (Garcia-Garcia and Drucker-Colin, 1999), sedation can be produced through many different pharmacological mechanisms (Riedel et al., 1998). For example, hypnotics and anxiolytics induce sedation by enhancing the effects of GABA, whereas antidepressants, antipsychotics and antihistamines produce similar effects by blocking cholinergic, noradrenergic, or histaminergic neurotransmission. At a behavioural level sedative drug effects manifest themselves as feelings of drowsiness and impaired performance in a variety of tasks, for example as slowed responses, or increased number of incorrect decisions. A non-pharmacological explanation how sedation can impair performance in many different tasks is offered by resource models of human information processing (Sanders, 1997). A basic assumption is that efficiency of human information processing depends on the availability of sufficient energetic or attentional resources. It is assumed that cognitive or psychomotor tasks require a minimum amount of resources in order to be performed adequately. Therefore, when a task or a processing stage within a task requires more resources than available, performance is sub-optimal, e.g. slower or less accurate. Sedative drugs are assumed to reduce energetic resources and thus impair performance in many tasks, especially those involving speeded performance and high or prolonged attentional demands. Clearly, this can be hazardous when driving a car or operating dangerous machinery.

Another important category of behaviorally toxic drug effects is memory disturbances. Although impairment of memory and cognition can be a by-product of sedation mediated by attentional deficits while acquiring information, it seems that some

drugs, in particular the benzodiazepines, have specific amnestic effects over and above their sedative effects (Curran, 1991).

Hypnotics and antihistamines

Research in this dissertation focuses on two classes of psychoactive drugs, hypnotics and antihistamines. Although these two classes of drugs are completely different with respect to their therapeutic aims and mechanism of action, they also have a few things in common. The first is that hypnotics and antihistamines are treatments for highly prevalent complaints. Estimates of the prevalence of sleep problems vary between 10-40%, and those of allergic rhinitis between 15-20% of the adult population in industrialized nations. Secondly, people complaining of sleep complaints or of allergic rhinitis are usually not severely disabled by their disorder. Most are otherwise healthy adults who actively participate in society and thus occasionally or regularly drive a car. As a consequence hypnotics and antihistamines are among the most frequently used licit drugs in drivers. A final correspondence is that both are classes of drugs where advances in pharmaceutical research resulted in several new drugs that have significantly less unwanted effects than their predecessors. In both classes the advantages of the newly developed drugs are primarily due to changes in pharmacokinetics. Both classes of drugs have their own distinct problems with respect to unwanted effects.

A major problem of hypnotics is residual sedation the morning after bedtime administration. For example, Volkerts and O'Hanlon (1986) showed that the benzodiazepine hypnotics, loprazolam 2 mg and flurazepam 30 mg, had residual adverse effects on performance of insomnia patients in an on-the-road driving test that were more severe than the effects of alcohol in the same test while blood alcohol concentrations are 1.0 g/L. These residual effects were largely attributed to the long elimination half-life of these drugs. Therefore, several new hypnotics were developed with considerably shorter half-lives and less residual effects than their predecessors. Nevertheless, these drugs may still have some residual effects.

The problem with the first antihistamines was that they crossed the blood-brain barrier, whereas their therapeutic site of action is in the periphery, far removed from the brain. Newer antihistamines have been developed that cross the blood-brain barrier less rapidly than their predecessors, because they are larger and more polarized, thus less lipophilic. In addition, the new antihistamines are more selective histamine H1-

antagonists, whereas older antihistamines also show affinity for serotonergic, adrenergic and cholinergic receptors, thus causing additional sedation (Simons, 1994). Even though newer antihistamines are relatively non-sedating as compared to the older ones, they may still have sedative effects when given in larger doses (see NHTSA, 2000; O'Hanlon and Ramaekers, 1995; Ramaekers and Vermeeren, 2000; Runge, 2000).

Assessing drug induced impairment of driving

It has been argued that impairing effects of drugs should be established before they are licensed for clinical use, in the same way that their efficacy and purely medical side effects are evaluated according to long established clinical trial procedures (O'Hanlon, 1984). Experimental performance studies are the most suitable way to reveal drug effects on performance. These should be well-designed psychopharmacological studies using objective measures of performance that are valid, reliable and sensitive. However, methodologies used to assess drugs effects on driving performance can vary widely, making it difficult to compare results from different studies. Guidelines for experimental research in this area were therefore needed.

An important aspect of the discussion regarding the methodology is the question how driving performance can be measured. Tests used should be valid, reliable and sensitive to drug effects. The experimental studies presented in this dissertation all used an over-the-road highway driving test. This test evolved from studies on driver fatigue conducted in the USA during the early 1970s and was standardized in 1984 for assessing drug effects on actual driving performance (O'Hanlon, 1984). It involves subjects driving a specially instrumented car over a 100-km (61 mile) primary highway circuit while maintaining a constant speed of 95 km/h (58 miles per hour) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. Subjects are accompanied by a licensed driving instructor, having access to dual controls. During the test the vehicle's speed and lateral position relative to the left lane delineation are continuously recorded. The primary performance parameter, Standard Deviation of Lateral Position (SDLP, in cm) can be interpreted as an index of allowed weaving and swerving, i.e. course-keeping error. It is a reliable characteristic of individual driving performance that has proven sensitive to many sedating drugs (see O'Hanlon and Ramaekers, 1995; O'Hanlon et al., 1995; Riedel et al., 1998). The test was calibrated for the effects of alcohol so that mean changes in performance under the influence of

medicinal drugs can be compared to those associated with BACs at various legal limits (Louwerens et al., 1987).

Aim of this dissertation

Research presented in this dissertation aims to establish the impairing effects of hypnotics and antihistamines on cognitive and psychomotor performance, in particular on car driving. For this, general issues relating to the methodology of experimental studies assessing drug effects on driving are first addressed. This is followed by a review of epidemiological evidence that use of hypnotics is associated with increased risk for accidents. In addition, information derived from experimental studies on the duration and severity of several common prescribed hypnotics is summarized. The latter is intended to provide prescribing clinicians with the information needed to compare drugs and doses and select the one most appropriate for the patient and to inform him or her more specifically about the expected effects of the drug. Finally, experimental studies establishing the impairing effects of hypnotics and antihistamines on driving performance and cognitive functions are presented. Five experimental studies assessed the effects of newly developed drugs (i.e. hypnotics and antihistamines) before they were about to enter the market, whereas one study assessed the effects on driving performance of an antihistamine that was already in clinical use, but in a new, possibly safer, dosing schedule (i.e., nighttime instead of daytime administration).

Outline of this dissertation

Chapter 2 briefly describes methodological guidelines for experimental research assessing medicinal drugs' effects on driving performance. These guidelines were established using a survey among international experts in the field of drugs and driving research. The chapter concludes with some recommendations to stimulate their application. After the methodological section a series of experimental studies follows, that were all conducted according to a double blind, placebo controlled crossover design.

Chapter 3 reviews epidemiological evidence that use of hypnotics is associated with increased risk for accidents. In addition, information derived from experimental studies on the duration and severity of several common prescribed hypnotics is summarized.

Chapter 4, 5 and 6 present studies designed to assess residual effects of hypnotics. *Chapter 4* describes a study comparing the effects of zolpidem 10 mg, flunitrazepam 2 mg and placebo on sleep and performance the morning after bedtime use in women complaining of insomnia. Effects were also compared to those of partial sleep deprivation (i.e. a maximum of 3 hours sleep). Chapters 5 and 6 present two studies assessing the residual effects of zaleplon and zopiclone in healthy volunteers. In the first study (*chapter 5*) zaleplon 10 and 20 mg, zopiclone 7.5 mg and placebo were administered at bedtime and during a brief awakening in the middle of the night in separate conditions. Effects on driving and cognitive performance were assessed in the morning, i.e., 10 and 5 hours after administration, respectively. The second study (*chapter 6*) was a partial replication, assessing the residual effects of zaleplon 10 mg, zopiclone 7.5 mg and placebo in healthy volunteers. In addition this study included an alcohol and an alcohol-placebo condition, however, in order to compare the effects of hypnotics directly with those of low dose of alcohol in the same subjects.

Chapter 7, 8 and 9 all concern the effects of antihistamines on driving. In the study described in *chapter 7* healthy females were administered a known sedating antihistamine, chlorpheniramine 8 and 12 mg (sustained release formulation), at bedtime and a nonsedating antihistamine, terfenadine 60 mg, in the morning. Effects on highway driving and car following performance were assessed in the morning and compared to those of flurazepam 30 mg and placebo. *Chapter 8* describes a study assessing the effects of fexofenadine in 4 dosing regimens, clemastine 2 mg and placebo on psychomotor and driving performance of healthy men en women. Drugs and placebo were administered over 5 days and effects on driving, choice reaction time, tracking and vigilance were assessed on day 1, 4 and 5 of each treatment period. On day 5, subjects were challenged with a moderate alcohol dose before testing to assess possible interactions between drugs and alcohol on performance. *Chapter 9* describes a study with a design similar to the previous. The study assessed the effects of emedastine 2 and 4 mg, cetirizine 10 mg and placebo, with and without alcohol on highway driving performance.

Finally *chapter 10* concludes with a brief discussion of some of the results from the studies that were left open.

Chapter 2

Methodological guidelines for experimental research in Drugs and Driving: accomplishments and future needs

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INTRODUCTION

The European Community's Committee for Proprietary and Medicinal Products (CPMP) has accepted a 3-tier warning system for identifying the driving hazard potential of every drug as part of the pan-European registration process. Drugs and possible doses of the same drug should be categorized with respect to their impairing effects on driving as either (1) presumed to be safe or unlikely to produce an effect, (2) likely to produce minor or moderate effects, or (3) likely to produce severe adverse effects or presumed to be potentially dangerous. It was decided that after January 1st 1994, package inserts in all Member States should contain a statement concerning the drug's effects on ability to drive or use machines. Determination of the degree of impairing effects of a drug/dose, or categorization according to this system, should be based on information provided by the field of human psychopharmacology. Experimental performance studies are the most suitable way to reveal a drug's behavioral toxicity before it enters the market, in the same way that its efficacy and purely medical side-effects are evaluated according to long-established clinical trial procedures. Data from different experimental studies should therefore be integrated in a meaningful and logical way. Although it was demonstrated in a study by Wolschrijn, De Gier and De Smet (1991), that drugs can be categorized on the basis of expert consensus, their task would have been much simpler if different investigators had employed similar methodologies. Differences between studies with respect to experimental design, performance tests, drug doses and subjects make it extremely difficult to reach any firm conclusions concerning the degree of behavioral impairment attributable to particular drugs. The fact that deficiencies in today's research methods are commonly recognized indicates that experts working in the field have a good idea of what constitutes a methodologically sound and practically relevant study. We surveyed a number of international experts in the field of drugs and driving with the objective of providing a preliminary set of guidelines based on a consensus of scientific opinion, regarding methodology for experimental research on medicinal drugs affecting driving performance. These guidelines are intended to enhance standardization of study designs and quality of research in general, and, as a prerequisite for the implementation the new drug categorization system. The study was commissioned by the National Swedish Road Safety Office and The Netherlands' Ministry of Transport and Public Works. A questionnaire was designed in the form of an intentionally provocative "Position Paper" proposing a series of methodological guidelines, accompanied by arguments providing a background. Thirteen propositions referring to various aspects of study design,

procedures, testing methods, analysis and reporting were put forward. A total of 87 questionnaires were distributed among international experts in the field of drugs and driving. About half (42) went to experts presently working in the United States and the United Kingdom. The remainder went to experts in continental Europe and Australia. Forty-seven percent (N= 41) of the recipients completed and returned the questionnaire.

PROPOSITIONS AND RESPONSE

Subjects

Composition of the subject sample: age and gender

Until now far too many studies on drugs and driving have been undertaken using healthy young male volunteers. However, young males are not representative for the whole driving population and generalization from this group to women and elderly is problematic. It was therefore proposed that the subject sample should comprise men and women, who range in age across ages found in the driving population. A majority of experts (90%) agreed that the subject sample should be more representative, but they commented that some restrictions could be made: for example, drugs that are solely used by women need not be tested with men, and drugs mainly used by the elderly need not necessarily be tested in young volunteers. It was therefore concluded that the subject sample should reflect a cross-section of the driving population and the target population of the drug with respect to age and gender.

Composition of the subject sample: healthy volunteers versus ambulant patients

A majority (80%) of experts supported the following guideline that under most circumstances it is adequate to attain results of practical relevance from studies employing healthy volunteers as subjects. This is only not the case when it is known or strongly suspected that healthy volunteers and ambulant patients would experience different drug reactions capable of influencing their driving performance. In general, healthy volunteers can be considered representative for the actual users of the drug, as they are unlikely to experience different adverse effects than real patients. However, the interaction of the drug effects with the underlying diseases may sometimes distinguish the response of patients from that of healthy volunteers. For example, patients treated with neuroleptics

or antidepressants are assumed to be impaired by the disorder itself and therapeutic relief is therefore expected to improve these patients' performance. The net effect of adverse and beneficial effects is therefore hard to predict.

Design and treatment

The severity of performance effects is highly dependent on the dose and duration of treatment. Too many experimental studies involved only single-dose drug administration and acute effect testing.

Treatment dose

It was therefore proposed that studies undertaken to demonstrate a new drug's effects on driving or skills related to driving for the first time should involve at least two conditions with the drug's doses differing between them. The doses administered should be the lowest and highest to be given therapeutically; or in multiples of the standard therapeutic dose, at least 1x and 2x, if there is only one. Most drugs are administered in differing doses within a therapeutic range. Furthermore dose-effect relationships provide valuable information on the safety margins with respect to a drug's impairing side effects: a particular drug/dose may not impair performance, either because the drug has no impairing effects, or because the effects are below a certain threshold. In the latter case the effect may become apparent with a higher dose. Also the rate of increase in performance impairment may be much higher for some drugs than for others. The proposition was supported by a majority of experts (83%).

Treatment duration

Too many studies determined a drug's effects after only a single dose instead of after repeated dosing. Although acute effects are relevant, they are expected to change over the time due to accumulation, tolerance and therapeutic response. Consequently, it was proposed that studies should involve multiple dosing over longer treatment periods, lasting until the drug's plasma concentration has achieved steady state, or until acute effects have stabilized due to the development of tolerance. The majority of experts (83%) agreed with this proposition. In a second question most (57%) recommended that treatment and testing last until steady-state or until a therapeutic effect normally occurs in patients (38%).

Control conditions

Control conditions are needed for evaluation and interpretation of results. It was proposed that three control conditions be applied in every study: (1) a placebo; (2) an active control from the same therapeutic class; and (3) a verum, or a standard reference, not necessarily from the same therapeutic class as the drug under study. Comparison with placebo enables the investigator to conclude that a significant difference in performance was caused by the drug if all other circumstances were constant. However, a nonsignificant effect does not necessarily mean that the drug does not affect performance: this result might be due to insensitive test procedures. To rule out this possibility, a control drug with a known impairing effect is included: when the control drug also fails to show an effect, the procedures were most likely insensitive; the results of the experiment are than inconclusive. A control drug can be either an impairing drug from the same therapeutic class. i.e. an active control or standard reference drug that is widely used. The first makes it possible to compare two alternative treatments and provides valuable information as to which of the drugs may be preferred with respect to impairing side effects. The second provides a means of comparing results relative to other studies. Each has its own merits and therefore it was proposed to use all three control conditions. Although the majority of experts (71%) agreed in principle with the proposition, almost one quarter did not, and many comments were made indicating that either an active control or a standard reference would suffice. Experts (45-50%) indicated a preference for ethanol sufficient to raise blood alcohol concentrations (BAC) to 0.5 or 0.8 g/L as standard reference. One problem with alcohol, however, is that it is very difficult to use it in double blind design. An equally preferred (42%) verum was diazepam 10 mg.

Tests

Besides subjects and design, a very important issue in experimental research is the choice of tests. Although it is impossible to identify specific tests that should be used, it is possible to indicate certain criteria that each test should meet in order to provide valid results. Common criteria for the quality of tests are reliability of results and validity of test performance with respect to its purpose.

Reliability

One criterion for selecting tests is the reliability of the test's results. When the same phenomenon is measured twice in equal circumstances the test results should be comparable, i.e. a test should have considerable test-retest reliability. Reliability depends on the measurement error. In drugs and driving research the relevant measure is usually not the absolute performance level itself, but a difference in performance between drug and placebo. Such a difference-score contains the combined error of two measurements, which reduces its reliability even below that of the absolute performance measure. The proposition put forward in the questionnaire contained exact criteria for test-retest reliabilities: $r > 0.70$ as a minimum for normal test-retest reliability, and $r > 0.50$ for the reliability of change. A rather large number of experts (29%) did not feel qualified to respond to the proposition. Of the remainder, the majority (78%) agreed.

Construct validity: measuring a drug effect on driving or a skill related to driving

Another criterion is the construct validity of the test. Construct validity of a test is the degree to which the test really measures the mental/behavioral function (i.e. construct) it is supposed to be measuring. Investigators in Drugs and Driving research are not concerned with the measurement of mental/behavioral function per se, but with the combination of mental/behavioral functions relevant for driving and drug effects. It was proposed and agreed upon by a majority of experts (85%) that each performance test used for determining drug effects on driving should posses construct validity in two dimensions: a test should not only measure a selected skill or function that is essential for safe driving, but it should also be sensitive to a specified pharmacological effect that could be inimical to performing effectively in any situation. ontent validity: composition of the test battery.

Content validity: composition of the test battery

Content validity is the degree to which a battery of tests measures all relevant aspects of the phenomenon of interest. Driving ability is not one single skill, but rather a combination of various skills. Tests comprising a battery should therefore not all measure the same skill, but each test should measure a different aspect relevant for driving. Even so, a drug may have a several different pharmacological effects that might affect driving. It was therefore proposed that test batteries applied for determining drug effects on driving should have content validity in two dimensions. The battery as a whole should

measure, on one hand, a representative range of skills involved in driving and, on the other hand, as many as possible pharmacological drug effects that are relevant for driving. The majority of experts (73%) agreed with this proposition. In a second question experts were asked to indicate the most important pharmacological effects of drugs and mental/behavioral functions that should be measured in studies determining drugs' effects on driving. All experts indicated that (a) sedation or drowsiness as the most relevant pharmacological effects, and more than two-thirds indicated (b) visual and perceptual disturbances as the next most relevant effects. The most important mental/behavioral functions to be measured for safe driving according to the experts are (1) divided attention, (2) continuous motor performance and (3) discrete perceptual-motor responses. The next most important functions were (4) sustained attention and (5) risk avoidance.

Laboratory tests, simulators or actual driving tests?

It was proposed that studies for establishing the driving hazard potential of a particular drug should proceed from conventional laboratory testing to the most realistic that can safely be applied. The final evidence that therapeutic doses of the drug in question would be safe or hazardous to a specified degree can best be obtained in the latter situation. A majority (68%) agreed with the proposition, yet some expressed doubt as to whether "the most realistic" test is automatically the best, and commented that this remains to be proven. The approaches were seen as mutually supportive. They supported the idea that testing should proceed from laboratory settings to tests that bear closer resemblance to actual driving, and that no conclusions should be based on the results of on class of tests alone. They require confirmatory results from each other.

Analysis and reporting of results

Purpose of the study and the hypothesis

Many investigators have proceeded in the past to analyze their data as if the purpose was always to detect a drug's adverse or beneficial effect on driving. Yet, in many cases the investigators' real purpose was to show a lack of any significant effects on performance. Anyway this is their frequent conclusion. They apparently failed to recognize that there is a fundamental difference between analyses applied for the purpose of revealing a hypothesized effect and those for confirming the lack of any effect. It was therefore

proposed in the questionnaire that the investigator should state the aim of the study, whereby he clearly distinguishes between the expectations that the drug will have an effect or have no effect on driving. When he sets out to demonstrate an effect he should minimize the probability ($p\alpha$) of making a Type I error, i.e. concluding that the drug has an effect which in fact it does not. When he sets out to show a lack of effect he should minimize the probability ($p\beta$) of a Type II error, i.e. overlooking an existing effect. Owing to the inverse relationship between these probabilities, both objectives cannot be realized simultaneously. Some experts (12%) did not feel qualified to respond to this proposition, but of the remainder 91% agreed.

Sample Size

The probability of detecting a drug effect when it actually exists depends to a great extent on the sample size: the smaller the sample, the less likely it becomes that a certain drug effect will lead to significant results. The experts (88%) agreed with the proposition that the sample size used in drugs and driving studies has often been too small and a criterion ought to be set to achieve a better balance between Type I and Type II error probabilities.

Statistical Plan

Statistical tests are decision tools to standardize or formalize the interpretation of the results. They do not provide evidence for the presence or absence of an experimental effect, but merely help the investigator reach the best conclusion on the basis of the data collected. The probability that the conclusion is wrong (Type I or Type II error) should be reported. In view of this, it was proposed that studies determining the effects of a drug on driving performance should use the most powerful statistical test for determining the significance of drug effect that can correctly be applied. Evidence that the test's assumptions are not violated should be provided. Finally, in case of repeated application of the same statistical tests to the data, investigators should indicate what measures were taken to correct for the increase in Type I error probability or so-called α- inflation. Some experts (10%) did not feel qualified to respond to this proposition. Of the remainder three-quarters (76%) agreed.

Common scale

To get a complete picture of the hazard potential of a drug for driving, it is necessary to combine results from several studies. To be able to compare results from different studies using different tests and different procedures, it was suggested to transform all test scores to a common scale, for example standard z, or t-scores, or to use population deviation scores (σ_{pop}) as units of measurement. This way measures become independent of particular tests, enabling comparison of drug effects across tests and studies. It was proposed that these procedures should be applied by every investigator participating in research aimed at categorizing the driving hazards of drugs. The majority (79%) of experts who felt qualified to respond to this proposition, agreed.

FUTURE NEEDS

The results from this survey indicate that experts agree on many issues and that it is therefore possible to draw up guidelines for research in this field. All thirteen propositions put to the experts were accepted, although sometimes with modifications and qualifications. However, the survey also revealed some gaps in existing knowledge and deficiencies in available data.

Definition of impairment

What is needed for the future is a definition of 'impairment'. Investigators should determine what they think is a practically relevant change in performance on a test or how a change on a certain test relates to increased risk while driving. Although this is very hard, there is already a need for specifying critical levels of performance impairment implicit in authorities' requests for investigators to specify the statistical power of their tests. An initial pragmatic criterion for impairment may be set on the basis of the effect sizes of reference drugs whose effects on performance are well documented and of a generally agreed upon relevance to actual driving performance. It is our opinion that investigators should calibrate changes on the particular tests they use with standard reference drugs, such as the benzodiazepines or alcohol. The effect of a particular dose of new drug on a test could than be interpreted by comparison with the dose-effect curve of a reference drug on that particular test. Besides comparing each new drug's effects to a

standard reference, interpretation can be in reference to 'normal' performance. Data on average performance and inter-individual variance in performance would very much facilitate the interpretation of drug effects as deviations from the norm. The concept supported by the experts was to collect data in a central repository from subjects of varying ages and developmental levels who received no treatment or placebo, so that distribution parameters can be established for describing 'normal' performance on tests used for screening purposes. More normative research should be conducted in the future. The organization of an international network providing input to the central depository of normative data would be a first step toward assembling the normative database needed for quantitatively assessing the abnormality of performance under the influence of drugs.

Validation of tests

It is crucial that investigators validate performance tests for determining drug effects on driving. Test performance, or the change therein, should be a reliable index of the real hazard potential of drugs. In our opinion, more direct evidence of test validity should be established by comparison of experimental and epidemiological data. Psychometric tests showing changes in test performance parallel to changes in relative risk of injurious traffic accidents, as established through epidemiological surveys, could be accepted as potentially possessing predictive validity. Furthermore, authorities responsible for post-marketing drug surveillance regularly record adverse event reports that indicate possible drug involvement in traffic accidents. Such information would be valuable to investigators involved in pre-marketing drug trials for evaluating their predictions and providing more insight into the pharmacological activities and types of performance failure that cause accidents.

RECOMMENDATIONS

A preliminary set of methodological guidelines is now available to all those who need to use them (Vermeeren et al., 1993). Final practical application, however, will require additional concerted action and development by all the parties involved; individual investigators, psychopharmacological research organizations, the pharmaceutical industry and regulatory authorities.

Definition of programmatic research

Several aspects of a drug's driving impairment potential should be investigated before recommendations are made for individual use. The degree of impairment varies depending on the dose, time after dosing, development of tolerance, the age and gender of the user, the user's mental and physical state, interaction with other substances and the demands of the situation. Obviously, not all of these factors can be tested in one experiment. The experts supported the idea that testing should proceed from simple laboratory tests, to more sophisticated simulators and finally include actual driving. A drug would proceed systematically from test to test on this continuum. Therefore a minimal sequence of interrelated studies in programmatic research for determination of a drug's hazard potential for driving should be defined. The definition of programmatic research could be accomplished at a consensus meeting of recognized experts acting in the field of experimental research on drugs and driving. Because drug manufacturers are responsible for screening a drug's impairing effect in an early stage of its development, and regulatory authorities review the results submitted in registration procedures, consensus must also involve these parties.

Professional organizations

It should be the responsibility of the professional organizations in the fields of psychopharmacology and traffic safety to bring the issue of methodological standardization and quality of research to the attention of their members they should support the application of the guidelines. In addition, international professional organizations might support workshops to evaluate and improve the present set of guidelines and publish revisions along with their rationale in the form of a handbook with standards on methodology of research in drugs and driving. This seems essential since the experts in this survey indicated that at least some of the issues were not properly dealt with until now because of a lack of knowledge. Specialized courses may also be inaugurated to educate and update the investigators working in this interdisciplinary area.

Investigators

Investigators should provide sufficient information in their reports for enabling a qualified reader to determine whether the work meets standards for good experimental practice. Journal editors and referees could assist the process by applying stricter criteria to the studies they review and publish, making sure that adequate information is available for detecting methodological flaws.

Drug manufacturers

Responsibility for the application and improvement of the guidelines should be taken by the pharmaceutical industry. More than ninety percent of all experimental research on medicinal drugs and driving is sponsored by the drug manufacturers. It is obvious that time and money spent on poorly designed studies that provide little or no information is wasted. If the drug manufacturers commit themselves to supporting research conducted according to sound methodological guidelines, they will not only contribute to the process of quality improvement in experimental human psychopharmacology, but also reduce the overall costs of new drug development by allocating resources to fewer studies that provide essential, unequivocal results.

Regulatory authorities

Without minimizing the importance of potential contributions by the scientific community and pharmaceutical industry, it is clear that the crucial impetus for methodological standardization leading to drug categorization must come from drug regulatory authorities. Unless the latter make it clear that guidelines are needed for meeting more rigorous registration requirements there is little hope that these will evolve or be universally applied. Failure to do so would simply mean that they would have to discharge their duty to protect the public safety with the same inadequate information they presently have.

The initiative, which has provided the present set of guidelines, is concluded. Further development of guidelines leading to their ultimate implementation now passes to those who would benefit most from the standardization of research methodologies. In our view, the greatest immediate beneficiaries would be the pharmaceutical industry and

supranational regulatory authorities. They might consider creation of a platform for continuing the work begun by experts contributing to this survey.

Chapter 3

Residual Effects of Hypnotics: Epidemiology and Clinical Implications

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ABSTRACT

The risk of hangover effects, i.e., residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration, is one of the main problems associated with the use of hypnotics. Yet, the severity and duration of these effects varies considerable between hypnotics and is strongly dependent on the dose. This paper reviews epidemiological evidence that use of hypnotics increases patients' risk for injurious accidents. It was found that risks increase with increasing half-life, but that use of hypnotics with short half-lives, such as triazolam, zopiclone and zolpidem, can also be associated with increased risks. Selection of the safest drug and dose possible among those available is a first step to minimize risks. Information on duration and severity of residual effects of 11 hypnotics (flunitrazepam, flurazepam, loprazolam, lormetazepam, midazolam, nitrazepam, temazepam, triazolam, zaleplon, zolpidem, zopiclone) is derived from expert ratings, a meta-analysis and actual driving studies. A summary of this information should enable prescribing clinicians to compare residual effects of various hypnotics in different doses and select the one considered most favorable in this respect within the range of possibilities of the individual patient. This information should also enable them to inform patients more adequately about the likelihood and duration of residual effects of a specific hypnotic dose.

INTRODUCTION

Residual daytime sleepiness and associated impairment of psychomotor and cognitive functioning the day after bedtime administration, sometimes called 'hangover' effects, constitute one of the main problems associated with the use of hypnotics. Reduced alertness and slowed reactions increase a person's risk to become involved in accidents at home, at work or on the road. In elderly ataxia and impaired motor coordination may increase risk of falling and hip fractures. The latter is of particular concern, since hip fractures constitute a major cause for placement in nursing homes. A number of epidemiological studies have shown that use of benzodiazepines is associated with increased risk of injurious car accidents (e.g. Barbone et al., 1998; Neutel, 1995, 1998) and falling and hip or femur fractures (Cumming and Klineberg, 1993; Herings et al., 1995;

Lichtenstein et al., 1994; Maxwell et al., 1997; Neutel et al., 1995; Ray et al., 1989; Ray et al., 1987).

Avoidance of residual effects of hypnotics seems therefore particularly relevant for elderly and persons whose activity the next morning involves skilled work and where impairment of performance could be a danger to themselves or others, such as driving a car. Since experimental studies have shown that there are substantial differences between hypnotics in their potential to produce residual effects, this can be achieved by selecting a drug and dose shown to have no effects more than 8 hours after bedtime ingestion.

The problem is, however, that information on the duration and severity of residual effects of hypnotics is not available in a way that allows clinicians to easily compare and choose from the many drugs and doses. All prescription hypnotics have comparable mechanisms of action, i.e. benzodiazepine receptor agonists, and a rapid onset of action. Their half-lives differ substantially however, ranging between 1 and 100 hours (table 3.1).

Since package insert labels contain non-specific warnings that are the same for all hypnotics, selection is usually based on the drug's half-life. In general, hypnotics with long half-lives are associated with more residual effects than those with short half-lives. Although half-life is a strong predictor of duration of action, the relation is not always consistent. Short half-life hypnotics can have residual effects, depending on the dose and rate of absorption, whereas long half-life hypnotics may have a relatively short duration of action when the drug is largely redistributed to peripheral tissue.

Duration and severity of residual effects should therefore be determined empirically, most suitably by experimental performance studies. Many of such studies have been carried out, yet differences between studies with respect to experimental design, performance tests and subjects make it extremely difficult to reach any firm conclusions concerning the duration and degree of behavioral impairment attributable to particular drugs and doses. This lack of agreement was noted by several investigators in the field of experimental human psychopharmacology, and lead to methodological guidelines to remedy the situation (ICADTS, 1999; Vermeeren et al., 1993). Most studies assessing residual effects of benzodiazepine hypnotics were performed before the introduction of the guidelines, however. Fortunately, it was demonstrated that consensus among experts was sufficient to allow some form of categorization of the residual effects of most of these older hypnotics, yet the results are only available in a technical report and have not been updated (Wolschrijn et al., 1991). Probably as a consequence of these difficulties no recent reviews comparing residual effects of hypnotics are available. The

Table 3.1 Average half-life (t½) of hypnotics and their active metabolites (indicated between brackets) and time of peak plasma concentrations (*tmax*).

Drug	t½	*tmax*
short half-life		
zaleplon	1.0 ±0.1	1.1 ±0.2
zolpidem	1.9 ±0.2	1.0 - 2.6
midazolam	1.9 ±0.6	0.7 ±0.5
triazolam	2.9 ±1.0	1.3 (0.5 - 4.0)
zopiclone	5	1
brotizolam	5 ±2 (5 ±2)	2 (0.5-3)
intermediate half-life		
loprazolam	8 - 12	5 ±3.6
lormetazepam (tablets)	10 ±2.5	3 (1.5-4.5)
lormetazepam (capsules)		1
temazepam (soft gelatine capsule, SGC)	11 ±6	0.8
temazepam (hard gelatine capsule, HGC)		2.5
long half-life		
flunitrazepam	15 ±5	1.2
nitrazepam	26 ±3	2
flurazepam	1 - 2 (74 - 24)	(3 - 48)
anxiolytic hypnotics		
oxazepam	8 ±2.4	2 (1-4)
lorazepam	14 ±5	1.2-2.6
diazepam	43 ±13	1.3 ±0.2

objective of the present paper is therefore to review and compare residual effects of currently used hypnotics.

Aim of this paper

The aim of this paper is to review empirical data from epidemiological and experimental studies on residual effects of currently available benzodiazepine and benzodiazepine-like hypnotics. It should convince clinicians of the importance of taking residual effects into

consideration when prescribing a hypnotic. Most importantly, it should enable them to compare residual effects of various hypnotics in different doses and select the one considered most favorable in this respect within the range of possibilities of the individual patient. Furthermore, if a prescribed hypnotic is likely to produce residual effects, this review should enable clinicians to inform their patients more specifically about the expected severity and duration of risks and provide them with some practical advice on how to minimize these risks.

Data from epidemiological studies on accident risks associated with use of hypnotics will be reviewed to establish the clinical relevance of residual effects in daily life. These studies may also shed some light on drug-, and patient characteristics that may increase risks for accidents.

Results from experimental performance studies will be used to compare severity and duration of residual effects of various hypnotics. Residual effects on psychomotor performance and attention have been studied most frequently and systematically, because they constitute an important hazard potential for traffic safety and work related accidents. Consequently, effects on these behavioral and mental functions will be the focus of this review. Yet, it is impossible to review the results of each study for more than ten different compounds in different doses. As mentioned before many studies were performed in the 1980s and are of varying methodological quality. Selecting only those that meet certain quality criteria would leave some important drugs with almost no data. It was therefore decided to use primarily the results from an expert survey (Wolschrijn et al., 1991), a meta-analysis of experimental studies (Berghaus, 1998), and experimental studies using a standardized and calibrated test (O'Hanlon, 1984; O'Hanlon et al., 1982). These data will be summarized for flunitrazepam 1 and 2 mg, flurazepam 15 and 30 mg, loprazolam 1 and 2 mg, lormetazepam 1 and 2 mg, nitrazepam 5 and 10 mg, temazepam 20, mg, triazolam 0.125, 0.25 and 0.5 mg, zaleplon 10 and 20 mg, zolpidem 10 and 20 mg, and zopiclone 7.5 mg. These drugs and doses constitute the most frequently prescribed hypnotics in Western societies. Since oxazepam, lorazepam and diazepam are primarily indicated for anxiety disorders, yet widely used as hypnotics too, effects of these drugs will also be discussed to a limited extend.

This will be preceded by some background information on the prevalence of insomnia and use of hypnotics; recent discoveries on the function of the benzodiazepine receptor subtypes; and the pharmacodynamics of hypnotics and pharmacokinetic aspects

related to their duration of action. The review will conclude with a discussion of the implications for accident prevention and patient education.

Previous reviews

Most reviews on the effects of hypnotics summarize the literature on efficacy and side effects of an individual drug, such as zaleplon (Patat et al., 2001), zopiclone (Goa and Heel, 1991; Nicholson, 1998; Noble et al., 1998; O'Hanlon, 1995), zolpidem (Langtry and Benfield, 1990; Rush, 1998). Only a few review and compare data of multiple hypnotics (Johnson and Chernik, 1982; Roth and Roehrs, 1985; Roth and Roehrs 1991). All agree that hypnotics with longer half-lives tend to produce more residual effects than drugs with shorter half-lives, but add that the relation is not straightforward.

Johnson and Chernik (1982) published an extensive and critical review of 52 placebo-controlled studies assessing residual effects of 11 benzodiazepine hypnotics on performance. They found that these drugs generally improved sleep, but not quality of daytime performance, as expected when adverse effects of poor sleep would be normalized by use of hypnotics. Moreover, all hypnotics were likely to be associated with residual effects at higher dose levels. Although long-acting drugs generally showed more performance decrement than short acting ones, half-life did not adequately explain the data. For example, across dose levels, they found that flurazepam produced less decrement than nitrazepam, and that temazepam produced less decrement than triazolam, in spite of their respective longer half-lives. Tasks showing the largest decrement were those involving speeded performance and memory for information presented during the night, indicating that the drugs mainly produced psychomotor slowing and anterograde amnesia. Johnson and Chernik concluded that dose level was the most important factor determining performance decrement; large doses increase impairment at any given time after administration and extend the effect over time.

Roth and Roehrs (1985) critically discussed the methodologies used in studies assessing residual effects of hypnotics, since they believed that any particular study can produce any effects desired. "Given the right dose and the right task, one can demonstrate a decrement or no effect on performanc" (pp 291). They pointed out several methodological issues that were largely neglected in the majority of studies, such as power calculations and external validity of tests used. Furthermore they emphasized the importance of dose equivalence with respect to the hypnotic effects when comparing

relative risks for residual effects between different drugs and the need to assess residual effects in different populations, notably at risk populations such as elderly. At that time they concluded that little was known on the effects of pharmacological and behavioral tolerance. Yet, five years later they tentatively concluded that behavioral tolerance to the residual effects of hypnotics develops (Roth et al., 1990).

Recently, Van Laar and Volkerts (1998) reviewed the effects of benzodiazepines on driving. Epidemiological studies show that use of these drugs in general is related to increased risk for traffic accidents. No distinction was made between hypnotics and anxiolytics, however. Although the risk was not considered extraordinarily high, it appeared to increase with increasing dose, multiple drug use and recency of drug use. According to Van Laar and Volkerts experimental driving and laboratory studies have shown that single bedtime doses of diazepam 10 mg, flunitrazepam 1 mg, loprazolam 1mg, lormetazepam 1 mg, nitrazepam 5 mg, oxazepam 30 mg, temazepam 20 mg, triazolam 0.25 mg may be relatively safe when used occasionally. Changes with continued use are unclear. Theoretically, benzodiazepines with a long half-life may accumulate and produce increasing sedation, while at the same time tolerance may develop which diminishes these effects. Yet, data on this issue were found to be limited and conflicting. Finally, they stress the importance of individual differences in response to drugs, resulting in the necessity to monitor each patient carefully.

In conclusion, most reviews lack comparison of the effects of individual drugs and doses. Instead, they extensively discuss the problems involved in comparing results from different studies due to methodological differences. The only advice that can be deduced from these reviews is that patients who need to be alert in the morning should use the lowest dose possible of a hypnotic with a short half-life. Hardly any specific information is provided on the duration of residual effects of individual drugs and doses. The present review will not discuss these methodological issues again.

BACKGROUND

Prevalence of insomnia

Since 1980 more than 20 studies have assessed the prevalence of insomnia (Leger et al., 2000). Most of them find that approximately one third of the general adult population

complains of occasional poor sleep, and that about one in ten people experiences moderate to severe symptoms of insomnia on a chronic basis (e.g. Balter et al., 1984; Leger et al., 2000; Mellinger et al., 1985; Pallesen et al., 2001; Simon and VonKorff, 1997). A European telephone survey among nearly 25000 adults showed that the most frequent insomnia symptom was disrupted sleep occurring at least three times a week (18%), followed by early morning awakening (11%), difficulties initiating sleep (10%) and nonrestorative sleep (9%; Ohayon and Roth, 2001). A similar pattern of complaints was found among Americans (Ancoli-Israel and Roth, 1999). Typically, the prevalence of insomnia is higher in women than in men (2:1) and increases with age. More than 50% of persons older than 65 years complain of poor sleep. Insomnia is highly associated with psychiatric problems, such as anxiety, depression and substance use or abuse, especially with caffeine, nicotine, alcohol and a number of medicinal drugs, such as stimulants, beta-blockers, oral contraceptives and MAO-I's (Reite, 1998). In addition there are several medical conditions associated with disturbed sleep, such as chronic pain, cardiovascular diseases, sleep apnea and periodic leg movement disorder and restless leg syndrome. Subjects with at least one insomnia symptom were shown to be 12 times more likely to have a sleep or mental disorder diagnosis than subjects without insomnia symptoms (Ohayon and Roth, 2001).

Although it is generally assumed that people complaining of insomnia are sleep deprived, the effects of sleep deprivation in healthy volunteers do not necessarily resemble the symptoms of insomniac patients (Benca, 2001). For example, many patients with chronic insomnia show signs of hyper-arousal and have normal to prolonged sleep latencies in the multiple sleep latency test (MSLT), whereas sleep deprived healthy controls show signs of hypo-arousal and shortened sleep latencies in the MSLT. In performance testing patients with insomnia were more like normal controls than sleep deprived controls, making it difficult to assume specific functional impairments due to poor sleep per se.

Pharmacological treatment of insomnia

Before the introduction of benzodiazepines insomnia was treated with bromide and barbiturates. Flurazepam was the first benzodiazepine introduced for the treatment of insomnia in the US in 1971. Although benzodiazepines had several advantages over barbiturates it soon became clear that they were not an ideal agent for treating insomnia

as their generally long half-lives resulted in significant residual effects (Bond and Lader, 1972; 1973; 1975; Borland and Nicholson, 1975; Hindmarch, 1977). The introduction of a variety of short-acting benzodiazepines during the 1980s reduced this problem (Hindmarch, 1979; Hindmarch and Clyde, 1980). However these drugs also had drawbacks, such as development of tolerance and problems with abrupt withdrawal (Aranko et al., 1983; Gillin et al., 1989; Kales et al., 1983b). These effects seemed to be less, however, for short half-life benzodiazepine receptor agonists from other chemical classes that were introduced around 1990, the cyclopyrrolone zopiclone, and the imidazopyridine zolpidem (Goa and Heel, 1991; Langtry and Benfield, 1990). At the end of the 1990s they were followed by zaleplon, a pyrazolopyrimidine, with a half-life of only 1 hour (Hurst and Noble, 1999).

Although the newer hypnotics seem to have a more favorable safety profile, use of hypnotic drugs has decreased considerably in the US and Europe since the 1980 (Lapeyre Mestre et al., 1999; Walsh and Schweitzer, 1999). In contrast, the use of antidepressants, such as trazodone and amitryptiline, for the treatment of insomnia has grown substantially (Walsh and Schweitzer, 1999). Furthermore, there is now consensus among clinicians that hypnotics should be used at their lowest possible doses, for limited durations and preferably on an as needed basis (Doghramji, 2000; Kirkwood, 1999).

Prevalence of hypnotic use

Population surveys show that between 0.7 and 7% of all adults report current use of sleep enhancing medication. Ohayon (Ohayon and Caulet, 1995; Ohayon et al., 1997, 1998) found a current use of 3.8% in Montreal, and 3.5% in the UK, while 5.3% of the latter respondents reported that they had used sleep-enhancing medication in the last year. Results of a recent survey in 4 European countries reveal lower rates of current use however: 2.5% in France, 1.6% in the United Kingdom and 0.7% in Germany and Italy (Ohayon and Vecchierini, 2002). Lapeyre-Mestre et al. (1999) report a current use of 6.2% in 1996 in Toulouse, France, and Pallesen et al. (2001) found a current use of 6.9% of prescription hypnotics in the winter of 1999 and 2000 in Norway.

Of the people complaining of poor sleep in these surveys approximately 20 to 30%, mostly females and elderly, report using of some form of sleep enhancing medication. Simon and VonKorff (1997) found that 28% of patients reporting major current insomnia used a psychotropic drug. Of those 14% received a benzodiazepine and 19% received antidepressants as compared 1% and 9% of patients without insomnia.

Not surprisingly, use of sleep promoting medication hypnotics is most frequent among persons with serious sleep complaints (Roehrs et al., 2002; Weyerer and Dilling, 1991). Hypnotic use is also higher in patients complaining of sleep onset difficulties than in patients with sleep maintenance problems (Bader and Ohayon, 2002). The latter study showed that although sleep initiation problems are less frequent than sleep maintenance problems, the former complaints seem to be associated with higher drug use. These problems are also associated with depression and anxiety.

Medication used

Sleep enhancing medication may not only be prescription hypnotics, but also anxiolytics, antidepressants and nonprescription (over the counter, OTC) drugs. In the US the drugs most frequently mentioned for treatment of insomnia changed dramatically between 1987 and 1996 (Walsh and Schweitzer, 1999). The two most frequently mentioned drugs for the treatment of insomnia in 1987 were triazolam and flurazepam, and in 1996 trazodone and zolpidem. Use of temazepam was stable over the years. The frequent mention of trazodone and amitryptiline indicates a shift towards the use of antidepressants in the treatment of insomnia. The forces underlying this shift were most likely the increasing evidence for and concern about dependence and side effects and increased recognition of depression in those reporting insomnia (Walsh and Schweitzer, 1999). A similar decrease in use of hypnotics was found in France between 1986 and 1996 (Lapeyre Mestre et al., 1999). Yet, in France it was accompanied by an increase in the use of analgesics, probably reflecting the effects of drug information programs for better management of pain and a change in OTC use of analgesic drugs in this period. OTC sleeping pills are mainly used by younger patients and by those with milder sleep complaints (Roehrs et al., 2002). These drugs were also found to be used less frequently and for shorter periods than prescription hypnotics.

The most frequently used hypnotics differ depending on the country and the drugs registered. The five most prescribed hypnotics in 4 major European countries between 1993 and 1997 were temazepam (16%), zopiclone (16%), nitrazepam (14%), zolpidem (13%) and flunitrazepam (11%) (Ohayon and Lader, 2002). Other frequently used hypnotics are flurazepam, loprazolam, lormetazepam and triazolam (Nowell et al., 1997; Ohayon and Lader, 2002; Patat et al., 2001).

In spite of the recommendation and consensus among clinicians that hypnotics should be used at their lowest possible doses, for limited durations Ohayon et al.(1998)

found that 76% of hypnotic users in their sample reported using the drug at least 3 days a week, and 61% had been using hypnotics for at least a year. A recent survey (Ohayon and Lader, 2002) supports the finding that most users take hypnotics for more than a year.

Mechanism of action of hypnotics

Pharmacodynamics

Currently available prescription hypnotics are all benzodiazepine receptor agonists. They act on the GABA-A receptor-complex to enhance the effects of GABA, the main inhibitory transmitter in the brain. GABA-A receptors consist of 5 subunits forming a rosette around a central channel that is selectively permeable to chloride ions. The subunits are proteins from three principal families designated alpha (α), beta (β) and gamma (γ). Whereas GABA binds to the β-subunit, hypnotics interact with the α-subunit. The binding of GABA to its receptor induces a conformational change that opens the ion channel whereupon chloride ions can enter the cell producing slight, short lasting hyperpolarization and thus a reduced excitability of the neuron. Hypnotics increase the affinity of the receptors for GABA and enhance the effects of GABA on the neuron.

Since 1987 many different subtypes of α-, β- and γ-subunits have been identified, which has significantly progressed the insights into the mechanism of action of hypnotics (Doble, 1999; Landolt and Gillin, 2000; Moehler et al., 2002). There are at least 6 different alpha subtypes (α1- α6), 4 beta subtypes (β1-β4) and 3 gamma subtypes (γ1-γ3). Yet, only certain combinations of subtypes seem to exist and appear to be localized in specific cell types. It seems that over 50% of all GABA receptors in the brain are composed of α1β2γ2, and correspond to what was previously defined as a benzodiazepine type-I or omega-1 (ω1) receptor. They are sensitive to all modern hypnotics (zaleplon, zolpidem, zopiclone and benzodiazepines), and are present throughout the brain, particularly on hippocampal and cortical interneurons. Receptors containing α2, α3 or α5 subunits correspond to benzodiazepine type-II or ω2 receptors and are also sensitive to zopiclone and benzodiazepines, but much less to zolpidem and zaleplon. Receptors containing α2 and α3 subunits are enriched in the limbic structures (amygdala) and spinal motor neurons.

Benzodiazepine receptor agonists have multiple actions. The most prominent central effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. It is now assumed that the sedative/hypnotic effects

are linked to the α1 subunit and anxiolytic effects to the α2 subunit, although distinguishing between these behaviors is problematic (McKernan et al., 2000; Moehler et al., 2002). In addition α1 seems to have an important role in amnesic effects produced by benzodiazepines and α2 in the myorelaxant effects (Moehler et al., 2002). This could explain why zolpidem and zaleplon are effective hypnotics, with fewer side effects.

Benzodiazepines mainly shorten sleep latency and diminish number and duration of awakenings during sleep, thus increasing the total time spent asleep during the night. Yet, the extra time asleep is mostly spent in stage 2 or light sleep. Compared to natural sleep percentage of time spent in the most restorative stages of sleep, i.e. deep sleep (stage 3 and 4) and REM sleep, is decreased following administration of a benzodiazepine. In contrast, zolpidem does not suppress REM sleep to the same extent as benzodiazepines do (Hardman et al., 2001). With continued use tolerance seems to develop to benzodiazepines effects on sleep stages, but rebound occurs when such use is discontinued. The increase in REM sleep may be especially prominent during the first nights after discontinuation.

Duration of effects

Under most circumstances choice of drug is determined by onset of action and duration of effect. All hypnotics have a rapid onset of action (between 30 and 90 minutes), whereas duration of action differs largely. Both are dose dependent. Onset of action is largely determined by the formulation and rate of absorption of the drug from the gastrointestinal tract after oral administration. Time to peak plasma concentration (t*max*) is often taken to indicate onset of action for rapidly absorbed benzodiazepines, such as diazepam and flurazepam. In case of the slowly absorbed loprazolam, however, t*max* is delayed with respect to onset of action. The pharmaceutical preparation (formulation) can influence the rate of absorption, e.g. temazepam is much slower absorbed from hard gelatine capsules than from soft capsules. Once they reach the blood, all benzodiazepines quickly reach their site of action, since all are lipophilic substances that easily traverse the blood-brain barrier.

Duration of action is often equated to elimination half-life, as indicated by the fact that hypnotics are often divided into categories based on their elimination half-life, as short acting (t½ less than 6 hours), intermediate acting (t½ between 6 and 24 hours) or long acting (t½ greater than 24 hours) drugs. A drug's action may be terminated by at least three mechanisms, however: disappearance from the receptor site by redistribution from

the brain to peripheral tissue, biotransformation by the liver to inactive metabolites, and acute tolerance of the receptors. In addition, dose is considered one of the most important determinants of a drug's duration of action. It will take longer for drug concentrations to drop below effective levels after administration of twice the recommended dose, and shorter after only half the recommended dose. The relation between half-life and duration of action is therefore not straightforward.

EPIDEMIOLOGY OF ACCIDENTS ASSOCIATED WITH HYPNOTIC USE

Epidemiological studies probably provide the most important information concerning the effects of medication on performance, namely the actual accident risks associated with their use. The unquestioned strength of these studies is therefore the relevance of their outcomes. Their weakness is, however, that they can only assess the risks associated with drugs that have been on the market for some time and that are commonly prescribed. New or rarely prescribed drugs have a low probability of showing up in epidemiological statistics and related research papers. Another limitation is that users and nonusers may always differ in ways other than their drug use that could affect their performance, such as the indication for use of the drug. Despite these limitations epidemiological studies provide important information and criteria to validate the conclusions from experimental studies.

Most epidemiologists have assessed risks of benzodiazepines as a group, rather than individually. For the purpose of this review it is necessary, however, to distinguish the risks associated with the use of anxiolytics from those of hypnotics. Sedative anxiolytics are likely to affect daytime performance and increase accident risks, whereas hypnotics can only affect performance when they are active at the time patients get out of bed. Few authors actually make this distinction (Barbone et al., 1998; Neutel 1995, 1998; Neutel et al., 1995, 1996). Instead, benzodiazepines are often classified by their half-life irrespective of their therapeutic use (e.g. Herings 1994; Herings et al., 1995; Passaro et al., 2000; Pierfitte et al., 2001; Ray et al., 1987, 1989, 1992)). Occasionally, authors provide information on specific drugs (e.g., Neutel 1995, 1998; Neutel et al., 1995, 1996). This review mainly focuses on those studies providing direct or indirect information on the risks associated with hypnotics.

Three types of accidents have been studied in association with benzodiazepine use: traffic accidents, falls and hip fractures. Traffic accidents are relatively rare events, but occur in all users of 18 years and older, whereas falls and hip fractures are more common, but mainly occur in elderly. Average annual incidence of falls is 36% in community dwelling elderly (Leipzig et al., 1999). They are a predominant cause of injuries in the elderly and a strong predictor for placement in a nursing home (Neutel et al., 2002).

Traffic accidents

The role of alcohol in traffic accidents is firmly established, but there are relatively few epidemiological data on the role of psychoactive medication. Studies to provide such data are not easy to perform. Crashes are infrequent events for individual drivers and those that cause injury even more so. Moreover, there are a large number of drugs available, that can be taken in a variety of doses and whose metabolic fate and behavioral effects show great variability between individuals. This makes it necessary to carry out a large number of studies in order to establish relative risks associated with specific drugs and doses.

A relatively simple epidemiological method to study drugs and driving is to assess the prevalence of drugs in blood or urine of injured or killed drivers. De Gier (1999) recently reviewed such studies carried out in Europe and concluded that benzodiazepines are the most frequently detected licit drugs other than alcohol in drivers. In studies on drivers stopped for suspicion of driving under the influence the prevalences of benzodiazepines varied between 13-75%; lower prevalences (2-13%) were found in drivers involved in crashes. Similar findings have been reported for Australia (Longo et al., 2000a,b). Blood samples from 2500 injured drivers tested positive for alcohol in 8.6%, for THC in 7.1% and for benzodiazepines in 1.8%. About half of them tested positive for one benzodiazepine only, whereas about a third tested positive for two benzodiazepines. Since the majority of plasma concentrations were at subtherapeutic or therapeutic levels, it may be assumed that the drugs were used therapeutically, rather than abused.

Figures like these reveal little about the importance of benzodiazepines as a cause of accidents. Without comparison to a control group it is difficult to determine whether a particular drug is over-represented in accidents. Case control and cohort studies are better able to establish the relation between drug use and accident. In case control studies the frequency of medication use in accident victims is compared with that in non-injured

controls, whereas in cohort studies groups of users and nonusers are identified and followed over time to compare the rate of accidents in each group. A number of case-control and cohort studies have studied the risk of traffic accidents after use of psychoactive medication. Some of the more recent ones made use of large electronic databases to collect information on specific drugs and doses, for example by linking prescription records of pharmacies to records of hospitalization or police records of motor vehicle crashes (table 3.2).

Two studies compared the risks associated with the use of hypnotics and anxiolytics separately, in drivers of 20 years and older (Barbone et al., 1998; Neutel 1995, 1998). The first study was performed by Neutel and colleagues in Canada (Neutel 1995, 1998). Her group assessed several medical events, such as falling and traffic accidents, within 2 months after filling a prescription for a benzodiazepine by patients registered between 1979 and 1986 in Saskatchewan health databases (Neutel et al., 1995). Data were collected for 78070 and 146726 patients who filled a prescription for a hypnotic (triazolam, flurazepam) or an anxiolytic (diazepam, lorazepam and oxazepam), respectively, and for 97862 persons in a control group. Analysis of data as a function of time after prescription showed that risks during the first week were extremely high. The odds ratio for anxiolytics was 13.5 and for hypnotics 9.1, yet confidence limits were wide. Risks decreased after the first week. Odds ratios for a traffic accident within two weeks after prescription of a hypnotic were 6.5 and for anxiolytics 5.6, and within 4 weeks after prescription 3.9 for hypnotics, and 2.5 for anxiolytics. During the second month odds ratios had dropped to 1.4 for hypnotics and 1.2 for anxiolytics. These data suggest that some form of tolerance develops for the adverse effects of benzodiazepines on driving performance. Alternatively, actual exposure to the drugs might diminish over time, because patients stop taking the medication. Further analyses, however, showed that risks were also reduced after a 3rd prescription for a hypnotic as compared to the 1st) prescription (OR 1.4 vs. 3.4, respectively). This supports the idea that some form of tolerance might develop (Neutel 1998

Factors that were shown to modify these risks are half-life and dose of a particular drug, and age and gender of the patient (Neutel 1995, 1998). Among hypnotics and anxiolytics, risks generally increased with dose and were most increased for drugs with longest half-lives: OR was 5.1 for flurazepam vs. 3.2 for triazolam, and 3.1 for diazepam vs. 2.4 for lorazepam and 1.0 for oxazepam.

Table 3.2 Risks for traffic accidents associated with the use of sedative-hypnotics and anxiolytics

Reference	*Study design*	*Study Population and comparison groups*	*Age*	*Outcome variable*	*Exposure variable*	*Results RR/OR (95% CI)*
Barbone et al., 1998	Case crossover	UK, 1992-1995 19386 drivers involved in a first traffic accident, 160 users of hypnotics	20+	Car crashes	Estimated from information on Rx	1.2 (0.8-1.7) for hypnotics (flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam, temazepam, zopiclone) 2.2 (1.5-3.1) for anxiolytics (alprazolam, bromazepam, chlordiazepoxide, clorazepate, diazepam, lorazepam, oxazepam)
Neutel 1995, 1998	Cohort	Saskatchewan, 1979-1986 323658 BZ users 97862 controls	20+	Injurious crashes within 28 days of Rx	First Rx for BZ in 6 months	6.5 (1.9-22.5) for hypnotics, wk 1-2 3.9 (1.9-8.3) for hypnotics, wk 1-4 3.2 (1.4-7.3) for triazolam, wk 1-4 5.1 (2.3-11.6) for flurazepam, wk 1-4 5.6 (1.7-18.4) for anxiolytics, wk 1-2 2.5 (1.2-5.2) for anxiolytics, wk 1-4 1.0 (0.3-3.7) for oxazepam, wk 1-4 2.4 (1.0-6.3) for lorazepam, wk 1-4 3.1 (1.4-6.5) for diazepam, wk 1-4
Honkanen et al., 1980	Case control	Finland, 1977 201 injured drivers 325 non-injured drivers	All Mean 35	Hospital emergency room visit for injury	Blood sample and interview	Alcohol most serious risk, diazepam also a risk factor
Skegg et al., 1979	Case control	UK, 1974-1976 57 injured drivers 1425 matched controls	All Most <35	Hospital admission or deaths for all injuries in road accidents	All drug use from Rx for 3 months before crash	RR= 4.9 (1.8-13.0) for minor tranquilizers, mostly BZ
Hemmelgarn et al., 1997	Nested Case Control	Quebec, 1990-1993 5579 injurious crashes	65+	Drivers injured in crash	Estimated from information on Rx	1.0 (0.8-1.3) for half life ≤ 24h, wk 1 1.5 (1.0-2.0) for half life > 24 h, wk 1 1.2 (0.9-1.5) for half life > 24 h, wk 2+

		13256 controls				No relation with dose
Leveille et al., 1994	Matched Case control	Puget Sound, 1988-1989 234 injurious crashes 447 controls from HMO files		Treatment for injury within 7 days of crash	BZ Rx from pharmacy	OR= 0.9 (0.4-2.0) for BZs (mostly flurazepam, triazolam)
Ray et al., 1992	Cohort	Tennessee, 1984-1988 495 injured drivers 2978 person years of BZ use 21578 person years no BZ use	65+	Injurious crashes from police reports	Rx filled at pharmacy	RR= 1.5 (1.1-2.0) for BZ use (diazepam, lorazepam, chlordiazepoxide)

It is noteworthy that males had risks 3.6 times higher than those of females and risks for those younger than 60 years were higher than for those of 60 years and older (for triazolam OR 3.5 vs. 2.9; for flurazepam OR 6.1 vs. 3.4, respectively).

The second study was conducted in the United Kingdom (Barbone et al., 1998). This group linked prescription records of 410306 individuals to police records of road accidents and identified a total of 19386 drivers involved in a first traffic accident between 1992 and 1995, of which 916 were users of benzodiazepines. For each case periods of drug exposure were calculated from prescription data and the odds of having an accident while exposed and unexposed were compared. The odds ratio for benzodiazepine use was 1.62. No significant increase in risks was found for use of hypnotics (OR 1.2). The only exception was zopiclone (OR 4.0), which was the only hypnotic in this study with a half-life shorter than 6 hours. All other hypnotics in this study had intermediate or long half-lives (i.e., flunitrazepam, flurazepam, loprazolam, lormetazepam, nitrazepam and temazepam). Most of the risks associated with benzodiazepines in this study were attributable to long half-life anxiolytics (OR 2.2). Both hypnotics and anxiolytics showed a dose-response relation for risks of traffic accidents, and, similar to the findings by Neutel, the risks were highest among younger drivers (<45 years), and decreased with increasing age. No significant difference was found between men and women (OR 1.7 vs. 1.5, respectively).

The difference in risks found by Barbone et al. and Neutel may partly be attributable to differences in study designs. Barbone et al. themselves note that case crossover studies are likely to underestimate risks in people treated chronically, because exposure would be the same at the time of the accident and during control periods. Since chronicity of treatment increased with age, in particular for hypnotics, risks associated with these drugs in elderly may have been underestimated. Analysis of risks in younger age groups also failed to show significant increases, however.

Although the high risk associated with use of zopiclone is surprising, the data are supported by results from experimental studies showing significant residual impairment of driving performance between 10 and 11 hours after bedtime administration of zopiclone 7.5 mg (Vermeeren et al., 1998a; Vermeeren et al., 2002; Volkerts and O'Hanlon, 1988). In addition there are indications that zopiclone may be misused or abused. A forensic toxicology study in Norway revealed that of suspected drugged drivers who tested positive for zopiclone, 80% had blood concentrations higher than those expected 8 hours after intake of therapeutic doses (Bramness et al., 1999).

Three studies assessed the relation between use of benzodiazepines and traffic accidents in elderly (Hemmelgarn et al., 1997; Leveille et al., 1994; Ray et al., 1992). Leveille et al. (1994) did not find an increased risk of traffic accidents for elderly users of benzodiazepine hypnotics, whereas Ray et al. (1992) did find increased risks for elderly users of benzodiazepine anxiolytics (OR 1.5). The most frequently used hypnotics in the study by Leveille et al. were triazolam (50%) and flurazepam (27%), which were both associated with significantly increased risks in elderly in the study by Neutel (1998). The failure to find an effect might be related to the lack of a clear distinction between exposure and non-exposure in the study by Leveille et al., since 42% of all prescriptions were to 'take as needed' and no daily recommended dose could be determined. Later, Hemmelgarn et al. (1997) found significantly increased risks for elderly users of long half-life benzodiazepines (OR 1.45; clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam and nitrazepam), but not for users of benzodiazepines with a half-life less than 24 h (alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam). Risks were highest in the first week of use and decrease thereafter.

In summary, use of benzodiazepines in general is associated with increased risks for traffic accidents in young and elderly, yet these effects seem most pronounced in drivers younger than 60 years. Whereas anxiolytics increased risks in young and elderly, the effects of hypnotics were less consistent. Nevertheless, there is sufficient evidence that use of hypnotics can increase risks for traffic accidents, depending on drug, dose and patients characteristics

Risk of falling and hip fracture

There is a substantial body of literature showing that use of benzodiazepines is a consistent risk for falls (table 3.3) and hip fractures (table 3.4) in elderly, in both community and clinical settings.

A meta-analysis of 40 epidemiological studies assessing risk factors associated with falling in elderly, yielded pooled odds ratios of 1.54 for use of sedative/hypnotics and 1.48 for use of benzodiazepines (Leipzig et al., 1999). Yet, the risks varied considerably between studies, which raises the question what factors might be responsible for such variations.

Table 3.3 Risks for falls associated with the use of sedative-hypnotics and anxiolytics

Reference	*Design*	*Study population*	*Comparison groups*	*Results OR/RR (95% CI)*	*OR/RR associated with specific drugs*
Neutel et al., 2002	Part 1. Prospective cohort/ Part 2. case crossover	Ottawa, 1995-1996 Nursing home residents, 76% aged 80+	Part 1 125 fallers 102 controls part 2 51 new drug starts	Part 1. 1.7 (1.0-2.9) for benzodiazepines 4.3 (1.8-10.1) for polydrug use (5-9 drugs) 6.1 (2.6-14.5) for polydrug use (>9 drugs)	Part 2. 11.4 (1.5-89.0) new starts for benzodiazepines and antipsychotics (mostly lorazepam and oxazepam, few thioridizine and haloperidol)
Tromp et al., 2001	Prospective cohort	The Netherlands 1995-1996 1285 Community dwelling elderly stratified for age and gender, Age 65+	428 fallers 857 controls	1.6 (1.2-2.3) for use of benzodiazepines 1.3 (1.0-1.7) for polydrug use (>3 drugs)	
Ray et al 2000, 2002	Prospective cohort	Tennessee, 1993-1996 nursing home residents, Age 65+	666 BZ users 1844 controls	1.4 (1.3-1.6) for current BZ users 1.2 (0.9-1.4) half-life <12 h 1.5 (1.3-1.6) half-life 12-23 h 1.7 (1.4-2.1) half life 24+ h 1.3 (1.1-1.5) doses ≤ 2mg diazepam 2.2 (1.9-2.6) doses > 8 mg diazepam 3.0 (2.3-3.8) in week 1 2.2 (1.6-3.0) in week 2-4 1.3 (1.2-1.4) in week 5+ 1.4 (1.3-1.5) daytime 1.8 (1.6-2.1) nighttime	Hypnotics: 2.8 (2.0-3.9) at night, for temazepam, triazolam zolpidem
Passaro et al., 2000	Prospective cohort	Italy, 1991 and 1993 Patients admitted to 58 hospitals and university centers; All ages (74% aged 65+)	1874 BZ users; 6034 non-users;	1.9 (1.0-3.3) half-life < 6 h 1.7 (1.2-2.8) half-life 12-23 h 0.8 (0.4-1.8) half-life 24+ h 1.6 (0.8-3.3) for combination of BZs 1.6 (1.0-2.6) for polydrug use (>5)	Hypnotics: 1.9 (1.03-3.3) triazolam Anxiolytics: 1.8 (1.2-2.8) mostly lorazepam, few oxazepam, alprazolam, bromazepam
Maxwell et al., 1997	Prospective cohort	Saskatchewan, 1979-1986 BZ users aged 20+	223868 New users; 49174	2.6 (1.6-44) new users, aged < 70 2.6 (1.0-7.1) repeat users, aged < 70 2.9 (2.2-3.9) new users, aged 70+	Hypnotics: triazolam and flurazepam 2.8 (2.2-3.6) new use

			repeat users; 129150 nonusers	2.4 (1.5-3.8) repeat users, aged 70+	2.4 (1.5-3.6) repeat use Anxiolytics: oxazepam, lorazepam, diazepam 2.0 (1.5-2.6) new use 1.6 (1.0-2.6) repeat use
Mendelson 1996	Case control	Chicago, 1993 Hospitalized patients Mean age 57 (rage 4-88)	253 fallers 253 age and sex matched controls		Hypnotics: 5.4 for temazepam Anxiolytics: 4.8 for lorazepam 12.5 for diazepam
Neutel et al., 1995, 1996	Prospective cohort	Saskatchewan, 1979-1986 BZ users aged 60+	223868 BZ users; 97554 controls	4.0 (2.4-6.6) for hypnotics, men 2.3 (1.7-3.2) for hypnotics, women 2.5 (1.4-4.3) for anxiolytics, men 1.6 (1.2-2.3) for anxiolytics, women 3.6 (2.5-5.2) hypnotics, wk 1-2 2.3 (1.6-3.4) hypnotics, wk 3-4 1.4 (1.1-1.9) hypnotics, wk 5-8	Hypnotics 3.4 (2.5-4.7) flurazepam 2.7 (2.0-3.6) triazolam Anxiolytics 2.2 (1.4-3.4) oxazepam 1.8 (1.3-2.5) diazepam 2.0 (1.3-3.1) lorazepam
Lord et al., 1995	Prospective cohort	414 community dwelling women, aged 65+	76 fallers 338 controls	0.8 (0.3-2.4) short acting BZ 7.0 (2.1-23.3) long acting BZ	hypnotics 0.7 (0.2-2.5) temazepam 3.9 (2.3-6.5) nitrazepam 5.2 (4.1-6.4) flunitrazepam anxiolytics 0.6 (0.1-4.0) oxazepam 2.1 (0.7-6.2) diazepam
Cumming et al., 1991	Cross-sectional	Missouri, 1987 Community dwelling elderly	108 fallers 1250 controls	0.8 (0.3-2.2) for half-life <24 h 2.2 (1.1-4.5) for half-life >24 h	Anxiolytics: 3.7 (1.5-9.3) diazepam
Campbell et al., 1989	Prospective cohort	Mosgiel, New Zealand Community dwelling elderly Age 70+	220 fallers 541 controls	1.9 (1.1-32.) for use of hypnotics	
Granek et al., 1987	Case control	Baltimore, 1984 446 residents from a long term care facility; aged 65+	184 fallers 184 controls	2.6 for use of sedative/hypnotic 6.9 for use of sedative/hypnotic + antidepressant	

Table 3.4 Summary of case-control studies assessing risks for hip or femur fractures associated with the use of sedative-hypnotics and anxiolytics.

Reference	*Study population*	*Comparison groups*	*Risks associated with half-life, dose, frequency of use and polydrug use (OR/RR)*	*Risks associated with specific drugs OR/RR*
Pierfitte et al., 2001	Bordeaux, 1996-1997 Patients presenting at hospital emergency rooms, aged 65+	245 cases 817 age and sex matched controls	No relation with use of BZ in general 1.1 (0.8-1.5) for short half life 1.2 (0.7-2.0) for long half life 1.5 (0.8-2.8) for polydrug use	Hypnotics: 2.7 (0.7-10.9) temazepam 2.7 (0.5-13.6) loprazolam 2.2 (0.4-13.4) nitrazepam 1.4 (0.5-4.4) flunitrazepam 1.3 (0.7-2.5) zolpidem 0.7 (0.4-1.4) zopiclone Anxiolytics: 1.8 (1.1-3.1) lorazepam
Wang et al., 2001	New Jersey 1993-1995 Subjects who had filled a claim for nonprescription medical service in 1994, age 65+	1222 cases 4888 controls	1.5 (1.2-1.8) for BZ use	2.0 (1.1-3.5) for zolpidem
Sgadari et al., 2000	US, 1992-1996 Nursing home residents, age 65+	9752 cases 38364 controls≥	1.1 (1.0-1.2) for BZ use 1.2 (1.0-1.4) for nonoxidative BZs (i.e., temazepam, lorazepam, oxazepam) 1.0 (0.9-1.2) oxidative BZs, half-life <24h 1.2 (1.0-1.5) oxidative BZs, half-life ≥24h 1.8 (1.1-3.0) oxidative BZs, half-life ≥24h, high dose	1.2 (1.0-1.4) temazepam, lorazepam, oxazepam
Cummings et al., 1995	Oregon, 1986-1988 White women, Age 65+	192 cases 8667 controls	1.2(0.8-2.1) for short acting BZ 1.6(1.1-2.4) for long acting BZ	
Herings et al., 1995	Netherlands1986-1992 Community dwelling elderly registered in medical record linkage system; Age 55+	493 cases 1311 age and sex matched controls	1.5 (1.1-2.0) for half-life <24 h (75%) 1.3 (0.7-2.4) for half-life >24 h (25%) 1.6 (1.2-2.1) for current use of BZ 1.6 (1.1-2.2) for continuous use 2.5 (1.1-5.5) for incident (new) use	Hypnotics 6.5 (2.2-45.6) chlordiazepoxide 3.8 (1.6-9.0) lorazepam 2.7 (1.1-6.9) flunitrazepam 1.8 (1.1-2.9) temazepam

			3.4 (1.0-11.5) for dose increase in continuous users 1.9 (1.3-2.7) for DDD 0.75-1.24 2.3 (1.2-4.1) for DDD >1.24 2.5 (1.3-4.9) for polydrug use	
Lichtenstein 1994	Saskatchewan, 1983-1985 Community dwelling elderly; Age 65+	129 cases 324 controls	2.1 (1.1-3.8) for use of BZ	
Cumming & Klineberg 1993	Sydney, 1990-1991 Community dwelling and hospitalised elderly; Age 65+	209 cases 207 controls	1.6 (1.0-2.5) for use of BZ	Hypnotics: 3.8 (1.6-8.9) temazepam 1.2 (0.5-2.7) nitrazepam Anxiolytics 0.6 (0.2-1.6) diazepam 0.8 (0.3-1.9) oxazepam
Ray et al., 1989	Saskatchewan, 1977-1985 Residents with a hospital record; Age 65+	4501 cases 24000 controls	1.1(0.9-1.3) for half-life <24 h, current use 1.7(1.5-2.0) for half-life ≥ 24 h, current use	Hypnotics: 1.0 (0.7-1.2) triazolam 1.9 (1.5-2.5) flurazepam Anxiolytics: 1.0 (0.6-1.8) lorazepam 1.4 (0.9-2.0) oxazepam 1.5 (1.2-1.8) diazepam 2.3 (1.5-3.5) chlordiazepoxide
Ray et al., 1987	Michigan, 1980-1982 Community dwelling elderly and nursing home residents; aged 65+ (42% 85+)	1021 cases 5606 controls	1.1 (0.8-1.6) for half-life <24 h (i.e., diphenhydramine, hydroxyzine, chloral hydrate) 1.8 (1.3-2.4) for half-life ≥ 24 h (i.e.,: flurazepam diazepam chlordiazepoxide)	Hypnotics: 1.9 (1.3-2.8) flurazepam Anxiolytics-Hypnotics: 1.5 (1.0-2.4) diazepam or chlordiazepoxide 1.8 (0.8-4.3) barbiturates excl. Phenobarbital

Half-life

It is generally assumed that risks of falling and hip fracture are higher after use of long half-life (≥ 24h) than short half-life (< 24 h) benzodiazepines, which is supported by at least four studies (Ray et al., 1987, 1989, 2000; Lord et al., 1995). Ray and colleagues conducted three of them (1987, 1989, 2000). In the first study (Ray et al., 1987) it was found that elderly treated with flurazepam, diazepam and chlordiazepoxide had an increased risk of hip fracture (OR 1.8), whereas no increased risk was found for those using diphenhydramine, hydroxyzine and chloral hydrate. In the second study (Ray et al., 1989) relative risks of hip fracture was significantly increased within 30 days after filling a prescription for chlordiazepoxide (RR 2.3), flurazepam (RR 1.9) and diazepam (RR 1.5), but not for triazolam, lorazepam, and oxazepam. In the third study (Ray et al., 2000) falls instead of hip fractures were assessed, and a similar lack of increased risks was found with use of short half-life benzodiazepines (mainly temazepam, zolpidem and oxazepam) and significantly increased risks with use of intermediate and long half-life drugs (mainly lorazepam, alprazolam and diazepam). Finally, Lord and colleagues (1995) found significantly increased risks for multiple falls after use of flunitrazepam (OR 5.2) and nitrazepam (OR 3.9), but not after use of temazepam.

However, in the first three studies, it cannot be excluded that the differences in risks associated with the short and long half-life drugs are due to other factors than half-life. In the first study the drugs belong to very different classes of drugs: the short half-life drugs were mainly sedating antihistamines, whereas the long half-life drugs were all benzodiazepines. Similarly, in the third study, the drugs differed by their dosing regimen: the short half-life drugs were predominantly hypnotics whereas the intermediate and long half-life drugs were predominantly anxiolytics. Only the fourth study comprised drugs form only one therapeutic class, i.e. hypnotics.

Does this mean that short half-life hypnotics are not associated with an increased risk of falling and hip fractures in elderly? Not necessarily. First of all, in the third study by Ray et al. (2000) further analysis of the data revealed that although short half-life drugs in this study were not associated with a significant increase in risk of falling, this was only true during the daytime. During the evening and the night, i.e. between 20:00 and 7:00 hours, risk for falling associated with use of benzodiazepines increased in general, and was highest for short half-life benzodiazepines (OR 2.2). Secondly, a number of studies have shown that hypnotics with short and intermediate half-lives can also be associated with significantly increased risks, for example triazolam (Neutel et al., 1996; Passaro et al.,

2000), temazepam (Cumming and Klineberg, 1993; Herings et al., 1995; Mendelson, 1996), and zolpidem (Wang et al., 2001). Moreover, two studies have even found what seems to be a negative association between half-life and risks, i.e. increased risks with short half-life drugs, but no increased risks associated with long half-life drugs. Cumming and Klineberg (1993) found temazepam to be the only benzodiazepine associated with significantly increased risks for hip fractures (OR 3.8); nitrazepam was not, despite its longer half-life. Similarly, Passaro et al. (2000) found significantly increased risks associated with short (OR 1.9) and intermediate (OR 1.8), but not with long (OR 0.8) half-life benzodiazepines in hospitalized patients of all ages. The significant finding for short and intermediate half-life drugs might be explained by the fact that the vast majority of all prescriptions in these classes were for triazolam and lorazepam, respectively, both previously found to be associated with increased risk of falling and hip fractures (Herings et al., 1995; Mendelson, 1996; Neutel et al., 1996, 2002; Pierfitte et al., 2001). Most surprising was the failure to find increased risks for long half-life benzodiazepines. According to the investigators this could be explained by the fact that users of long-half-life drugs in their study were younger and healthier than the controls, suggesting that clinicians were more likely to prescribe long acting benzodiazepines to patients in better clinical conditions, assumingly because of the established risks associated with this class of drugs (i.e., confounding by indication).

In conclusion, these findings indicate that although risks of falling and hip fracture may increase with increasing half-life, the relation is not clear cut. Risks clearly depend on other factors as well. The above illustrated the role of time since administration and sensitivity of the patient. The role of dose, metabolic pathway, tolerance and the interaction with other drugs will be considered in the following sections.

Dose

Two studies showed that risks of falling and hip fracture increase with increasing dose (Herings et al., 1995). In addition to the association with half-life, Ray et al. (2000) also found that risks for falling increased with dose; from 1.3 after use of benzodiazepines in doses equivalent to diazepam ≤ 2 mg to 2.2 after doses equivalent to 8 mg diazepam or more. Herings et al. (1995) failed to find a relation between risk of femur fraction and benzodiazepine half-life, but did show a highly significant relation between dose of hypnotics and risk of fractures. The benzodiazepines most frequently used by patients in their study were the hypnotics nitrazepam (27%) and temazepam (23%), and the

anxiolytics oxazepam (18%) and lorazepam (11%), all of which have a half-life <24 h. Of these, temazepam and lorazepam were associated with significantly increased risks of femur fracture (OR 1.8 and 3.8, respectively), whereas nitrazepam and oxazepam were not. Of the long acting benzodiazepines only chlordiazepoxide and flunitrazepam were found to be associated with increased risks (OR 6.5 and 2.7, respectively), showing that long half-life was not consistently associated with increased risks. Risks did increase systematically with dose, however; odds ratios increased from 1.0 for those exposed to daily doses of less than 0.75 of the defined daily dose (DDD), and 1.9 for those exposed to daily doses between 0.75 and 1.24 DDD, to 2.3 for those exposed to daily doses of 1.25 DDD or more.

Metabolic pathway

Related to elimination half-life is the way drugs are metabolized. All benzodiazepines are metabolized by conjugation; some directly, but most need to undergo oxidation first. The rate of oxidative reactions in the liver decreases with advancing age, thus resulting in higher blood concentrations and longer elimination half-lives. It is therefore often proposed that benzodiazepines undergoing direct conjugation such as temazepam, lormetazepam, oxazepam and lorazepam (i.e., non-oxidative benzodiazepines) could be safer for elderly than oxidative benzodiazepines. One study (Sgadari et al., 2000) specifically addressed this issue and found only partial support for this hypothesis. Risk of femur fracture associated with use of oxidative and nonoxidative benzodiazepines was compared between groups of elderly aged 65 to 74 years, 75 to 84 years and 85 years and older. On average, the use of benzodiazepines was associated with a slight, but significant increase in the risk for femur fracture (OR 1.1), which seemed mainly due to high doses of oxidative benzodiazepines with long (>24 h) half-lives. Overall, oxidative benzodiazepines were not more harmful than non-oxidative agents. Age dependent increases in risk of femur fractures were only found among elderly receiving high or as needed doses of oxidative hypnotics risks, suggesting that in patients younger than 85 years and in those receiving low doses, oxidative hepatic processes were still adequate to metabolize oxidative benzodiazepines, whereas oxidative capacity may have been exceeded in patients aged 85 years or older and in those receiving high doses. It was concluded that oxidative benzodiazepines are only more harmful than nonoxidative benzodiazepines when they are given in high doses to very old individuals. It should be

noted, however, that most (63%) oxidative benzodiazepines in this study had short (triazolam) or intermediate (alprazolam, estazolam) half-lives.

Tolerance

Results from a number of studies suggest that some form of tolerance may develop for the effects of benzodiazepines involved in falling. Neutel (1996) found that risks for falling were highest at the initiation of treatment. After use of hypnotics (triazolam and flurazepam) risk of hospitalization for fall related injuries decreased from 3.6 in the first two weeks, to 2.3 in weeks 3 and 4, to 1.4 in the second month after filling the prescription. A similar trend was found for anxiolytics (OR 2.6, 1.4 and 1.1 respectively). These data are supported by those of Ray et al. (2000), who found that risks for falling among nursing home residents decreased form 3.0 in the first week of treatment, to 2.2 in weeks 2 to 4, to 1.3 in the second month of treatment. Furthermore, Herings et al. (1995) report higher risks for femur fracture in incidental users, than continuous users (2.5 vs. 1.6). In addition, Maxwell et al. (1997) demonstrated that risks for fall related injuries were lower after a third prescription for benzodiazepines than after a first one. Stratification of their data by age, however, showed that risks only decreased (from 2.9 to 2.4) with repeat use in persons of 70 years and older; risks for new and repeat users younger than 70 years were identical (OR 2.6). Together, these data strongly suggest that pharmacokinetic or pharmacodynamic changes account for the development of tolerance. It is also possible, however, that patients change their behavior in response to noticeable drug effects on their balance, e.g., be more careful when they stand or walk (behavioral tolerance). This explanation is not supported, though, by the finding that incidental use is associated with higher risks than continuous use (Herings et al., 1995). This issue deserves further study in the light of the recent trend to recommend 'as needed' use of hypnotics.

Polydrug use

Use of combinations of different drugs consistently and substantially increases risks of falling and hip fracture (Blake et al., 1988; Cumming et al., 1991; Granek et al., 1987; Herings et al., 1995; Neutel et al., 2002; Passaro et al., 2000; Pierfitte et al., 2001; Tromp et al., 2001). For example, Granek (1987) found that risks of falling more than doubled in elderly using sedative/hypnotics in combination with antidepressants, NSAIDs, cardiac drugs or diuretics. Mendelson et al. (1996) found that the effect is not limited to elderly. In their study of falls in hospitalized patients of all ages, those who fell were 3.7 times

more likely to receive two psychotropic drugs, and 9.5 times more likely to receive three psychotropic drugs, than patients who did not fall. Neutel et al. (2002) recently compared risks of falling associated with various drug classes. Although few classes were by themselves associated with increased risk, use of 5 or more different drugs increased risks by a fourfold as compared to use of 4 drugs or less. For more specific drug classes, the highest risk (OR 11.0) was found for combinations of benzodiazepines with antipsychotic drugs. The authors conclude that number of different drugs taken is a more important risk factor, than class of drugs taken.

Discussion

Epidemiological studies have shown that use of hypnotics and anxiolytics is associated with increased risk of traffic accidents, particularly in the younger, and with increased risk of falling and hip fractures in elderly. The hypothesis that short half-life benzodiazepines are safer than long half-life benzodiazepines is partially supported by epidemiological data. In general, risks increase with increasing half-life, but a short elimination half-life offers no guarantee that a particular drug will be safe. For example temazepam, triazolam, zolpidem and zopiclone were found to be associated with increased risks, despite their relatively short half-lives. Other important factors determining risk are dose, tolerance and polydrug use. Risks were shown to increase with increasing dose and number of drugs used simultaneously, and to decrease after repeated dosing. Finally, the hypothesis that non-oxidative benzodiazepines are safer for use in elderly patients than oxidative benzodiazepines could not be supported by epidemiological data. Use of the non-oxidative benzodiazepines, lorazepam, oxazepam and temazepam, has been found to be associated with increased risks.

A problem with the results of these studies is the great variation in risks found. Some studies even fail to find significantly increased risks. It has been argued, that in some studies the risks may be underestimated because actual drug exposure is overestimated (Ray et al., 2002). A frequently used measure of drug exposure in prospective studies is drug use at the time of baseline measurement. If drugs are actually used intermittently during the period of follow up, exposure is overestimated and risks may consequently be underestimated. Similarly, when risks are in fact only increased during the first days following the start of new drug treatment, risks averaged over longer periods will be much lower (Neutel et al., 2002). Likewise, many studies grouped all

benzodiazepines with half-lives of 24 hours or less as 'short half-life' benzodiazepines. This may average out the risks associated with specific drugs and dosing regimens (i.e. anxiolytics). Half-lives of 10 to 24 hours can hardly be considered as short with respect to hangover effects of hypnotics.

Another problem is that epidemiological studies can only detect significantly increased risks for drugs that have been commonly prescribed, such as temazepam, triazolam, zolpidem, oxazepam, lorazepam and flurazepam. The fact that a drug was not found to be associated with a significantly increased risk may be due to a lack of power. Sample sizes of most studies are too small to detect new or rarely prescribed drugs. For example Pierfitte et al.(2001) only found a significant risk associated with lorazepam. Other drugs, such as temazepam, nitrazepam and loprazolam, had similar odds ratios, but the confidence intervals were wide as a result of small numbers of observation. Furthermore, it should be kept in mind that epidemiological data reflect statistical associations and do not demonstrate causality. It is extremely difficult to distinguish the effects of disease from those of medication. Moreover, if clinicians, for whatever reason, prescribe drugs considered as most safe only to relatively fragile patients, and drugs considered less safe to stronger patients, the risks found in epidemiological studies may be comparable.

Finally, the finding that use of hypnotics is associated with higher risks of falling during the night than the day, raises questions with respect to the validity of many epidemiological studies for establishing the relation between residual effects of hypnotics and falling or hip fracture in elderly (Ray et al., 2000). It seems that, despite the use of hypnotics, elderly may wake up and get out of bed during the night, thus running a risk to fall. Such accidents cannot be attributed to a drug's residual effects. It seems highly unlikely, however, that insomniac patients drive a car in the middle of the night after using a sleeping pill. For this reason, epidemiological data on traffic accidents after use of hypnotics may be more valid indications of their residual effects, than data on falls and hip fractures after use of these drugs.

EXPERIMENTAL STUDIES OF RESIDUAL EFFECTS OF HYPNOTIC

Whereas epidemiological studies can show that use of hypnotics is associated with increased risks for injuries, they are not the best way to compare effects of specific drugs

and doses. This is more appropriately done in experimental performance studies, in which the effects of drugs and doses of drugs can be studied systematically in homogeneous groups of subjects under constant circumstances. As already indicated in the introduction, many of such studies have been carried out, yet the experimental designs, performance tests and subjects used differ widely between studies, making it extremely difficult to review and compare them all. Therefore three other sources of information that compare, or allow comparison of, the effects of various hypnotics in different doses will be used. One is a survey among experts rating the severity of residual effects of hypnotics in different doses and at different times after administration (Wolschrijn et al., 1991). Second, a meta-analysis of experimental studies (Berghaus, 1998) and third, residual effects as assessed using a standard highway driving test.

Expert ratings

In 1989 and 1990 a worldwide survey was conducted among a group of 45 experts engaged in research on the effects of drugs on traffic safety, to determine whether a consensus existed concerning the severity of drug effects (Wolschrijn et al., 1991). Experts were requested to rate the impairment produced by those drugs and doses with which they had research experience. The main result of this survey was a proposal for a new package-label warning system allowing categorization of one or more doses of drugs as likely to produce no, minor to moderate and severe impairment (table 3.5).

Additionally, the survey resulted in a list of drugs categorized for their impairing effects on driving performance. For this expert ratings were assigned rank scores (i.e., 0, 1, 2 and 3 for no, minor to moderate and severe impairment, respectively) and average rank scores were calculated for different drugs, doses and formulations. For hypnotics the system was extended to include three time intervals; 8-12 hours (morning) 12-16 hours (afternoon) and 16 to 22 hours (evening) after administration.

The results for 11 hypnotics and 3 anxiolytics often used as hypnotics are presented in table 3.6. Results showed that immediately upon arising after 8 hours of sleep, the only hypnotic rated as unlikely to produce residual effects was zolpidem 10 mg. Low doses of short half-life hypnotics (i.e., brotizolam 0.125 and 0.25 mg, lormetazepam 0.5 and 1 mg, midazolam 7.5 and 15 mg, temazepam 10 and 20 mg, triazolam 0.125 mg and zopiclone 7.5 mg) were generally rated as likely to produce only minor impairment at that time, whereas the residual effects of higher doses and longer half-life hypnotics or

anxiolytic hypnotics were on average rated as moderate to severe upon arising. According to the experts, the residual effects of flunitrazepam 2 mg, flurazepam 30 mg, loprazolam 2 mg and lorazepam 5 mg were most persistent: the residual effects of these drugs and doses were rated to be severe or moderate the entire day after bedtime use. Although experts sometimes disagreed regarding the degree of impairment of a drug (e.g., whether the effect is moderate or severe), they generally did agree upon the rank order of effects between drugs and doses (e.g., triazolam 0.25 mg produces more severe effects than temazepam 10 mg between 8 and 12 hrs after ingestion). Wolschrijn et al. (1991) therefore concluded that the resulting rank order should at least enable clinicians to choose the least impairing drug within a group.

Meta-analysis

The Bundes Anstalt Fur Strassenwesen (Berghaus, 1998) conducted a meta-analysis of 812 experimental studies assessing the effects of 248 medicinal drugs on driving, including 11 hypnotics. Drugs and doses were evaluated for the percentage of performance measures that were found to be significantly different from placebo at various times after ingestion. Performance measures included assessments of psychomotor performance, visual perception, attention, information processing and driving. Table 3.7 shows the percentages of impairment found between 8 and 18 hours after ingestion of hypnotics and anxiolytic-hypnotics.

Table 3.5 Categorization system of drugs affecting psychomotor performance (Wolschrijn et al., 1991).

Category	*Label*	*Definition*
I	Unlikely to produce an effect	In various experimental circumstances negligible or no impairment is demonstrated
II.1	Can produce minor adverse effects	Some impairment is seen in experimental circumstances
II.2	Can produce moderately adverse effects	Impairment is seen in various experimental circumstances
III	Likely to produce severely adverse effects	Repeated demonstrations of gross impairment in various experimental circumstances

Table 3.6 Summary of expert categorizations of residual effects on psychomotor performance of hypnotics and anxiolytic-hypnotics (Wolschrijn et al., 1991). Indicated are mean rating scores: 0 unlikely to produce effects, 1 minor effects, 2 moderate effects, and 3 severe effects.

Drug	*Dose*	*Time after ingestion (hours)*			
	(mg)	*0 to 8*	*8 to 12*	*12 to 16*	*16 to 22*
Short half-life hypnotic					
zolpidem	10	2.5[a]	0.0[a]	0.0[a]	0.0[a]
zolpidem	20	2.5[a]	2.0[a]	1.0[a]	0.0[a]
midazolam	7.5	3.0	1.5[b]	0.7	0.4[a]
midazolam	15	3.0	1.4[b]	1.0	0.4[a]
triazolam	0.125	2.0	1.4[b]	0.9	0.3
triazolam	0.25	2.7	1.8[b]	1.2	0.5
triazolam	0.5	3.0	2.7	2.0	1.1
zopiclone	7.5	2.8	1.4	0.3	0.0
brotizolam	0.125	2.0[a]	0.8[a]	0.4[a]	0.4[a]
brotizolam	0.25	2.7[a]	1.0[a]	0.8[a]	0.4[a]
Intermediate half-life hypnotic					
loprazolam	0.5	-	2.0[a]	1.3[a]	1.0[a]
loprazolam	1	2.5[a]	2.7[a]	2.0[a]	2.0[a]
loprazolam	2	3.0[a]	3.0[a]	2.7[a]	2.5[a]
lormetazepam	0.5	-	0.8[a]	0.3	0.8[a]
lormetazepam	1	2.0	0.6	0.6	0.7
lormetazepam	2	3.0	2.0	0.7	0.7
lormetazepam (SGC)	1	2.0	0.7	0.9	1.0
lormetazepam (SGC)	2	3.0	2.0	1.4	1.3
temazepam	10	2.4	1.0[b]	0.8	1.0
temazepam	20	3.0	1.3[b]	1.0	0.9
temazepam	30	3.0	1.7[b]	1.4	1.1
temazepam (SGC)	10	2.5	1.0	0.9	0.9
temazepam (SGC)	20	3.0	1.0[b]	0.9	0.7
Long half-life hypnotic					
nitrazepam	2.5	2.6	1.7[b]	1.1[b]	0.8
nitrazepam	5	2.6	1.9[b]	1.4[b]	1.0
nitrazepam	10	3.0	2.8	2.1[b]	1.6[b]
flunitrazepam	0.5	3.0	2.1[b]	1.9	1.3
flunitrazepam	1	3.0	2.8	2.3	1.4
flunitrazepam	2	3.0	2.6	2.6	1.8[b]
flurazepam	15	3.0	2.7	2.4	1.9
flurazepam	30	3.0	3.0	2.6	2.0
Anxiolytic-hypnotics					
oxazepam	10	2.0	1.6	0.8	0.6
oxazepam	20	2.0	1.7	1.3	1.2
oxazepam	30	3.0	2.2	1.6	0.4
oxazepam	50	3.0	2.5	1.9[b]	1.1
lorazepam	1	2.9	2.3	2.0	1.8[b]
lorazepam	2.5	3.0	3.0	2.2	1.9
lorazepam	5	3.0	3.0	2.7	2.3
diazepam	10	2.9	2.1	1.4[b]	1.0
diazepam	15	2.9	2.6	2.1	1.2
diazepam	20	3.0	2.8	2.1	1.7[b]

[a]: rated by 5 experts or less; [b] wide variation, i.e. no consensus among experts

To determine what percentage of significant differences could be considered as clinically relevant, the effects of blood alcohol concentrations (BAC) of 0.3 g/L were used as a criterion. It was estimated that on average 20% of the performance measures with this BAC would be significantly affected. So time intervals during which consistently 20% or more of all performance measures were significantly affected were defined as the duration of significant impairment. According to this criterion only nitrazepam 10 mg, flunitrazepam 2 mg, flurazepam 30 mg and lorazepam 1 and 2 mg would produce clinically significant impairment 8 or more hours after ingestion. It should be noted, however, that the power of many studies to detect minor or moderate impairment may not have been high, since more than 70% of all studies included in the meta-analysis were conducted with 12 subjects or less, who were usually healthy young males.

Standardized highway driving test

Few performance tests have been applied unchanged for several years, providing comparable data on the effects of a variety of drugs and doses. One such test is a highway driving test which was standardized in the early 1980s (O'Hanlon, 1984; O'Hanlon et al., 1982) and subsequently applied in over 75 studies. The test evolved from studies on driver fatigue conducted in the USA during the early 1970s. It involves subjects driving a specially instrumented car over a 100-km (61 mile) primary highway circuit while maintaining a constant speed and a steady lateral position between the boundaries of the slower traffic lane. Subjects are accompanied by a licensed driving instructor, having access to dual controls. Speed and lateral position relative to the lane delineation are continuously recorded during the one hour drive by apparatus aboard the vehicle. After completion of the test the data are reduced to yield several measures, including the primary performance parameter, Standard Deviation of Lateral Position (SDLP, in cm). SDLP can be interpreted as an index of weaving or road tracking error. It is a reliable characteristic of individual driving performance (test retest r= 0.7 to 0.9) and has proven sensitive to many sedating drugs (O'Hanlon and Ramaekers, 1995; O'Hanlon et al., 1995; Riedel et al., 1998). The test was calibrated for the effects of alcohol in a closed circuit study wherein 24 social drinkers were tested sober and after controlled drinking to raise blood alcohol concentrations in steps of 0.3 g/L to a maximum of 1.2 g/L (Louwerens et al., 1987). In line with the relation between BAC and accident risk as estimated in a large epidemiological study by Borkenstein (1974), the relation between BAC and SDLP was

Table 3.7 Summary of results for hypnotics from a meta-analysis of experimental studies assessing medicinal drug effects on driving performance (Berghaus, 1998). Indicated are percentage performance parameters found to be significantly different from placebo between 8 and 12 hours, and at 15 and 18 hours after ingestion of various hypnotics and doses of hypnotics. N indicates the total number of performance parameters studied.

Drug	*Dose*	*Time after ingestion (hours)*					
		8-12		*15*		*18*	
		%	*N*	*%*	*N*	*%*	*N*
Short half-life hypnotics							
zolpidem	20	0	45	0	5	0	10
midazolam	≤10	0	13	0	4	0	2
midazolam	15	12	34	-	-	-	-
triazolam	0.25	2	115	46	11	10	10
triazolam	0.5	9	63	10	20	8	13
zopiclone	7.5	13	68	17	29	-	-
brotizolam	0.1-0.6	26	23	17	6	0	3
Intermediate half-life hypnotics							
loprazolam	0.5-2.0	32	28	42	12	25	8
lormetazepam	1	7	42	0	12	11	9
lormetazepam	2	71	7	0	6	0	1
temazepam	10	2	44	0	4	0	2
temazepam	20	5	89	19	31	0	2
temazepam	30-40	7	32	0	8	50	2
Long half-life hypnotics							
nitrazepam	5	16	88	29	17	0	12
nitrazepam	10	44	94	23	31	33	12
flunitrazepam	1	7	61	0	7	-	-
flunitrazepam	2	30	67	50	6	100	1
flurazepam	15	5	20	53	15	25	8
flurazepam	30	47	43	47	17	31	13
Anxiolytic-hypnotics							
oxazepam	15	17	6	0	3	0	1
lorazepam	1	4	23	0	6	-	-
lorazepam	2	23	22	0	4	-	-
diazepam	5	23	22	20	15	0	2
diazepam	10	19	73	17	18	0	2

shown to be an exponential function. Based on this relation BACs of 0.5, 0.8 and 1.0 g/L were associated with mean changes in SDLP of 2.4, 4.2 and 5.1 cm. Mean changes in driving performance under the influence of hypnotic drugs can thus be compared to

those associated with BACs at various legal limits. Figures 3.1 to 3.3 show the results from eleven studies employing comparable procedures for assessing the residual effects of hypnotic drugs on driving performance. Results are presented separately for hypnotics with short (figure 3.1), intermediate (figure 3.2) and long (figure 3.3) half-lives.

Five studies assessed the residual effects after two nights of treatment in females complaining of insomnia and who formerly used hypnotics (Brookhuis et al., 1986; O'Hanlon, 1983; O'Hanlon and Volkerts, 1986; Volkerts and O'Hanlon, 1986, 1988). In the others, testing occurred after a single night of treatment, or subjects were healthy male or female volunteers (Vermeeren et al., 1995, 1998a; 1998b, 2002; Volkerts et al., 1992a; 2000). In all studies, driving tests were undertaken in the morning between 10 and 11 hours after intake; in six studies a second driving test was performed in the afternoon between 16 and 17 hours after ingestion. Effects of zaleplon, zolpidem, and zopiclone were also assessed after administration of these drugs in the middle of the night, i.e., 4 hours (Volkerts et al., 2000) or 5 hours (Vermeeren et al., 1998a) before testing.

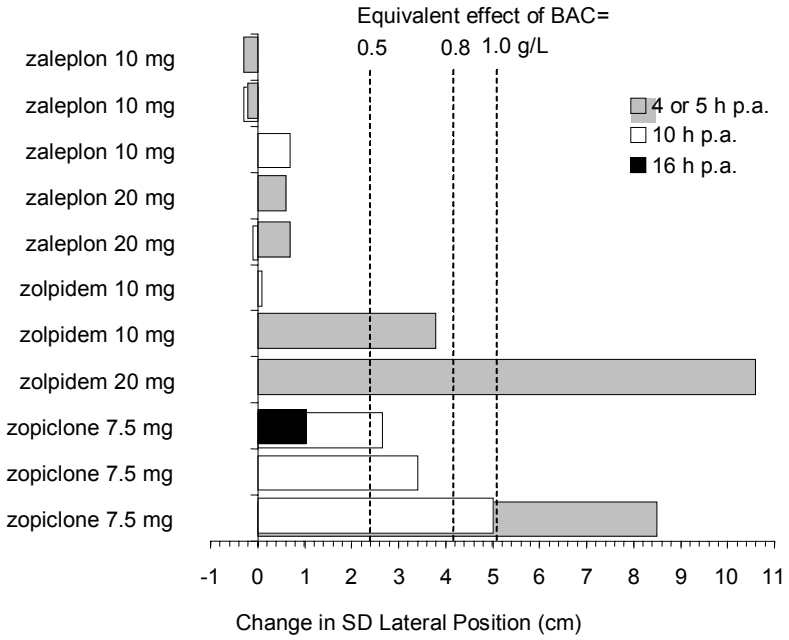

Figure 3.1 Residual effects of short half-life hypnotics on driving performance as measured in a standard highway driving test. Indicated are mean changes from placebo in Standard Deviation of Lateral Position (SDLP in cm; an index of weaving) in morning (i.e., 4 or 5 hours post administration [h p.a.] in middle-of-the-night or 10 h p.a. at bedtime), and afternoon tests (i.e., 16 h p.a. at bedtime). Also shown by vertical broken lines are mean changes produced by blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 g/L.

The most severe residual effects were found for flurazepam 30 mg and loprazolam 2 mg (O'Hanlon, 1983; Vermeeren et al., 1998b; Volkerts and O'Hanlon, 1986). The average degrees of impairment were worse than those associated with a BAC of 1.0 g/L in the morning, and equivalent to 0.8 g/L in the afternoon. Drugs that had residual effects in the morning equivalent to BACs between 0.5 and 0.8 g/L were nitrazepam 10 mg, flunitrazepam 2 mg, zopiclone 7.5 mg, oxazepam 50 mg, and lormetazepam 2 mg (capsules). Thereafter these effects rapidly declined for hypnotics with short and intermediate half-lives (zopiclone 7.5 mg, lormetazepam 2 mg and oxazepam 50 mg), but remained significant or even increased for hypnotics with long half-lives (flunitrazepam 2 mg and nitrazepam 10 mg, respectively). Drugs that had no significant residual effects in the morning and afternoon were zaleplon 10 and 20 mg, zolpidem 10 mg, lormetazepam 1 mg (capsules), temazepam 20 mg (soft gelatine capsules) and nitrazepam 5 mg. Moreover, zaleplon 10 and 20 mg had no significant effects on driving even after middle-of-the-night administration (Vermeeren et al., 1998a; Volkerts et al., 2000).

Not shown in figures 3.1 and 3.2 are the results of a study comparing the residual effects of triazolam 0.5 mg, midazolam 15 mg and temazepam 20 mg (in soft gelatine

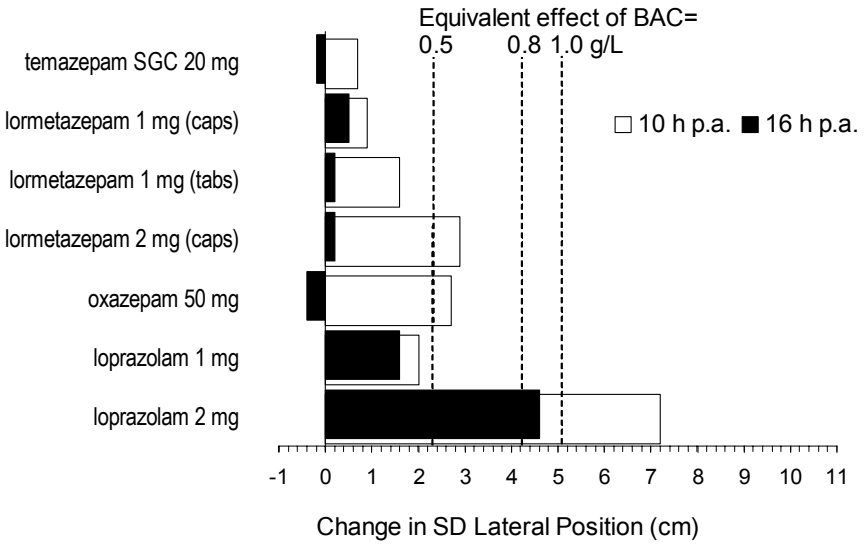

Figure 3.2 Residual effects of intermediate half-life hypnotics on driving performance as measured in a standard highway driving test. Indicated are mean changes from placebo in Standard Deviation of Lateral Position (SDLP in cm; an index of weaving) in morning (i.e., 10-11 hours post administration [h p.a.] at bedtime), and afternoon tests (i.e., 16 h p.a. at bedtime). Also shown by vertical broken lines are mean changes produced by blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 g/L.

capsules) after daytime sleep in shift workers (Riedel et al., 1988). Results are not comparable to those of the other studies, because the procedures differed: the driving test was performed in the afternoon, between 7.5 and 8.5 hours after morning ingestion of drugs or placebo. Nonetheless, results confirmed previous ones suggesting that temazepam SGC 20 mg is unlikely to produce residual effects on driving. In contrast, triazolam 0.5 mg produced residual impairment equivalent to a BAC over 1.0 g/L after the first treatment and equivalent to a BAC of 0.8 g/L after the fifth consecutive treatment. Midazolam 15 mg had minor effects on the fifth day of treatment, but none on the first.

A number of results are noteworthy as illustrations that dosage and absorption rate may sometimes be more important than half-life in determining residual effects. The repeated finding that zopiclone 7.5 mg has significant moderate to severe residual effects clearly illustrates that a short half-life does not guarantee a drug is devoid of residual effects, whereas the lack of effect of nitrazepam 5 mg illustrates the reverse is also not true, i.e., a long half-life does not necessarily mean that a drug will have a long duration of action. Both findings suggest that dose is a crucial factor for these drugs. The importance

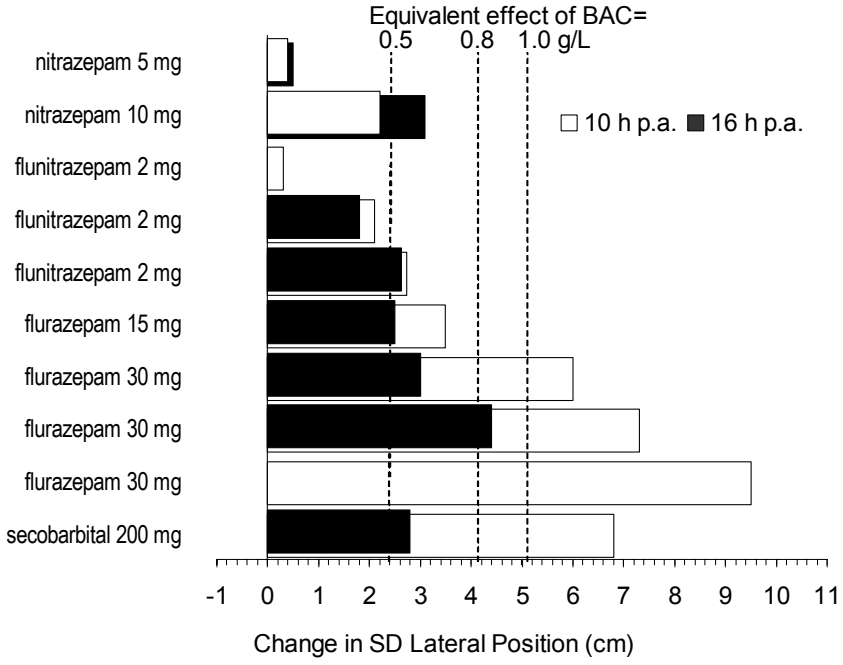

Figure 3.3 Residual effects of long half-life hypnotics on driving performance as measured in a standard highway driving test. Indicated are mean changes from placebo in Standard Deviation of Lateral Position (SDLP in cm; an index of weaving) in morning (i.e., 10-11 hours post administration [h p.a.] at bedtime), and afternoon tests (i.e., 16 h p.a. at bedtime). Also shown by vertical broken lines are mean changes produced by blood alcohol concentrations (BAC) of 0.5, 0.8 and 1.0 g/L

of slow absorption rate is illustrated by the residual effects of temazepam in hard gelatine capsules (t*max* 2.5 h), lormetazepam in tablets (t*max* 3 h) and loprazolam (t*max* 5 h, range 1-12 h; McInnes et al., 1985). Half-lives of these drugs are roughly equivalent, but residual effects clearly increase with increasing time to peak plasma concentration. Since these drugs should induce sleep well before they reach peak plasma concentrations, the latter are probably considerably higher than the threshold for inducing sleep. Consequently, it may take relatively long before they will have dropped below this threshold.

Summary of results

For most hypnotics and doses results of expert ratings, meta-analysis and the driving test are in agreement. Results will be summarized for a number of hypnotics (table 3.8). Anxiolytic hypnotics will only briefly be discussed.

Short half -life hypnotics

Zaleplon

It is clear that zaleplon in doses of 10 and 20 mg is the hypnotic least likely to produce residual effects due to its extremely short half-life (1 hour). Zaleplon had no significant residual effects on psychomotor performance, attention, and actual driving regardless of its dose and time of administration in the driving studies (Vermeeren et al., 1998a, 2002; Volkerts et al., 2000). These findings are supported by other studies failing to find significant effects of zaleplon on performance more than 2 hours after administration (Danjou et al., 1999; Hindmarch et al., 2001; Troy et al., 2000). The only significant findings after middle of the night administration of zaleplon were minor impairments of memory within the first 4 hours (Stone et al., 2000; Troy et al., 2000; Vermeeren et al., 1998a). The reader is referred to O'Hanlon (2002) and Patat et al. (2001) for recent reviews of zaleplon's effects on performance.

Zolpidem

Zolpidem 10 mg is generally considered free of residual effects when taken at bedtime before 8 hours of sleep (Darcourt et al., 1999; Lader and Hindmarch, 1996; Rush, 1998; Unden and Roth, Schechter 1996). Yet, it may have moderate to severely impairing effects within 5h p.a., that may be detectable until 7 h p.a. (Danjou et al., 1999; Erman et al.,

Table 3.8. Categorization of the residual effects of hypnotics

Drug, dose, formulation	*Time after bedtime administration*			
	4-8 h (2^{nd} half of the night)	*8-12 h (morning)*	*12-16 h (afternoon)*	*16-22 h (evening)*
zaleplon 10 mg zaleplon 20 mg	I. Unlikely	I. Unlikely		
zolpidem 10 mg midazolam 7.5 mg temazepam SGC 20 triazolam 0.125 mg lormetazepam 1 mg (caps)	II.2 Moderate	I. Unlikely		
lormetazepam 1 mg (tabs) lormetazepam 2 mg (caps) midazolam 15 mg temazepam 30 HGC mg triazolam 0.25 mg zolpidem 20 mg	III. Severe	II.1 Minor	I. Unlikely	
loprazolam 1 mg nitrazepam 5 mg	III. Severe	II.1 Minor	II.1 Minor	I. Unlikely or minor
flunitrazepam 1 mg triazolam 0.5 mg zopiclone 7.5 mg	III. Severe	II.2 Moderate	I. Unlikely	I. Unlikely
flunitrazepam 2 mg	III. Severe	II.2 Moderate	II. Minor to moderate	II.1 Minor
nitrazepam 10 mg flurazepam 15 mg	III. Severe	II.2 Moderate	II.2 Moderate	II.2 Moderate
flurazepam 30 mg loprazolam 2 mg	III. Severe	III. Severe	III. Severe	II.2 Moderate

2001; Hindmarch et al., 2001; Patat et al., 2001; Volkerts et al., 2000; Zammit 2000). Residual impairment has been reported in some studies with higher doses (e.g. Troy et al., 2000).

Zopiclone

In his review of the residual effects of zopiclone, Nicholson (1998) concludes that overnight ingestion of zopiclone 5 mg is free of residual effects, whereas 10 mg is associated with marked impairment. Results are less consistent for 7.5 mg. The latter is also illustrated by the findings that the experts considered its effects as minor to moderate, whereas results from the driving tests have repeatedly suggested that they are

moderate to severe at least until 12 hours after bedtime administration (Vermeeren et al., 1998a, 2002; Volkerts and O'Hanlon, 1988; Wolschrijn et al., 1991). Two reviews conclude, however, that the inconsistencies in results are most likely due to differences in the study designs and sensitivity of tests and procedures (Nicholson, 1998; O'Hanlon, 1995). Nicholson (1998), therefore concludes that zopiclone 7.5 mg should be avoided by those whose activity the next day involves skilled work and where impairment of performance could be a danger to themselves or others. This recommendation is supported by epidemiological findings showing a significantly increased risk for traffic accidents associated with use of zopiclone (Barbone et al., 1998).

Triazolam

Triazolam 0.5 mg can produce marked residual effects. For this reason the recommended dose was lowered to 0.25 mg in the US in 1987. The residual effects of triazolam 0.25 mg on psychomotor performance seem to be mostly confined to the first hour after arising (Cluydts et al., 1986; Troy et al., 2000). No studies were found that assessed the residual effects of triazolam 0.125 mg after 8 hours of sleep, but studies of daytime administration suggest that the severity and duration of impairment following triazolam 0.125 mg is equivalent to that produced by zolpidem 5 mg (Lobo and Greene, 1997; Mintzer et al., 1997; Rush and Griffiths 1996). This suggests triazolam 0.125 mg is unlikely to produce residual impairment the morning after bedtime use.

It is clear that triazolam's residual effects are strongly dose dependent. Perhaps differences in doses used might partly explain why some epidemiological studies found significantly increased accident risks associated with the use of triazolam (Neutel 1998; Passaro et al., 2000), while others have not (Leveille et al., 1994; Ray et al., 1989).

Midazolam

Relatively few studies have assessed midazolam's residual effects after bedtime administration as a hypnotic, which may be due to the fact that this drug is mainly used as premedication for minor surgery. Most failed to find significant residual effects 8 hours or more after bedtime administration, yet two studies demonstrated minor, but significant, residual effects on driving and divided attention at 8 and 9 hours after administration (Moskowitz et al., 1990; Riedel et al., 1988). At 10 hours after ingestion the only significant impairment found was on memory (Godtlibsen et al., 1986; Jackson et al., 1993). It may therefore be concluded that the risk for residual effects 8 hours or more

after bedtime use of midazolam 15 mg is low, but not absent.

Intermediate half-life hypnotics

Temazepam

Temazepam is available in two formulations: soft gelatine capsules (SGC) and hard gelatine capsules (HGC). The latter has a slower rate of absorption, resulting in an increase in duration of action. Numerous investigators have assessed temazepam's residual effects on laboratory tasks, and almost none of them found significant effects of a 20 mg dose in soft gelatine capsules, after 8 hours, whereas higher doses in hard gelatine capsules were occasionally found to produce significant residual effects (Borbely et al., 1984; Hemmeter et al., 2000; Hindmarch, 1982; Porcu et al., 1997; Warburton and Wesnes 1984). The meta-analysis showed a very low incidence of significant residual effects and no dose dependent increase in effects of temazepam in doses of 10, 20 and 30 mg. Yet, no difference was made between formulations. No significant residual effects of temazepam SGC 20 mg were found in the driving test (O'Hanlon and Volkerts, 1986; Riedel et al., 1988). It may the therefore be concluded that temazepam 20 mg in soft gelatine capsules (SGC) is unlikely to produce residual effects.

Lormetazepam

Lormetazepam is also available in two formulations, capsules and tablets, of which tablets result in a slower rate of absorption. Lormetazepam 1 mg in capsules can be categorized as unlikely to produce residual effects based on expert ratings, meta-analysis and a driving study (Brookhuis et al., 1990). The same dose in tablets was shown to have minor, yet significant effects on driving (Volkerts and Abbink, 1990). The effects of lormetazepam 2 mg in capsules seem minor to moderate. They were rated as moderate between 8 and 12 hours after administration by the experts, and found to be approximately equivalent to that of a BAC of 0.5 g/L on driving performance in the morning (Brookhuis et al., 1990). Effects on driving had disappeared in the afternoon. The meta-analysis comprised very few studies assessing the effects of 2 mg and no distinction was made between formulations.

Loprazolam

Loprazolam is characterized by steep dose-response curve. Residual effects of 1 mg on driving were nearly equivalent to those produced by a BAC of 0.5 g/L, but the effects of 2 mg were more severe than those produced by a BAC of 1.0 g/L., i.e., at least a three-fold increase (Volkerts and O'Hanlon, 1986). Furthermore, the reduction of effects over the course of the day was found to be small for both doses. Few other studies assessed the residual effects of loprazolam, resulting in few expert ratings and a lack of differentiation between doses in the meta-analysis. Nonetheless, the residual effects of loprazolam 2 mg can be categorized as severe and slowly diminishing. The residual effects of loprazolam 1 mg seem minor to moderate between 8 and 12 hours after administration.

Long half-life hypnotics

Nitrazepam

Residual effects of nitrazepam 10 mg can be categorized as moderate to severe and persisting over the entire day, whereas those of nitrazepam 5 mg are less likely and seem minor. The residual effects of nitrazepam 10 mg on driving in the morning and afternoon tests were equivalent to those of BACs between 0.5 and 0.8 g/L and lasted throughout 8 days of consecutive treatment (O'Hanlon and Volkerts, 1986). Meta-analysis confirmed that nitrazepam 10 mg is likely to impair performance the entire day after bedtime administration and experts rated the effects initially as severe and declining to moderate (Berghaus, 1998; Wolschrijn et al., 1991). Nitrazepam 5 mg was occasionally found to produce significant residual impairment between 8 and 12 hours after the administration (e.g., Bourin et al., 1987; Godtlibsen et al., 1986; Laurell and Tornros, 1986; Morgan, 1985; Subhan and Hindmarch, 1984a), but not on performance in the driving test (Volkerts and O'Hanlon, 1986). There was no consensus among experts with respect to the severity of residual effects of nitrazepam 5 mg.

Flunitrazepam

Flunitrazepam 2 mg is likely to produce moderate residual effects that persist over the day (Berghaus, 1998; Wolschrijn et al., 1991). The effects of flunitrazepam 1 mg were rated as similarly impairing in the morning, but more rapidly declining. Contrary to expert opinion, however, results from the meta-analysis suggest that residual effects of

flunitrazepam 1 mg are unlikely or minor. Two out of three studies assessing the residual effects of flunitrazepam 2 mg on driving showed effects that were approximately equivalent to those associated with a BAC of 0.5 g/L and persisted until 17 hours after administration (Volkerts and O'Hanlon, 1986). A third study failed to find significant residual effects on driving which might be related to the fact that subjects were tested after the first night of treatment, instead of after the second night as in the earlier studies (Vermeeren et al., 1995). The effects of the lower dose have not been assessed in the driving model. The reader is referred to Woods and Winger (1997) for an extensive review of flunitrazepam, including its effects on psychomotor performance, driving and memory.

Flurazepam

Flurazepam 30 mg is likely to produce severe residual effects that persist over the day (Berghaus, 1998; Wolschrijn et al., 1991). Residual effects of flurazepam 15 mg are somewhat less pronounced in the morning, but also (Vermeeren et al., 1998b) persist over the day. Flurazepam 30 mg was repeatedly found to have residual effects on driving that were more severe than the effects of alcohol while BAC is 1.0 g/L (Brookhuis et al., 1990; O'Hanlon, 1983; Vermeeren et al., 1998b). Furthermore, the effects were found to increase during 8 nights of continuous use, indicating accumulation of the drug in plasma (Brookhuis et al., 1990). Residual effects of flurazepam 15 mg on driving were found to be between 0.5 and 0.8 g/L (O'Hanlon, 1983).

Anxiolytic hypnotics

Experts rated the residual effects of oxazepam 10 to 50 mg, lorazepam 1 mg and diazepam 10 mg on average as moderate and those of lorazepam 2.5 to 5 mg and diazepam 15 to 20 mg as severe (Wolschrijn et al., 1991). Meta-analysis found that lorazepam 2 mg and diazepam 5 and 10 mg produced significant residual impairment. No information is available for higher doses due to a lack of studies assessing their effects (Berghaus, 1998). Oxazepam 50 mg is the only anxiolytic hypnotic assessed in the driving model. It was found to produce residual effects comparable to those associated with a BAC of 0.5 g/L in the morning, which had completely disappeared in the afternoon (Volkerts et al., 1992a).

Tolerance

It is often assumed that tolerance will develop for the residual impairing effects of hypnotics. Yet, relatively few investigators actually tested this assumption. Two studies assessed the effects on performance in the driving test during a week of continued use of temazepam SGC 20 mg, lormetazepam SGC 1 and 2 mg, nitrazepam 10 mg and flurazepam 30 mg (Brookhuis et al., 1990; O'Hanlon and Volkerts, 1986). Residual impairment following flurazepam 30 mg slightly increased over 7 nights of continued use and persisted until the morning after the first washout night, suggesting accumulation rather than development of tolerance within the first week of treatment. Residual effects of nitrazepam 10 mg did not diminish from the 2nd to the 7th night of treatment, yet, had disappeared after one washout night. Residual effects of lormetazepam SGC 2 mg were most pronounced after four nights of treatment, suggesting initial accumulation followed by development of tolerance within the first week of treatment. Lormetazepam SGC 1 mg and temazepam SGC 20 mg showed no residual effects throughout a week of treatment. According to Berghaus (1998) their meta-analysis shows that the overall percentage of performance parameters showing significant impairment for various hypnotics (averaged over dose and time after dosing) is reduced with repeated use and that this reduction appears more rapid for hypnotics with a shorter half-life. These data suggest that tolerance to residual performance impairment may develop to some extend, yet it may not be complete and may take longer than a week depending on the drug and dose.

It has also been argued that if a drug continues to have sleep enhancing effects during the night, there is no reason to assume that tolerance will be complete for its residual effects on performance. Unless, perhaps behavioral adaptations are made in the way tasks are performed, so-called 'behavioral tolerance'. Behavioral tolerance is defined as "a reduction in the potency of a drug secondary to an intentional change in the behavior of the user based on cognitive anticipation of the possibility of adverse effects" (Carvey 1998). When a drug produces predictable effects on a users' performance, they may adapt their behavior so that the effects of the drug are less pronounced. For example, alcoholics learn to reduce stumbling and falling by avoiding rapid movements and walk next to solid objects that they can hold for postural stabilization. Something similar may occur for users of hypnotics. For example, Roehrs et al. (1986) found that tolerance developed within 9 days to residual effects of flurazepam 30 mg on

performance in divided attention and vigilance tasks, but not to residual sedation as measured by the multiple sleep latency test (MSLT). Since results from the MSLT indicated that the pharmacological activity of the drug had not changed, the authors concluded that the adaptation to the effects on performance must be accounted for by mechanisms of behavioral tolerance.

CLINICAL IMPLICATIONS AND CONCLUDING REMARKS

The aim of this paper was to review the evidence that residual effects of hypnotics increase patients' risk for injurious accidents, and to provide information how to reduce these risks. For this empirical data from epidemiological and experimental studies on residual effects of currently available benzodiazepine and benzodiazepine-like hypnotics were reviewed.

Experimental studies show that hypnotics can produce residual sedation and impairing effects on psychomotor performance, attention and memory the day after bedtime use. These residual effects on performance impair the patients' quality and safety of activities of daily living and increase patients' risks of becoming involved in accidents. Epidemiological studies confirm this by showing that use of hypnotics is associated with excess risks of accidents, such as falling, hip fractures and traffic accidents. It is likely these drugs also increase the risk of a variety of occupational accidents, yet studies on this are scarce. Both experimental and epidemiological studies show that excess risk varies with treatment related factors, such as drug, dose, time after dosing, and frequency of dosing, and with patient related factors such as age and gender.

It seems worthwhile to select the safest alternative possible. Menzin et al. (2001) recently developed a model to calculate the potential impact of the use of safer hypnotics on the numbers of motor vehicle accidents and their associated costs. According to their model hypnotics that produce residual effects on driving equivalent to those associated with a BAC of 0.5 g/L would increase motor vehicle accidents by 25%, whereas hypnotics that produce impairment comparable to that associated with BAC of 0.8 or 1.2 g/L would increase the risk two or five times, respectively. The model was applied to a hypothetical cohort of 100,000 drivers with insomnia who were treated either with a hypnotic that would not increase risks or one that produces effects comparable to a BAC of 0.8 g/L. Use of the latter over 14 days in France was expected to result in 503 excess

accidents per 100,000 drivers of which 16 would involve injuries in addition to property damage.

Obviously, treatment of insomnia should preferably be accomplished without medication, for example by increasing sleep hygiene. Yet, if use of sleep enhancing medication cannot be avoided, its effects should be confined to the night as much as possible. Clinicians who prescribe hypnotics should recognize that there are considerable differences between hypnotics and doses in their potential to produce residual effects. Although choice of a drug is primarily determined by clinical efficacy, risk of accidents due to residual effects should be taken into consideration in selecting a hypnotic. Selection of the safest drug and dose possible among those available is a first step to minimize risks. A second step is to adequately inform patients about any risks and ways to minimize them by adjusting their behavior.

The review of information derived from experimental studies should enable clinicians to compare residual effects of various hypnotics in different doses and select the one considered most favorable in this respect within the range of possibilities of the individual patient. Although the information is not new, it was not available in a convenient way. The summary of results provided in table 3.8 is intended as a quick reference guide for the duration and severity of residual effects on psychomotor performance of a number of commonly prescribed hypnotics. It can be used to select hypnotics and doses generally considered unlikely to produce residual effects.

Before prescribing a hypnotic, clinicians should determine whether and how often patients' activities the day after use of a hypnotic require optimal alertness, for example when driving a car. Active consideration should also be given to whether the patient has a history of injurious accidents, such as falls or hip fractures. Clinicians should further determine whether the hypnotic in the dose they intend to prescribe by itself or in combination with other drugs or patient characteristics is likely to produce residual effects and consider safer alternatives. Since residual effects strongly depend on the dose, it is recommended to start with the lowest dose possible, in particular in elderly. Yet, when efficacy of this dose is not sufficient, the dose should not be doubled without consideration of the consequences for residual effects. Doubling the dose might produce a disproportional increase in the severity of residual effects. Patients should be informed of this too. Since the use of hypnotics in combination with other psychoactive drugs largely increases the risks, use of multiple drugs should be avoided. For example, some

antidepressants can inhibit the metabolism of some benzodiazepines and thus lead to increased plasma levels and prolonged duration of action.

Clinicians should not rely upon the package insert labels for informing their patients about drug effects on performance. Warnings are often stated too general and not taken seriously by a majority of patients. The advice to patients to be very careful after using a hypnotic would probably have more impact if it were more specific with respect to time. Patients should therefore be adequately informed of the duration and severity of residual effects of the hypnotic in the dose prescribed. In case a hypnotic likely to produce moderate to severe effects cannot be avoided, it should be considered to prohibit driving completely at the start of treatment. Patients should always be advised not to drive when they feel sleepy, dizzy or not concentrated. Yet, it should also be made clear to them that the absence of such feelings does not mean their performance is normal. Finally, clinicians should keep a careful eye on the patient after prescription of a hypnotic, in particular at the start of treatment.

Chapter 4

Acute effects of zolpidem and flunitrazepam on sleep, memory and driving performance, compared to those of partial sleep deprivation

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ABSTRACT

The aims of the present study were to determine whether the imidazopyridine zolpidem and the benzodiazepine flunitrazepam differentially affect sleep architecture, and whether zolpidem had any residual effects on driving performance or memory functions the morning after nightly drug administration. These effects were compared with flunitrazepam, partial sleep deprivation and placebo. Seventeen women who complained of chronic sleep disturbances underwent four experimental sessions on separate nights at weekly intervals – initially, during partial sleep deprivation, and after single doses of zolpidem 10 mg, flunitrazepam 2 mg and placebo administered in a double-blind, crossover design. Polysomnographic recordings were made each night and verbal and driving test were performed the following morning and subjective assessments of sleep quality, daytime sleepiness and activation, effort to perform the tests and driving quality determined by questionnaire. Polysomnographic recording showed that zolpidem and flunitrazepam significantly shortened sleep onset latency. Zolpidem respected the overall sleep architecture, without disturbance of NREM3/4 sleep and REM sleep. Flunitrazepam significantly decreased REM sleep over the whole night. Zolpidem and flunitrazepam enhance deep NREM3/4 sleep during the first two hours of sleep. Subjectively, flunitrazepam improved sleep quality and duration, but subjects reported feeling more drowsy and less active during the day after placebo. Both hypnotics significantly reduced the recalled frequency of nocturnal awakenings. Psychometric tests showed that flunitrazepam caused significant memory impairment the next morning, whereas zolpidem did not produce any disturbance of memory function. Driving performance was not disturbed by any drug treatment or partial sleep deprivation. We conclude that zolpidem 10 mg is an effective hypnotic, which causes no psychometric dysfunction the next day. Sleep architecture remained unaffected by zolpidem and cyclicity was maintained without enhancement of duration.

INTRODUCTION

Zolpidem is a hypnotic belonging to a new chemical class, the imidazopyridines, which are structurally unrelated to the benzodiazepines. Zolpidem is a selective ligand for the central ω1 receptor subtype (Langer et al., 1988), with high intrinsic activity and a potent

hypnotic effect (Langer et al., 1985). In contrast to the benzodiazepines, zolpidem shows no myorelaxant, anticonvulsant or anxiolytic effects (Depoortere et al., 1986; Perrault et al., 1990; Zivkovic et al., 1988).

Clinical material, involving both healthy volunteers and insomniac populations, has clearly, demonstrated the hypnotic efficacy of zolpidem in daily doses ranging from 5 to 20 mg (Frattola et al., 1990; Lorizio et al., 1990; Schlich et al., 1991; Wheatley, 1989). Moreover sleep architecture generally remains unaffected at these dosages, apart from an enhancing effect upon slow-wave sleep (Maarek et al., 1992; Monti, 1989).

The pharmacokinetic profile of zolpidem, with a half-life of 1.5 to 2.4 hours (Bianchetti et al., 1988; Langtry and Benfield, 1990; Thenot et al., 1988) and lack of active metabolite, suggests that there should be no residual sedation or performance impairment upon awakening (Langtry and Benfield, 1990).

The aims of the present study were to determine the imidazopyridine zolpidem and flunitrazepam, a reference benzodiazepine hypnotic, differentially affect the sleep architecture and to compare their effects on sleep with a placebo. In addition, we aimed to determine whether zolpidem 10 mg has any residual effects on memory or driving performance the morning following drug administration in a group of subjects considered as representative of the majority of hypnotic users – women who complain of chronic, moderate or severe insomnia. Zolpidem's effects on sleep and performance were compared to placebo and flunitrazepam 2mg, as well as against partial sleep deprivation to simulate the occurrence of severe insomnia. The latter condition was included to provide a more viable comparison for assessing a patient's performance the following day.

METHODS

Patients and medication

The study was conducted in accordance with the latest revision of the Declaration of Helsinki. All subjects for inclusion were informed of its design and purpose in the written 'Information for Volunteers' and indicated their informed consent in writing prior to inclusion. The protocol was reviewed and approved by the medical Ethical Committee of the University of Limburg.

Eighteen women were recruited to undergo 4 experimental sessions on separate nights at weekly intervals. They complained of insomnia and had previously received treatment with the benzodiazepine hypnotics. One subjects dropped out for reasons unrelated to the medication. The remaining 17 subjects had an average age of 40.8 ± 7.2 years.

All patients had experienced sleep disturbances for at least the preceding 6 months, and presented with at least two of the following criteria: sleep latency of more than 30 minutes; more than 2 spontaneous awakenings; less than 6 hours total sleep duration; or chronic feelings of fatigue and sleepiness during the daytime. Some subjects were using or had recently used hypnotics; current daily users were excluded from the study and all subjects had a hypnotic free period of at least 2 weeks prior to enrolment. Other exclusion criteria included: a history of drug abuse; alcoholism; psychoses; chronic diseases of the cardiovascular, respiratory, hepatic, or renal systems; pregnancy; or a requirement for chronic medication. All subjects were required to hold a current driving license and to have operated a vehicle for at least 5000 km per year over the preceding 3 years.

The subjects underwent a training session 1 week prior to entering the study, which included one habituation night in the laboratory for Polysomnographic recording, followed by a memory test and a driving test in the morning.

One week after the training session, all subjects underwent partial sleep deprivation (PSD) in pairs. After retiring at 23:00 hours, the lights were turned off 30 minutes later to mark the start of the sleep period. Three hours later they were awakened, arose and watched videotapes until morning. A memory test – word learning test – and a driving test were undertaken between 9-9.5 and 10-11 hours, respectively, after "light-off" (start of sleep period).

Administration of single doses of zolpidem 10 mg, flunitrazepam 2 mg and placebo were accomplished through a three way, double blind, crossover design. Each patient's drug regimen was scheduled for 1 week after PSD, with subsequent test regimens at weekly intervals. The placebo or drug was administered upon retiring at 23:00 hours or 24:00 hours, respectively, and the sleep period began 30 minutes later. Subjects remained in bed over the next 8 hours and were awakened, when necessary. The word learning test and driving test were conducted 9-9.5 hours and 10-11 hours, respectively, after "light-off".

Polysomnography

Polysomnography was used to study the course and composition of sleep. The electrophysiological signals were registered using an Oxford Medilog 9000 recorder and analyzed according to the criteria of Rechtschaffen and Kales (1968). Analysis of sleep onset, sleep structure and the ratio of effective sleep time (EST) to total sleep time (TST) were used to assess the hypnotic effects of the test drugs relative to placebo. TST is defined as the period (in minutes) from the beginning of sleep until final awakening, while EST is defined as TST minus the cumulative periods of awakening.

Psychometric testing

The word learning test is a multi-trial, free recall test based on the Groningen 15 word learning test (Brand and Jolles, 1985; Deelman et al., 1980). The subjects viewed a computer display of 15 commonly used monosyllabic words (nouns) at a rate of one every two seconds. As soon as the presentation stopped the subject verbally recalled as many words as possible. The first immediate recall trial was followed by four more trials in which the same words were repeated in the same order. The number of words correctly recalled after each presentation were summed to yield a total Immediate Recall score. After completion of the 5th immediate recall the subjects were engaged in a nonverbal distracting task (a computer game). After 20 minutes the instruction was given to recall the previous learned words (Delayed Recall).

The on-the-road driving test was undertaken in an instrumented station-wagon. Speed and lateral position recordings were extensively edited using automatic and interactive computer routines. The primary dependent variable was the standard deviation of the lateral position (SDLP), an index of weaving amplitude for road tracking error during constant-speed motorway travel (95 km/hour). It is sensitive to the hangover effects of hypnotics, among which flunitrazepam 2 mg (O'Hanlon and Volkerts, 1986; Volkerts et al., 1984, 1985).

Subjective quality and estimated duration of sleep were recorded by the subjects 10 to 30 minutes after awakening in the morning using the Groningen Sleep Quality Scale (Mulder-Hajonides van der Meulen, 1981). This comprises 14 questions, which require the subjects to judge the quality of their sleep; the score corresponds to the number of complaints, ranging from 0 (good sleep) to 14 (the worst possible). Daytime sleepiness and activation were measured before and after the memory and driving tests using the Stanford Sleepiness Scale (Hoddes et al., 1973), and the Activation-Deactivation Adjective

Check List (Thayer, 1967). The Stanford Sleepiness Scale comprises seven descriptions of stages of sleepiness, ranging from 1 (wide awake) to 7 (nearly asleep). The Activation-Deactivation Adjective Check List activation score is based upon subjective ratings (1 to 4) of 10 adverbs indicative of differing levels of activation, with the sum score ranging from 10 (not active) to 40 (very active). The subject's recollection of effort needed to undertake both tests was measured using the Perceived Mental Effort Scale (Zijlstra and Van Doorn, 1985), while the subject's judgment of driving quality was assessed by a visual analogue scale ranging from extremely bad (-100 mm) to extremely good (+100 mm).

Data analysis

Statistical analyses, unless otherwise stated, were carried out using the MANOVA module of the SPSS/PC+ (version 2.0) statistical program series for repeated measures analysis of variance. Dependent variables were tested separately, first to determine the significance of the overall treatment effect. If the overall effects was significant at $p < 0.10$, separate mean pair comparisons with placebo were performed to determine the specific treatment conditions that contributed most to the effect.

The PSD was omitted from the analyses of polysomnographic data. Performance data and subjective assessments for all 4 regimens were analyzed in the same way using the SPSS/PC+ Program series.

RESULTS

An assessment of the subjects' sleep complaints was made during the week prior to their enrolment into the study. They were required to complete every morning the sleep quality scale, estimated total sleep duration, and the total number of nocturnal awakenings during the night. The subjects claimed to sleep on average less than 6 hours per night (mean ± SD, 5.7 ± 1.8 hours), and estimated that they woke up about twice a night (mean ± SD, 1.7 ± 1.8). The number of sleep complaints on the Groningen Sleep Quality Scale averaged 7.1 (SD = 3.9), which equaled the sleep quality measured in a group of 59 depressed patients (Mulder-Hajonides van der Meulen, 1981).

Polysomnography

The polysomnographic recordings of one subject during a single trial proved unusable, and these data were omitted from the analysis. Although the women in this study complained of severe insomnia, Polysomnographic recordings did not support their claim. The subjects' average TST using placebo was normal and provided little opportunity for improvement within the fixed 8 hours bedtime (table 4.1). Nevertheless, there were measurable drug effects.

The TST ($F_{1,15}$ = 6.31, p = 0.024) and the EST ($F_{1,15}$ = 5.78, p = 0.030) were significantly longer with flunitrazepam than with placebo. Initiation of sleep was hastened by both zolpidem and flunitrazepam compared with placebo. The intervals between lights-off and the onset of non-rapid eye movement stage 1 sleep (NREM 1) were reduced by both zolpidem ($F_{1,15}$ = 4.18, p = 0.044) and flunitrazepam ($F_{1,15}$ = 9.36, p = 0.008). The reduction in latency to NREM 2 time was significant for flunitrazepam ($F_{1,15}$ = 9.25, p = 0.008) and approached significance for zolpidem ($F_{1,15}$ = 4.18, p = 0.061), while the latency to NREM 4 was only significantly shortened by zolpidem ($F_{1,15}$ = 5.21, p = 0.039) but not by flunitrazepam ($F_{1,15}$ = 2.01, p = 0.178). Flunitrazepam nearly doubled the interval between onset of first REM and the first REM cycle relative to placebo ($F_{1,15}$ = 18.77, p = 0.001). Apparently, this was due to suppression of the first REM episode in many individual cases.

There were no significant differences in the composition of sleep between zolpidem and placebo over the whole night. Following flunitrazepam, however, subjects spent significantly more time in NREM 2 ($F_{1,15}$ = 8.07, p = 0.012) and less in REM ($F_{1,15}$ = 26.44, p < 0.001). The differences between the time spent in NREM3/4 after the placebo regimens were not significant ($F_{2,14}$ = 1.34, p = 0.294).

Since zolpidem is a short acting hypnotic, its effects might be confined to the first part of the sleeping period and not easily seen when data from the whole night are being considered together. Therefore, the sleep composition data were collected and analyzed in each of the three consecutive two-hour periods beginning with sleep onset. The results are shown in table 4.2.

During the first two hours after sleep onset, the time awake was significantly reduced both by zolpidem ($F_{1,15}$ = 4.67, p = 0.048) and flunitrazepam ($F_{1,15}$ = 4.49, p = 0.051). Furthermore, there was a highly significant REM suppression with flunitrazepam ($F_{1,15}$ = 36.84, p < 0.001), while at the same the NREM3/4 increased significantly

Table 4.1 Mean (±SE) of the polysomnographic parameters during the nights of treatment with either placebo, zolpidem 10 mg or flunitrazepam 2 mg in 16 patients.

Polysomnographic parameter	*Placebo*	*Zolpidem*	*Flunitrazepam*
Time in bed (TIB), from lights off until rising (min)	467 ± 3	462 ± 6	472 ± 2
Total sleep time (TST), from sleep onset until awakening	451 ± 7	455 ± 6	465 ± 3*
Wake after sleep onset (WASO), cumulative period of waking time within TST (min)	27.2 ± 7.8	21.6 ± 7.2	17.5 ± 5.1
Effective sleep time (EST), total time asleep within TST (min)	424 ± 12	433 ± 11	448 ± 7*
Sleep latency time before NREM1 (SLT1), from lights off until first minute of NREM1 (min)	16.3 ± 4.3	7.4 ± 1.5*	7.1 ± 2.0*
Sleep latency time before NREM2 (SLT2), from lights off until first minute of NREM2 (min)	23.2 ± 6.3	10.8 ± 1.7	9.4 ± 2.1*
Sleep latency time before NREM4 (SLT4), from lights off until first minute of NREM4 (min)	48.7 ± 6.7	35.3 ± 4.1*	38.2 ± 4.2
REM latency time NREM2 to REM, interval between SLT2 and first minute of REM (min)	84.8 ± 7.5	103.0 ± 11.2	157.0 ± 14.5**
NREM1 %, percentage time spent in NREM1 sleep of TST (%)	5.6 ± 0.6	5.9 ± 0.7	5.2 ± 0.6
NREM2 %, percentage time spent in NREM2 sleep of TST (%)	50.5 ± 2.5	48.6 ± 1.3	56.3 ± 2.0*
NREM3/4 %, percentage time spent in NREM3/4 sleep of TST (%)	17.4 ± 1.4	20.4 ± 1.4	19.3 ± 1.5
REM %, percentage time spent in REM sleep of TST (%)	20.4 ± 1.0	20.1 ± 1.3	15.5 ± 0.9***

Significant differences from placebo: * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$

($F_{1,15} = 12.53$, $p = 0.003$). Flunitrazepam also highly significantly reduced NREM 1 ($F_{1,15} = 4.67$, $p < 0.05$). Similar effects were seen with zolpidem during the first two hours of sleep: the REM sleep was suppressed ($F_{1,15} = 4.67$; $p < 0.05$); NREM3/4 increased ($F_{1,15} = 9.06$, $p = 0.009$), and NREM 1 slightly reduced ($F_{1,15} = 4.04$, $p = 0.062$). During the

Table 4.2 Mean (±SE) sleep composition parameters.

Parameter	*Period*	*Placebo*	*Zolpidem*	*Flunitrazepam*
Wake after sleep onset (minutes)	0-2	6.0 ± 2.5	2.7 ± 1.6 *	2.0 ± 1.0 *
	2-4	6.2 ± 2.1	3.3 ± 1.9	3.0 ± 1.0
	4-6	7.9 ± 5.1	6.6 ± 3.2	9.2 ± 3.5
NREM 1 (minutes)	0-2	7.5 ± 0.9	5.3 ± 1.0	3.0 ± 0.4 ***
	2-4	3.4 ± 0.7	3.2 ± 0.7	5.1 ± 1.2
	4-6	4.8 ± 1.0	6.0 ± 1.0	4.9 ± 0.6
NREM 2 (minutes)	0-2	43.6 ± 2.7	42.9 ± 2.4	46.8 ± 3.3
	2-4	51.6 ± 3.7	47.8 ± 3.7	62.5 ± 4.3 *
	4-6	53.8 ± 5.1	54.3 ± 4.3	58.3 ± 3.4
NREM3/4 (minutes)	0-2	32.5 ± 2.5	42.4 ± 3.3**	46.6 ± 3.3 **
	2-4	23.2 ± 2.7	27.4 ± 3.7	19.7 ± 4.0
	4-6	6.9 ± 3.0	5.9 ± 2.0	5.2 ± 2.0
REM (minutes)	0-2	10.4 ± 1.6	6.9 ± 1.5 *	1.5 ± 0.7 ***
	2-4	15.7 ± 2.6	18.3 ± 2.6	9.7 ± 1.7 *
	4-6	26.6 ± 2.2	27.1 ± 2.7	21.4 ± 2.8 *

Significant differences from placebo: * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$

remainder of the night, the sleep architecture with zolpidem was not significantly different from the second two hour period ($F_{1,15} = 4.75$, $p = 0.045$). In the second period this was accompanied by a significant decrease in NREM 2 ($F_{1,15} = 7.56$, $p = 0.015$).

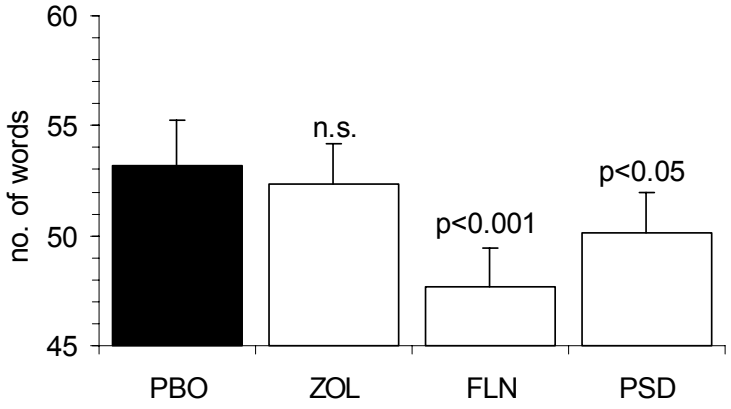

Figure 4.1 Mean (±SE) Immediate Recall scores in the word learning test on the mornings following the nightly administration of placebo (PBO), zolpidem 10 mg (ZOL), or flunitrazepam 2 mg (FLN), and after partial sleep deprivation (PSD) in women (n= 17) complaining of chronic insomnia. Significance levels indicate the difference from placebo.

Performance

Word learning

The mean Immediate Recall scores on the mornings following the different regimens are shown in figure 4.1. Analysis showed that Immediate Recall was significantly impaired by flunitrazepam ($F_{1,16}$ = 15.41, p = 0.0001) and PSD ($F_{1,16}$ = 9.36, p = 0.034), although there was no significant change from placebo with zolpidem ($F_{1,16}$ = 0.33, p = 0.572).

Figure 4.2 shows the mean Delayed Recall scores for the four treatment regimens. Analysis showed no significant change after zolpidem ($F_{1,16}$ = 0.81) or PSD ($F_{1,16}$ = 1.68), but the Delayed Recall with flunitrazepam was significantly worse than with placebo ($F_{1,16}$ = 15.38, p = 0.001). This could reflect either the failure of the subjects to learn the words in the first part of the test, or their failure to retrieve the words from memory after a delay. To determine the nature of this effect, the Delayed Recall score was re-analyzed as a percentage of the 5th Immediate Recall score, i.e., the retention score. Retention of previously learned words after placebo, zolpidem, flunitrazepam and PSD were 88%, 80%, 69%, and 81%, respectively. Analysis showed that retention of previously learned words was significantly worse with flunitrazepam than placebo ($F_{1,16}$ = 11.97, p = 0.003). Subjects judged the effort (table 4.3) required to perform these memory tests as significantly higher with flunitrazepam, than placebo ($F_{1,15}$ = 6.71, p = 0.021), but

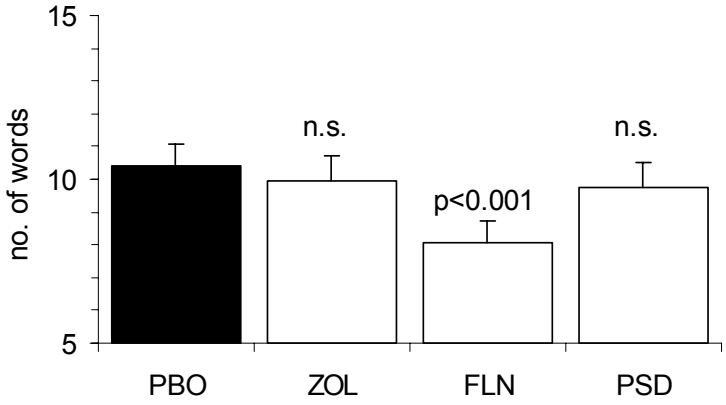

Figure 4.2 Mean (±SE) Delayed Recall scores in the word learning test on the mornings following the nightly administration of placebo (PBO), zolpidem 10 mg (ZOL), or flunitrazepam 2 mg (FLN), and after partial sleep deprivation (PSD) in women (n= 17) complaining of chronic insomnia. Significance levels indicate the difference from placebo.

indicated no difference between zolpidem and placebo ($F_{1,15}$ = 1.43, p = 0.251). Despite the extra effort, the subjects' performance was worse after flunitrazepam.

Driving test

One test drive, following the use of flunitrazepam, had to be stopped prematurely by the instructor at 75% of the total test time, as he judged that the subject was too drowsy to continue safely. Despite this, there was on average little difference in the driving performance with any of the four regimens. The mean ± SE SDLP after placebo, zolpidem, flunitrazepam, and PSD were 21.9 ± 1.0, 22.0 ± 1.0, 22.2 ± 0.9 and 22.7 ± 1.2, respectively. Analysis revealed no significant differences between treatments ($F_{3,14}$ <1). Although there were considerable changes within individual driving performances with active drugs or PSD relative to placebo, the mean SDLP values were nearly normal for each regimen. In earlier studies the mean SDLP in a group of untreated healthy volunteers was 21 ± 4 cm (Ramaekers et al., 1992b; Robbe and O'Hanlon, 1995).

Even so, subjects rated their driving quality as being not significantly different and normal for all regimens (F<1, table 4.3). On average they needed moderate effort to perform the 1 hour driving test after PSD, and some effort on the morning after the drugs or placebo (table 3), but these differences were not significant ($F_{3,14}$ = 2.20, p = 0.133).

Table 4.3 Mean (±SE) of the subjective assessments in 17 women treated by partial sleep deprivation (PSD), placebo, zolpidem 10 mg, or flunitrazepam 2 mg.

Subjective parameter	*Scale range*	*Time period*	*PSD*	*Placebo*	*Zolpidem*	*flunitrazepam*
Perceived effort						
- *memory test*	0 to 150 mm		63 ± 7 [a]	56 ± 7	60 ± 8	80 ± 8
- *driving test*	0 to 150 mm		58 ± 8	36 ± 8	40 ± 6	35 ± 6
Subjective driving quality	-100 to +100 mm		-9 ± 10	3 ± 11	7 ± 10	14 ± 11
Stanford Sleepiness Score	1 to 7	1	3.6 ± 0.3*	2.2 ± 0.2	2.7 ± 0.3	3.5 ± 0.5*
		2	3.6 ± 0.3* [a]	2.1 ± 0.2	2.4 ± 0.2	3.1 ± 0.4 [a]
		3	2.9 ± 0.3*	1.8 ± 0.2	2.2 ± 0.2	2.7 ± 0.4*
		4	4.0 ± 0.5	2.1 ± 0.3	2.7 ± 0.2	2.9 ± 0.4
AD-ACL activation score	10 to 40	1	21.7 ± 1.4*	27.5 ± 1.9	25.4 ± 1.9	21.9 ± 2.0* [b]
		2	20.6 ± 1.6* [a]	27.1 ± 2.0	25.7 ± 1.8	22.8 ± 2.6
		3	22.6 ± 1.6* [a]	28.7 ± 2.1 [a]	27.3 ± 2.1	25.1 ± 2.5*
		4	20.6 ± 2.0* [a]	28.7 ± 1.8	25.0 ± 1.4 [a]	24.3 ± 2.1

Time period: 1= before word learning test; 2= after word learning test; 3 before driving test; 4= after driving test. Significant differences from placebo: * $p < 0.05$. ([a]= 16 subjects, and [b]= 15 subjects).

Subjective sleep quality and duration

Flunitrazepam significantly improved the subjective rating of sleep quality ($F_{1,16} = 15.08$, $p = 0.001$); the mean (± SE) number of complaints dropped from 6.9 ± 1.1 after placebo to 2.6 ± 0.5 after flunitrazepam. Although the mean number of complaints after zolpidem was also less (5.1 ± 1.0), there was no significant improvement in subjective sleep quality with placebo ($F_{1,16} = 1.67$, $p = 0.215$). Furthermore, subjects believed they slept longer with flunitrazepam ($F_{1,16} = 26.18$, $p < 0.001$), but not with zolpidem ($F_{1,16} < 1$); the mean (± SE) estimated sleep duration with placebo was 5.8 ± 0.3 hours, with zolpidem it was 6.2 ± 0.4 hours, and after flunitrazepam 7.5 ± 0.2 hours. Both zolpidem and flunitrazepam had significant effects on the estimated number of awakenings; these dropped from a mean (± SE) of 3.8 ± 0.7 on the placebo nights, to 1.9 ± 0.4 awakenings

after zolpidem ($F_{1,14}$ = 7.81, p = 0.014), and 0.8 ± 0.3 with flunitrazepam ($F_{1,14}$ = 19.88, p = 0.001

Daytime sleepiness and activation

The data were analyzed for 10 and 15 subjects, respectively. Analysis showed that subjects felt significantly more sleepy during the day following PSD ($F_{1,14}$ = 5.49, p = 0.034). Mean daytime sleepiness scores on the morning after zolpidem were not significantly different from placebo ($F_{1,14}$ = 2.12, p = 0.167). Activation scores from the Activation-Deactivation Adjective Check List following flunitrazepam ($F_{1,9}$ = 9.47, p = 0.013) and PSD ($F_{1,9}$ = 7.45, p = 0.023) were significantly reduced compared with placebo, but there was no significant effect after zolpidem ($F_{1,9}$ = 1.85, p = 0.207).

DISCUSSION

Self reported quality and duration of sleep over one week in their respective home environments closely resembled those following placebo in the laboratory. The mean number of sleep complaints was 7.1 ± 3.9 at home and 6.9 ± 4.3 in the laboratory. Similarly, the mean ± SD estimated sleep duration at home was 5.8 ± 1.8 hours, which is approximately the same as after placebo in the laboratory, i.e., 5.8 ± 1.3 hours. Thus it appears that in so far as the subjects were able to relate, they slept for about the same time in the laboratory as at home. Their subjective feelings of bad sleep were, however, not con formed by polysomnographic data. It appeared that the subjects' sleep after placebo differed little from what would be expected of healthy women of the same age. The discrepancy between subjective and objective sleep duration in this study is not unusual. Carskadon et al. (1976) found that individuals who complain chronically of poor sleep generally underestimate its duration in comparison with objective measures of sleep time. The reason for this is unclear, but it suggests that there is more to subjectively good sleep than shown by the objective polysomnographic parameters.

Notwithstanding the subjects' objectively good sleep and the fact that their bedtime was limited to 8 hours, flunitrazepam increased the time the subjects were actually asleep, mainly by reducing the latency to sleep onset. Although zolpidem had the same effect on sleep onset, it did not significantly prolong the TST nor the EST. It did, however, hasten the onset of deep (NREM3/4) sleep. Sleep composition over the whole

night was not changed by zolpidem, whereas flunitrazepam was followed by REM suppression throughout the night. This was accompanied by a general increase in superficial NREM 2 sleep. Such shifts typically are seen following the administration of benzodiazepine hypnotics.

The results indicate that zolpidem's effects are restricted to the first part of the night; like flunitrazepam it hastens sleep onset and improves sleep maintenance. Zolpidem alone enhance deep NREM3/4 sleep. Although zolpidem's effects on REM during the first 2-hour interval was measurable, none was apparent over the whole sleeping period; this indicates that the initial mild REM suppression was followed by an approximately equal REM recovery after zolpidem. This contrasts with the expected effects of flunitrazepam reducing the REM sleep over the whole night.

Contrary to subjective feelings, polysomnography indicated that the performance after placebo could not have been affected by sleep loss, and should therefore be considered as normal. Limiting the bedtime to only three hours, of which the subjects slept for only 2.4 ± 0.5 hours, had little effect upon performance. Even though the subjects indicated that they felt very sleepy and inactive on the morning after PSD, this resulted in limited impairment of their memory function and no impairment of their driving. This shows that these women were well able to perform despite their sleep loss and subjective feelings of inadequacy.

Although subjects indicated that they felt most sleepy and least active on the mornings after PSD, their memory functions were less affected than with flunitrazepam. In the light of the current debate as to whether the benzodiazepines' effects upon memory are secondary to, or independent of, their sedative effects, our results seem to favor the latter opinion. If sedation alone is responsible for the amnestic effects, judging from the subjective feelings, the effects should have been worse after PSD.

Zolpidem's lack of "hangover" effects on memory is further evidence that, in this respect, the drug is clearly different from the benzodiazepines. Our results confirm those from a number of other studies (Bensimon et al., 1990; Jackson et al., 1993; Scharf et al., 1991). Surprisingly, flunitrazepam 2 mg did not significantly affect the subjects' driving performance. Some residual effect on the driving test was expected on the basis of two earlier studies, where flunitrazepam 2 mg was shown to have a moderate but significant effect on SDLP. In these two studies, each of which comprised 16 women with insomnia, the mean SDLP increased from 18.9 cm and 20.5 cm with placebo to 21.0 cm and 23.3 cm, respectively, after flunitrazepam (Volkerts et al., 1984; Volkerts et al., 1985). There is

at least one difference between these studies and the present one. The subjects of these earlier studies were treated with flunitrazepam 2 mg for two consecutive nights, and tested after the second night, which might explain the discrepancy. Flunitrazepam's half-life varies between 15-and 35 hours, while those of its two active metabolites are 23 and 31 hours, respectively. It may be that the effects of flunitrazepam and its metabolites accumulate over the first days, and that the effects are less pronounced on the first morning relative to the second. However, it should be noted that one of our subjects who had taken flunitrazepam, was withdrawn from the driving test because she became too drowsy to continue safely. Zolpidem had no impairing effects on memory or driving performance on the morning after intake, and this has been confirmed by several other authors (Bensimon et al., 1990; Jackson et al., 1993; Scharf et al., 1991).

In conclusion, we can say that zolpidem has been shown to be an effective hypnotic without any psychometric impairment on the following day. Zolpidem does not disturb sleep architecture. These results show that zolpidem is a unique, novel hypnotic with clearly differing qualities from the benzodiazepines in general.

Chapter 5

Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance

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ABSTRACT

Zaleplon, a new pyrazolopyrimidine hypnotic, possesses an unusually short elimination half-life (ca. 1 hour). This study was conducted to determine whether middle-of-the-night administration of zaleplon affects memory or driving performance the following morning. Twenty-eight healthy volunteers participated in a double blind, 7-way, crossover study. They ingested capsules twice on each treatment night; once before initiating sleep and again after being briefly awakened 5 hours later. Treatments were: placebo at both times, zaleplon 10 or 20 mg, or zopiclone 7.5 mg followed by placebo, or the same in reverse order. Subjects arose 3 hours after the second dose. One hour later, sleep quality and mood were assessed by questionnaires and balance and memory in a test battery. A standardized actual driving test was undertaken between 5 and 6 hours after the second dose. All drugs similarly improved sleep quality but only zopiclone hindered awakening. Evening zaleplon doses were without significant effects. Late-night zaleplon had minor effects in one memory test. Evening zopiclone shared these effects and also significantly impaired driving performance. Late-night zopiclone's effects were significant in every test. Its effects on driving were severe. Major Conclusion: Zaleplon 10 and 20 mg can be taken up to 5 hours before driving with little risk of serious impairment.

INTRODUCTION

Zaleplon is a novel pyrazolopyrimidine sedative-hypnotic which binds selectively as an agonist at the ω1 benzodiazepine receptor subtype. It possesses an unusually rapid rate of elimination and forms no active metabolites. After oral dosing in healthy young volunteers, zaleplon reaches peak plasma concentration within 0.9-1.5 hours and is eliminated with a monoexponential half-life of only 0.9-1.1 hours (Beer et al., 1994). It is more rapidly eliminated than any hypnotic currently used in clinical practice, the closest being midazolam, triazolam and zolpidem, all with average $t_{1/2\beta}$ values of around 2.5 hours in young adults (Garzone and Kroboth, 1989; Bianchetti et al., 1988). Clinical studies have shown that zaleplon is a safe and effective hypnotic, with a minimum effective dose for nonelderly patients of 10 mg. No serious adverse events were reported by volunteers treated with zaleplon in single doses up to 60 mg, only mild headache and dose-related extensions of the drug's pharmacological activity.

Like most hypnotics, zaleplon can be used for the treatment of sleep initiation problems at the beginning of the night, but its extremely short duration of action may also allow patients to take the drug later in the night and be free of residual effects the next morning. This would be advantageous for patients having sleep maintenance problems or difficulties resuming sleep after being awakened in the middle of the night. Longer acting hypnotics are efficacious, but often at a cost of residual daytime sedation that impairs performance. It is therefore unwise to take such hypnotics in the middle of the night, especially if one needs to engage in potentially dangerous activities, like driving, only a few hours later. Only very short acting hypnotics would be safe to use in such instances. At least two studies have examined the possibility for existing hypnotics. Tobler et al. (1991) examined the residual effects of midazolam 7.5 mg given 3 hours into the sleeping period on typing performance the next morning, approximately 7 hours after administration, in a placebo-controlled study with 17 healthy volunteers. They found no significant effects on performance. However, the midazolam dose was only half that normally prescribed to young adults. The investigators rationalized their choice of a low dose as one that might be more readily accepted for inducing the resumption of sleep after early awakening. Wickstrøm et al. (1988) compared the daytime residual effects of triazolam (0.25 and 0.5 mg), zopiclone (7.5 and 15 mg), flunitrazepam (1 and 2 mg), and ethanol to those of placebo in combination with partial sleep deprivation in healthy young volunteers. They were kept awake the first part of the night to simulate insomnia. At 2 a.m. they were given a drug and allowed to sleep for 3 hours. Performance was assessed 4, 6, 8 and 10 hours after administration. Wickstrøm et al. found no significant differences in performance between placebo, ethanol, and lower doses of the three hypnotics and concluded that it would be safe for at least younger patients to take these drug doses in the middle of the night and engage in all normal activities the next day. However, results from a study by Volkerts and O'Hanlon (1988) do not support the conclusions pertaining to zopiclone. They administered zopiclone 7.5 mg and placebo, each on two consecutive nights, at 10 p.m., to 16 female subjects who had previously used hypnotic drugs for the treatment of insomnia. They undertook two driving tests in the day following the second doses, 10-11 and 14-15 hours after administration. Zopiclone significantly impaired driving in the morning, though not in the afternoon.

Zaleplon's unique pharmacokinetic profile suggests that it could be administered up to about 4 hours before final awakening without having residual effects on performance in the morning. By that time the drug's plasma concentration should be less

than one quarter of Cmax. Allen et al. (1993) compared the effects of single doses of zaleplon 20 mg, lorazepam 2 mg and placebo on a battery of psychomotor and memory tests in 12 healthy males. They found that recovery to predrug levels of performance was rapid following zaleplon. Psychomotor performance was no longer affected at 3 hours after administration, and amnestic effects were no longer found 5 hours after administration.

The present study was designed to measure the residual effects of zaleplon 10 and 20 mg on memory functions and actual driving performance. Zaleplon's effects were compared to those of placebo and, as the active control, zopiclone 7.5 mg. Subjects ingested capsules two times in each condition; when they retired to bed and when they were awakened in the middle of the night. The first dose was administered 8 h 45 min and 10 h before the memory and driving tests, and the second, 3h 45 min and 5 h before. Treatment effects on subjective sleep parameters were also measured.

METHODS

Subjects

Twenty-nine healthy male and female volunteers (ages, 23-40 years) were recruited via newspaper advertisements and paid for participating in this experiment. Subjects were screened by a medical history questionnaire and a physical examination. The latter included a 12-lead ECG, blood chemistry and hematology, and urinary tests for β-HCG and drugs of abuse. Exclusion criteria included pregnancy, any history or current evidence of severe gastrointestinal, hepatic, renal, cardiovascular neurological or mental disorders, alcohol or drug abuse, or primary insomnia; requirement for chronic use of any systemic medication except oral contraceptives; use of any psychotropic drug within 30 days of prestudy screening; blood donation or participation in any other clinical trial within the previous 2 months; consumption of more than 5 beverages containing caffeine per day, or more than 10 cigarettes per day, and drinking more than 28 glasses of alcohol containing beverages per week.

One subject dropped out after the second treatment period for reasons unrelated to treatment. A total of 28 subjects (14 male, 14 female) completed the study. Their mean ± SD age was 31 ± 5.7 y. Height and weight of the men was 181 ± 8 cm, 79 ± 15 kg, and of the women, 166 ± 7 cm, 66 ± 7 kg. Six were smokers.

All subjects possessed a valid driving license and reported having driven between 8,000 and 60,000 km per year (mean, 18,000 km/year) during the preceding 3 years. They agreed not to use drugs of abuse or systemic medication, except oral contraceptives, aspirin and acetaminophen, for 1 week prior to and during treatments. Subjects were prohibited from consuming alcohol for 24 hours before treatments. On test days, their consumption of caffeine containing beverages was limited to one cup of tea at breakfast. Smoking was prohibited for at least 30 minutes prior to, and during testing. Subjects were instructed to sleep normally and avoid strenuous exercise on nights/days before treatments.

Design and treatments

The study was conducted according to a double-blind, double-dummy, placebo and active-drug controlled, 7-way cross-over design. Treatment conditions were defined by the combination of medication and its time of administration. Subjects ingested three gelatine capsules immediately before they retired for sleep and three more when awakened 5 hours later. All capsules contained placebo in the control condition (PLAC). Zaleplon 10 mg, zaleplon 20 mg, and zopiclone 7.5 mg were each given in the evening and middle of the night in separate conditions defined as ZA10$_E$, ZA20$_E$, ZOPI$_E$, ZA10$_N$, ZA20$_N$, and ZOPI$_N$. Evening drug administration was followed by placebo night administration, and the opposite. The same sets of treatment orders from two, mirror image 7x7 Williams Squares were randomly assigned to both male and female subjects. Successive treatments were scheduled at weekly intervals for all subjects.

Procedure

Subjects were individually trained to perform all tests. One week before participation in the first treatment condition, subjects slept in an institutional environment and rehearsed all tests, including driving. Three subjects whose sleep was disturbed were allowed a second habituation night on which all managed to sleep normally.

Four subjects were treated on the same night and tested on the following day. Pairs proceeded in parallel with 1 hour difference between their activities. The first pair arrived at the sleeping facility at 9 p.m. They were questioned about the use of systemic medication, and after the first treatment, about adverse events during the washout period. Vital signs were recorded and urine was assayed for the presence of cannabinoids. This pair retired to bed at 10.30 p.m. after ingesting the first part of their medication in the

presence of an investigator. They were awakened by a telephone call 5 hours after going to bed. The time before they answered was recorded by the investigator using a stopwatch to mark the onset of the first ring and the vocal response of the subject. This wake-up call RT (in seconds) was taken as an index of how easy or difficult it was to arouse a subject. The investigator administered the second part of their medication and instructed them to resume sleeping. They were awakened in the same manner 3 hours later at 6.30 a.m. Subjects were served a standardized breakfast; their vital signs were again measured and a blood sample was taken. Body Sway, Word Learning (Immediate Recall), Spatial Memory, Syntactic Reasoning and Semantic Verification tests were performed from 7.15 to 8 a.m., and the driving test from 8.30 to 9.30 a.m., i.e. 10-11 or 5-6 hours after receiving active medication. The Delayed Recall and Recognition parts of the Word Learning test were performed at 10.00 a.m.

Body Sway was measured using the stabilometry method of the International Society of Posturography (Kapteyn et al., 1983). Subjects stood on a force platform for 60 seconds with the feet open at an angle of 30°, first with their eyes open and fixed on a target 2 meter away, and then with their eyes closed. The analog outputs of transducers within the platform were digitized, sampled, and analyzed by a computer. The system (Electropostugraph, ELP Brussels) calculated the momentary vector of force extending downward from the center of gravity of the body and its movement around the vertical axis over time. Two related parameters were measured during both the eyes open and closed recording epochs, namely the length of the vector's path (POS-L1 and POS-L2, in mm) and the area circumscribed by the vector (POS-S1 and POS-S2, in mm2).

In the Word Learning Test (Rey, 1964), subjects were shown a sequence of 15 monosyllabic nouns on a computer display at a rate of one per two seconds. Immediately thereafter they were required to verbally recall as many words as possible. The sequence was repeated on four more trials, and the highest separate trial score was the Immediate Recall score (WLT-IR). After a 3-hour delay, subjects again recalled as many words as possible without prompting. The number correctly recalled was the Delayed Recall score (WLT-DR). To correct for a failure in initial acquisition, delayed recall was also scored as a percentage of immediate recall, i.e. Relative Recall (WLT-RR). Finally, the subjects were shown a series of 30 words on the computer display, comprising the original set and 15 new words in random order, They were asked to indicate as quickly as possible whether the given word was one of the previously learned set. The number of correct responses (WLT-RS) and average reaction time (WLT-RT) were recorded.

In the Spatial Memory Test (Vermeeren et al., 1995), subjects were briefly shown a fixation point at the center of the computer display. Shortly thereafter a target appeared for 500 milliseconds at a random location. Immediately, or after a delay of 2 or 4 seconds, a cursor appeared at the center of the display. The subjects' task was to relocate the cursor as accurately as possible over the recalled position of the target, using a trackball, and depress a button on the trackball at the selected position. Each test consisted of 75 trials, divided equally among the three response delays. Regression lines were calculated to describe localization error (mm) as a linear function of delay. The derived slope constant (SMT-SL) is a measure of spatial memory decay, and the intercept (SMT-IC) is an incidental measure of perceptual-motor coordination.

In the Semantic Verification Test (Collins and Quillian, 1969), subjects were serially presented with 30 short sentences on the display relating to everyday knowledge. Half the sentences were true (e.g., "Crows fly in the air") and half were false (e.g., "Pencils are furniture"). Subjects responded as quickly as possible. The dependent variable was reaction time of correct responses (SVT-RT), which is a measure of ease of access and speed of retrieval from long term memory.

In the Syntactic Reasoning Test (Baddeley, 1968), subjects read a series of 32 sentences, each describing the order of two letters; e.g., "B follows A". Each sentence was followed by the display of the letter-pair in the same or opposite order: "A - B" or "B - A". Subjects responded as quickly as possible by indicating whether or not the letter order matched that described in the preceding sentence. The dependent variable was reaction time of correct responses (SRT-RT), which is a measure of speed of processing in working memory.

The driving test was originally developed during the 1970s for driver fatigue research in the USA. It was standardized for drug screening purposes in 1982, and it has been used in more than 50 separate studies for measuring drug effects on driving performance (O'Hanlon and Ramaekers, 1995; O'Hanlon et al., 1995). The subject drives a specially instrumented car over a 100 kilometer (61 miles) primary highway circuit. He or she is accompanied by a licensed driving instructor, having access to dual controls. The subject's task is to maintain a constant speed of 95 kilometers (58 miles) per hour and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle's speed and lateral position relative to the left lane delineation are continuously recorded. These signals are digitally sampled at 4 Hz and edited, off-line, to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic

situations. The remainder is then reduced to yield the standard deviation of lateral position (SDLP in cm) for each successive 5-km segment, and as the square-root of pooled variance over all segments, for the test as a whole. SDLP is an index of road tracking error or "weaving". It is a very reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is r= 0.85. It has also proven sensitive to many sedating agents including alcohol in blood concentrations as low as 0.35 g/L (Ramaekers et al., 1992b; Vuurman et al., 1994).

Before starting the laboratory tests, subjects used six 100 mm visual-analog scales to describe their ease of initiating and awakening from sleep and its quality for both segments of the preceding night, separately. They likewise indicated their subjective feelings using the Bond and Lader (1974) 16-item mood rating scales for providing three factor-analytically defined summary scores - "alertness", "contentedness", and "calmness". The driving instructors used similar visual-analog scales for describing the subject's driving quality and sedation at the conclusions of those tests.

Statistical analysis

Psychometric and driving performance parameters were analyzed preliminary using analysis of variance (ANOVA) with subjects, periods, treatments and first-order carryover as factors. As carry-over was significant for only 2 (POS_S1 $p < 0.0321$; alertness $p < 0.0453$), out of 16 parameters, it was dropped from the model. Each parameters mean values after both evening and midlle-of-the-night administrations of each drug was separately compared to that recorded in the placebo condition using a set of six t-tests. Error variance pooled over all conditions was used as the common denominator for all contrasts comparing a given set. The sequential Bonferroni pα-adjustment (Overall and Rhoades, 1987) was applied for correcting the increase in overall Type-I error probability associated with multiple tests. Though all drug-placebo contrasts with $p < 0.05$ will be given, only those exceeding the adjusted-α criterion are defined as statistically significant. All statistical tests were conducted using SAS (version 6.09).

RESULTS

Missing data

An insidious failure in the test vehicle's lateral position sensor occurred during data collection. Before it was recognized and corrected, data from 17 tests had been rendered invalid. The affected tests were repeated after completion of the subjects' scheduled series. Statistical analyses of all performance measures were conducted two ways, i.e., considering all measures in affected conditions as missing (Wyeth Ayerst Research-data on file) and using the repetitions to form a complete data set. Both showed the same effects as being significant or nonsignificant. Results of the latter analyses are presented here. Another anomaly occurred during the administration of the Word Recognition test. On one occasion the test began before the subject was prepared. Owing to the subjects' preview of the material, the test could not be restarted. Finally, two response times to the morning calls are missing, because subjects had accidentally put the phone off the hook.

Sleep

Analyses showed significant treatment effects on ease to initiate sleep and sleep quality in both segments of the night (figure 5.1; $F_{6,156} > 4.5$, $p \leq 0.0003$). Though subjects were normal sleepers, initiating sleep in the evening was judged significantly easier after every hypnotic drug than after placebo ($p \leq 0.0001$). The evening doses of every drug likewise promoted significantly better sleep quality during the first part of the night than placebo ($p \leq 0.0029$). After awakening for the second treatment dose, subjects resumed sleeping more easily when the prior treatments were evening or night zopiclone doses ($p = 0.0001$ and 0.0030, respectively) or zaleplon 10 or 20 mg immediately beforehand ($p = 0.0148$ and 0.0021, respectively). Subjects also indicated that they slept better during the second segment following either early or late zopiclone doses and immediately following both zaleplon doses ($p \leq 0.0001$). The evening administrations of zaleplon had no effects on the second segment as compared to placebo. Subjective ease of awakening showed a nearly significant overall treatment effect in the middle of the night ($F_{6,156} = 2.07$; $p = 0.0600$) and a significant effect in the morning ($F_{6,156} = 3.41$; $p = 0.0034$). Subjects judged it harder to wake up after zopiclone than after placebo. In the middle of the night, the

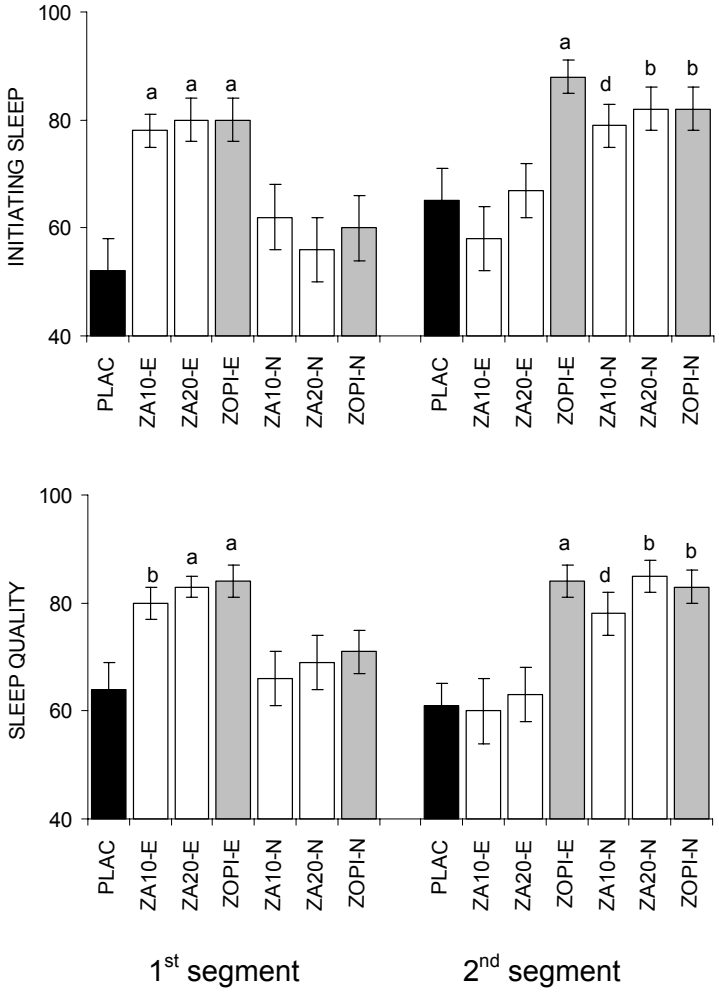

Figure 5.1 Subjective ease to initiate sleep and sleep quality in both segments of the night in each treatment condition. Significant drug-placebo differences are indicated by: [a] $p < 0.0010$; [b] $p < 0.0100$; [c] $p < 0.0125$; [d] $p < 0.0166$; [e] $p < 0.0250$; [f] $p < 0.0500$.

difference was not significant according Bonferroni criteria (p = 0.0112, ≤ 0.0083), yet, in the morning it was (p = 0.0002; figure 5.2, top).

Response times to wake-up calls were skewed so all data were transformed into natural log (ln) values to permit analyzing. Figure 5.2 (bottom) shows antilog retransformation yielding geometric means. There were significant overall treatment effects in the middle of the night ($F_{6,156} = 3.77$; $p = 0.0016$) and in the morning ($F_{6,154} = 2.95$; $p = 0.0093$). In the middle of the night, it took subjects significantly longer to respond to the phone after zopiclone in the evening ($p < 0.0001$) than after placebo. Mean RT was also longer after zaleplon 20 mg, but not significantly after Bonferroni

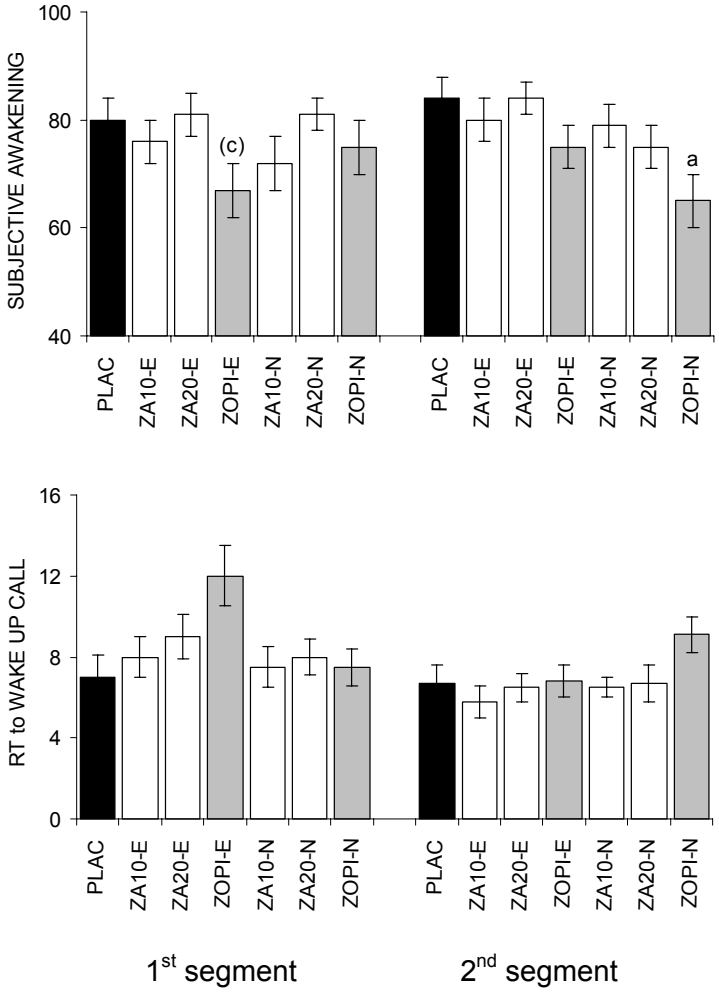

Figure 5.2 Subjective subjective and objective ease to awaken after both segments of the night in each treatment condition. Significant drug-placebo differences are indicated by: [a] $p < 0.0010$; [b] $p < 0.0100$; [c] $p < 0.0125$; [d] $p < 0.0166$; [e] $p < 0.0250$; [f] $p < 0.0500$. Drug-placebo differences with $p < 0.05$, but nonsignificant according to sequential Bonferroni criteria are indicated between brackets.

correction ($p = 0.0328$, $\alpha = 0.0100$). In the morning, mean RT was longer after the middle-of-the-night dose of zopiclone than after placebo, but not significantly after Bonferroni correction ($p = 0.0159$, $\alpha = 0.0083$)

Table 5.1 Overall Treatment Effect and mean ± SE of mood and performance parameters in the laboratory tests in each treatment condition. Significance of drug-placebo differences are indicated by [a] $p < 0.0010$; [b] $p < 0.0100$; [c] $p < 0.0125$; [d] $p < 0.0166$; [e] $p < 0.0250$; [f] $p < 0.0500$ (significant according to Bonferroni criteria); Drug-placebo differences with $p < 0.05$, but not significant according to sequential Bonferroni criteria are indicated between brackets ([1] df = 6,155;)

	Effect of Treatment								
	$F_{6,156}$	p	*PLAC*	$ZA10_E$	$ZA20_E$	$ZOPI_E$	$ZA10_N$	$ZA20_N$	$ZOPI_N$
Subjective mood scale									
alertness	4.25	.0005	77± 3	77 ± 4	77 ± 4	74 ± 4	73 ± 3	71 ± 4	63 ± 5[a]
contentedness	1.99	.0708	81 ± 3	80 ± 3	84 ± 3	86 ± 2	79 ± 3	82 ± 3	78 ± 4
calmness	1.56	.1616	82 ± 3	79 ± 4	80 ± 3	85 ± 2	82 ± 3	84 ± 2	85 ± 3
Body sway test									
POS-L1 (mm)	4.09	.0008	195 ± 2	198 ± 2	198 ± 2	197 ± 3	194 ± 2	195 ± 3	214 ± 8[a]
POS-S1 (mm^2)	4.67	.0002	42 ± 4	45 ± 4	49 ± 5	54 ± 6	43 ± 3	47 ± 5	80 ± 17[a]
POS-L2 (mm)	4.24	.0006	205 ± 3	202 ± 4	201 ± 3	206 ± 5	204 ± 4	203 ± 4	219 ± 7[a]
POS-S2 (mm^2)	3.91	.0012	44 ± 3	40 ± 3	46 ± 6	53 ± 7	45 ± 5	48 ± 5	72 ± 18[a]
Word learning test									
WLT-IR (#)	3.46	.0031	13.4 ± 3	13.1 ±.3	13.3 ±.3	12.7 ±.3	12.7 ±.4	12.7 ±.4	11.9 ±.5[a]
WLT-DR (#)	8.74	.0000	8.4 ± 6	8.0 ±.7	8.6 ±.6	7.0 ±.6[c]	7.0 ±.8[d]	6.9 ±.7[b]	5.4 ±.7[a]
WLT-RR (%)	6.47	.0000	62 ± 4	61 ± 5	65 ± 4	54 ± 4	55 ± 6	52 ± 5[*]	43 ± 5[a]
WLT-RS (#)	6.80[1]	.0000	27.5 ± 5	27.3 ±.5	27.4 ±.5	26.9 ±.5	26.6 ±.5	26.5 ±.5[*]	24.7 ±.7[a]
WLT-RT (ms)	8.09[1]	.0000	805 ± 33	770 ± 28	781 ± 27	836 ± 38	806 ± 28	799 ± 25	935 ± 43[a]
Spatial memory test									
SMT-IC (mm)	9.80	.0000	6.69 ± 52	6.86 ±.49	6.36 ±.49	7.30 ±.63	6.90 ±.53	6.89 ±.57	9.29 ±.66[a]
SMT-SL (mm/s)	1.56	.1625	.99± 11	.95 ±.10	1.05 ±.12	1.16 ±.15	0.93 ±.09	1.13 ±.12	1.21 ±.16
Semantic verification test									
SVT-RT (ms)	5.01	.0001	750± 29	758 ± 33	757 ± 27	782 ± 26	751 ± 27	731 ± 25	835 ± 31[a]
Syntactic reasoning test									
SRT-RT (ms)	5.80	.0000	1594 ± 100	1666 ± 98	1652 ± 86	1767 ± 112[(f)]	1712 ± 29	1708 ± 121	2028 ± 152[a]

Mood, body sway and memory performance

Table 5.1 lists the mean ± SE values and indicates the significance of overall treatment effects and separate drug placebo differences for each parameter measured in the laboratory performance tests and subjective mood ratings. Forty-five minutes after arising, subjects rated their alertness differently in the various conditions. In particular, it was lower (p = 0.0001) in ZOPI$_N$ than PLAC. Otherwise there were no significant mean differences in alertness between drug and placebo conditions and also none in contentedness and calmness.

The evening doses of zaleplon 10 and 20 mg had no effects that differed significantly from placebo's. The evening zopiclone dose significantly impaired delayed recall in the Word Learning test (p = 0.0109). It also slowed response speed in the Syntactic Reasoning test, but not significantly after Bonferroni correction (p = 0.0412, α= 0.0100).

Middle-of-the-night administration of zaleplon 10 mg was devoid of significant effects, except for significant impairment of delayed recall (p = 0.0131). Given at this time, zaleplon 20 mg did the same (p = 0.0061). The effect on recognition, a related measure in the same test, was not significant after Bonferroni correction (p = 0.0466, α = 0.0100). In contrast, the middle-of-the-night administration of zopiclone significantly affected body sway ($p \leq 0.0010$) and practically every memory parameter ($p \leq 0.0001$).

Driving performance

Seven driving tests (3.6% out of 196 comprising the complete data set) were terminated before scheduled completion because the driving instructor (in 5 tests) or the subject (in 2 tests) judged that it would be unsafe to continue. The instructors terminated four rides in ZOPI$_N$ and one in ZOPI$_E$. One subject stopped the ride in ZOPI$_E$, and another in ZA20$_N$. SDLP scores for these rides were adjusted according to a planned, last-value-carried-forward procedure. That is, data collected during the last 5 km segment before stopping were inserted for each of the unfinished segments.

Figure 5.3 presents mean ± SE SDLP values recorded after every treatment. The overall treatment effect was highly significant ($F_{6,156}$ = 33.91; $p < 0.0001$). This was mainly attributable to zopiclone's residual effects which differed significantly between PLAC and both ZOPI$_E$ and ZOPI$_N$ ($F_{6,156}$ = 36.03 & 100.83; $p < 0.0001$). Zopiclone 7.5 mg

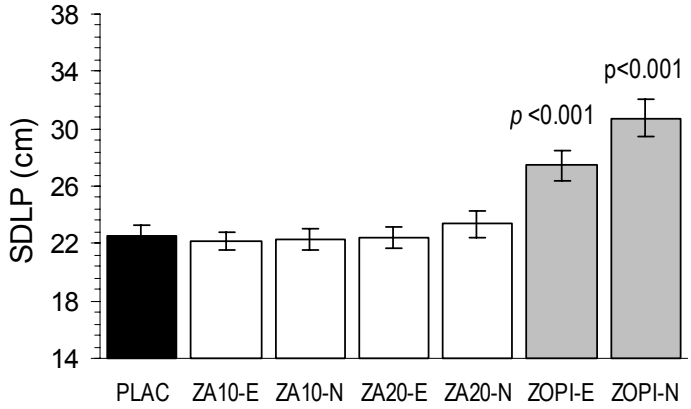

Figure 5.3 Mean ±SE SDLP in each treatment condition. Indicated are significant drug-placebo differences.

administered in the evening produced a 5.0 cm rise in mean SDLP, and in the middle of the night, an 8.25 cm rise. In contrast, no zaleplon dose significantly affected SDLP, neither 10-11 nor 5-6 hours after administration ($F_{6,156} < 1$).

Subjects drove with a mean ± SE SD speed of 93.6 ± 2.2 km/hr. Differences in mean SDSP followed the same pattern as SDLP. There was a significant overall treatment effect ($F_{6,156}= 2.82$; $p = 0.0123$), reflecting a significantly higher SDSP in $ZOPI_N$ than in PLAC ($p= 0.0058$). The rise in SDSP in $ZOPI_E$ was not significant ($p = 0.0574$). There was no significant effect of zaleplon on SDSP.

The driving instructors discriminated significantly between treatment effects on both the subjects' driving quality ($F_{6,156}= 7.09$; $p < 0.0001$) and their appearance of being sedated ($F_{6,156}= 11.62$; $p < 0.0001$). They judged the subjects' driving quality to be similarly good after placebo and all zaleplon treatments, but significantly worse in $ZOPI_N$ ($p = 0.0001$). The difference in $ZOPI_E$ was not significant ($p = 0.0625$). Accordingly, the instructors rated subjects as appearing significantly more sedated in $ZOPI_N$ ($p < 0.0001$) than in PLAC. The difference in $ZOPI_E$ is not significant after Bonferroni correction ($p = 0.0181$, $\alpha= 0.0100$). The instructors failed to discriminate any significant differences between the subjects' appearance after placebo and the zaleplon treatments.

DISCUSSION

The results of the driving test are the most relevant with respect to the drugs' safety after being taken in late-night doses. The effects of zaleplon 10 mg on the subjects' driving performance were not discernibly different from those of placebo, regardless of the time of administration. The effects of zaleplon 20 mg were likewise not significantly different from those of placebo. One subject chose to terminate a test when it was half completed after taking zaleplon 20 mg 5 hours earlier, because he had difficulties in trying to visually focus on the road and other traffic. However, his SDLP, recorded until the time of stopping, was exceptionally low (14.3 cm), indicating no objective loss of vehicular control.

Zopiclone's effects on driving performance were adverse. Even when the drug was administered 10 hours before the test, it produced a mean 5.0 cm rise in SDLP from the level recorded after placebo. That effect is equivalent to the mean change shown by 24 "social drinkers" who undertook the test while having a blood alcohol concentration of about 1.0 mg/ml (Louwerens et al., 1987). The effect of zopiclone 7.5 mg on SDLP in the present study was greater in magnitude than that produced by the same drug and dose in an earlier study employing the same standardized test (Volkerts and O'Hanlon, 1988). In that case, zopiclone 7.5 mg produced a significant 2.5 cm mean rise in SDLP above the placebo level. However, subjects in that study were tested after the second consecutive nightly dose and may have begun to develop tolerance for the drug's residual sedating effects. Zopiclone's effects on driving performance were far worse after late-night administration. Subjects then drove with a mean SDLP that was 8.25 cm higher than their placebo level. Five (18%) of the subjects had to stop the test after driving with SDLPs above the established normal limit, i.e., 35 cm. Clearly it would be inadvisable to take zopiclone 7.5 mg 5 hours and, arguably, even 10 hours before attempting to operate a motor vehicle. The same seems true for any equipotent hypnotic possessing the same or a slower rate of elimination.

The amnestic effects of zopiclone were obvious 3.75-4.5 hours after middle-of-the-night administration. They were significant in all four memory tests. Middle-of-the-night doses of both zaleplon 10 and 20- mg impaired delayed recall, but early doses of zaleplon had no significant effects, while the early zopiclone dose still impaired this parameter 11.5 hours after its administration. Zopiclone's amnestic effects were expected. Previous studies have shown them in volunteers who were tested 4-6 hours after 7.5 mg

doses (Subhan and Hindmarch, 1984b; Griffiths et al., 1986; Warrot et al., 1987). To our knowledge, however, only one other study has previously found that these effects persist for as long as 11 hours (Fossen et al., 1983). Zaleplon's amnestic effects after middle-of-the-night administration were dose-dependent, but much smaller than those of zopiclone and anticipated on the basis of earlier results from Allen et al. (1993).

When taken 3.75-4.5 hours before testing, zopiclone dramatically increased body sway, though no effects were seen when it was taken between 8.75-9.5 hours before. This confirms previous findings by Allain et al. (1995), showing peak impairment of postural balance at 4.05 hours following the ingestion of zopiclone 7.5 mg in 16 healthy young males. The effect diminished but was still significant at 7.05 hours after administration; it had returned to the placebo level at 10.05 hours after administration. In the present study, zaleplon 10 and 20 mg administered in the middle of the night had no effects on body sway, neither with eyes open nor with eyes closed. Generalizations from the effects of hypnotics in young healthy volunteers to those occurring in geriatric patients should be made cautiously. Nonetheless, our findings suggest that zaleplon might be safer than other hypnotics in current use by the elderly, specifically because zaleplon causes less, or in any case shorter periods of, postural instability. That consequence of chronic hypnotic medication has been shown to increase the risk of hip fracture from falling in geriatric patients (Ray, 1992).

The volunteers' sleep ratings were surprisingly sensitive to differences among the drug and placebo effects and entirely consistent with the drugs' pharmacokinetic profiles and their times of administration. Zaleplon and zopiclone's effects on initiation of sleep in the evening and sleep quality during the first part of the night were essentially the same. They differed, however, when subjects were awakened by the telephone call in the middle of the night. Though awakening after prior treatment with zaleplon 10 or 20 mg was judged to be as easy as following placebo, after zopiclone it was rated slightly, but not significantly, more difficult. The subjects' impressions of zopiclone were confirmed by the time it took them to answer the wake-up call: this drug significantly retarded their responses.

Middle-of-the-night administration of all drugs, as well as evening administration of zopiclone, facilitated resumption of sleep and promoted better sleep quality during the second part of the night than placebo. The evening administration of zaleplon neither hastened nor retarded further sleep nor affected sleep quality relative to placebo alone. These results imply that the earlier hypnotic effects of zaleplon had dissipated, while

zopiclone's persisted after the first wake-up call. They also show that there were no middle of the night rebound effects after zaleplon's hypnotic activity had waned. This could be an important finding because other short-acting hypnotics, in particular triazolam, seem to produce rebound activation responsible for early-morning insomnia (Kales et al., 1983a).

Again, the drugs' differential effects became apparent upon final awakening. Zopiclone administered 3 hours before arising significantly increased the subjects' difficulty in awakening, subjectively, though not objectively, and it reduced their feelings of alertness. On the other hand, zaleplon administered at the same time had no effects on awakening and alertness that differed from placebo's.

In conclusion, the results of this study show that zaleplon 10 mg, certainly, and 20 mg, probably, can be taken up to 5 hours before driving with little risk of serious impairment. It seems like zaleplon is the first hypnotic that can safely be used in middle of the night by young adults, if needed, even when their activities over the next day include driving.

Chapter 6

Differential residual effects of zaleplon and zopiclone on actual driving: a comparison with a low dose of alcohol

Pubished as:

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ABSTRACT

Study Objectives: To compare residual effects of zaleplon 10 mg, zopiclone 7.5 mg, and placebo, and a social dose of alcohol on car driving, memory, and psychomotor performance.

Design: Two-part placebo controlled, crossover study. Part 1 was single blind, Part 2 double blind.

Setting: University research institute.

Participants: Thirty healthy volunteers (15 men and 15 women, mean age 32 ± 7 years)

Interventions: In Part 1 alcohol and alcohol-placebo drinks were administered around noon. In Part 2 single oral doses of zaleplon 10 mg, zopiclone 7.5 mg and placebo were administered at bedtime.

Measurement and Results: A highway driving test, laboratory tests of word learning, critical tracking and divided attention, and subjective assessments of sleep, mood and effects of treatments on driving. Driving started 40 minutes after a second alcohol dose in Part 1, and 10 hours after drug intake in Part 2. The results demonstrated that alcohol, at average plasma concentrations of approximately 0.30 g/L, significantly impaired performance in all tests. Zaleplon's residual effects did not differ significantly from those of placebo in any test. In contrast, zopiclone had significant residual effects on driving, divided attention and memory. The magnitude of impairment in the driving test observed the morning after zopiclone 7.5 mg was twice that observed with alcohol.

Conclusion: Zaleplon 10 mg has no residual effects on driving when taken at bedtime, 10 hours before driving. In contrast, zopiclone 7.5 mg can cause marked residual impairment. Patients should be advised to avoid driving the morning after zopiclone administration.

INTRODUCTION

Residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration is one of the main problems associated with the use of hypnotics. This poses a crucial problem for users of hypnotics who must operate vehicles. Epidemiological studies have shown that the use of benzodiazepine (BZ) hypnotics, as well as zopiclone is associated with increased risk of injurious car accidents

(Barbone et al., 1998). Risks increased relatively more if the patient was young, male, used a higher dose of a particular drug, or used a drug with a longer elimination half-life (Neutel, 1998).

Zaleplon is a new pyrazolopyrimidine hypnotic, characterized by a rapid elimination half-life of approximately 1 hour (for a review Dooley and Plosker, 2000). Peak plasma concentrations are reached within 0.5 to 1.1 hours after single oral doses (Beer et al., 1994; Greenblatt et al., 1998; Rosen et al., 1999). Zaleplon is extensively metabolized by aldehyde oxidase and CYP3A4 pathways to pharmacologically inactive metabolites, 5-oxo-zaleplon and 5-oxo-N-desethylzaleplon, which are excreted in urine (Vanover et al., 1994). Zaleplon, like zolpidem, preferentially binds to $GABA_A$/BZ type-1 ($\alpha 1\beta j\gamma 2$) receptors, whereas benzodiazepines and the cyclopyrrolone zopiclone bind nonselectively to type 1 and type 2 receptors (Damgen and Luddens, 1999). In animal models, zaleplon produced sedative, anxiolytic, myorelaxant and anticonvulsive effects. However, like zolpidem, zaleplon displays weaker anxiolytic-like activity than that displayed by nonselective hypnotics such as triazolam and zopiclone (Griebel et al., 1998; Griebel et al., 1996; Sanger et al., 1996). Clinical trials have shown that zaleplon is effective in the treatment of sleep onset insomnia (Elie et al., 1999; Walsh et al., 2000). The recommended hypnotic dose is 10 mg for adults.

Zaleplon's pharmacokinetic profile predicts a very short duration of sedative activity and an absence of impairing effects on driving performance the day after bedtime administration. Three studies were conducted to assess the effects of zaleplon on performance of healthy volunteers after evening or middle-of-the-night administration. In a previous study we compared the residual effects of zaleplon 10 and 20 mg with zopiclone 7.5 mg and placebo on performance in a standard highway driving test and in a battery of conventional psychomotor and memory tests (Vermeeren et al., 1998a). Results showed that zaleplon taken in the evening or during a scheduled awakening in the middle of the night (i.e., 10 or 5 hours before the driving test, respectively) had no residual effects on driving, regardless of dose and time of administration. The only significant effects measured after zaleplon administration were minor impairments of delayed recall following middle-of-the-night administration of both doses. Danjou et al. (Danjou et al., 1999) administered zaleplon 10 mg as little as 2 hours before arising at 8 a.m. and assessed performance within the first hour after awakening. The tests used were digit symbol substitution, choice reaction time, memory scanning and immediate and delayed recall of a list of 20 words. Results showed no significant differences between zaleplon

and placebo. Finally, Troy et al. (2000) tested their subjects during a scheduled awakening in the beginning of the night and upon arising in the morning, 1:15 and 8:15 hours respectively, after bedtime administration of zaleplon 10 and 20 mg. At 1:15 hours after administration, the high dose significantly affected digit symbol substitution, divided attention, immediate and delayed free recall and paired associate learning, whereas performance after the therapeutic dose did not differ from that after placebo. In the morning both doses had slight, yet significant, residual effects on delayed free recall, but no residual effects on performance were seen in any of the other tests.

These results strongly suggest that zaleplon can be taken safely at bedtime, or even later in the night, without the risk of memory or psychomotor impairment the next morning. However, before concluding that zaleplon 10 mg is safe enough for unsupervised use by individual patients who drive, more supporting evidence is required. According to methodological guidelines for experimental research on medicinal drugs affecting driving performance, studies assessing a drug's effects on driving performance should include a verum, i.e., a drug-dose for which the effects on driving are known, to interpret the degree of impairment obtained in various tests (ICADTS 1999; Vermeeren et al., 1993). The recommended verum is alcohol in a dose sufficient to raise blood alcohol concentrations (BACs) to 0.5 g/L.

Ideally, effects of alcohol and drugs on performance should be assessed at the same times of day, since there may be circadian variation in performance or pharmacokinetics. However, for the present study this meant that alcohol should be consumed very early in the morning, which was not considered an appropriate time for normal volunteers and as such not a valid assessment. It was therefore decided to assess the effects of alcohol on a later time of day than those of the hypnotics.

The objectives of the present study were primarily to replicate our previous finding that zaleplon, taken in the recommended dose of 10 mg at bedtime, has no residual effects the next morning on car driving performance, memory or psychomotor skills related to driving. The secondary objective was to compare the residual effects of zaleplon 10 mg and zopiclone 7.5 mg with those of alcohol at a peak BAC of 0.5 g/L on the same tests and in the same subjects.

METHODS

Subjects

Thirty volunteers, 15 men and 15 women, between 21 and 45 years of age, were recruited through newspaper advertisements. Inclusion criteria were good health and driving experience of more than 5,000 km per year over the preceding three years. Volunteers were screened with a medical history questionnaire and a physical examination, including a 12-lead electrocardiogram, blood chemistry and hematology, and urinary tests for β-human chorionic gonadotropin and drugs of abuse (opiates, amphetamines, cocaine, cannabis, benzodiazepines and barbiturates). Volunteers who met any of the following exclusion criteria could not participate in the study: pregnancy or lactation; history or presence of any clinically significant physical or mental disorders, primary insomnia, alcoholism, or drug abuse; acute illness; use of systemic medication except oral contraceptives within the previous two weeks; participation in any other clinical trial within the previous three months; weight beyond +20% according to body mass index; or excessive consumption of caffeine (more than 5 cups per day) or nicotine (more than 10 cigarettes per day).

No drugs or systemic medications except oral contraceptives, aspirin and acetaminophen, could be taken from two weeks before treatments until the end of the study. Use of alcohol was prohibited for 24 hours before and throughout each treatment period. Caffeine was prohibited on test days. Smoking was prohibited from 30 minutes before and throughout testing.

Mean ± SD age of the subjects was 31.6 ± 6.9 years. Mean ± SD height and weight were 183 ± 8 cm and 80 ± 11 kg, respectively, for men, and 169 ± 4 cm and 60 ± 6 kg, respectively, for women. All were light to moderate social drinkers, reporting an average weekly alcohol consumption of 5.9 ± 5.6 units (one unit corresponding to a glass of wine or beer). Three subjects were smokers.

The study was conducted in accordance with the Declaration of Helsinki and its amendments. The protocol and informed consent form were approved by the Ethics Review Committee of Maastricht University. Written informed consent was obtained from each subject before enrollment.

Study design and drug/alcohol administration

This placebo- and active-drug-controlled study was composed of two parts. Part 1 was a

single-blind, two-period, crossover study to evaluate the effects of a single dose of alcohol and alcohol-placebo, administered in the afternoon, on subjects' psychomotor, memory and driving performance. Part 2 was a double-blind, three-period, crossover study to evaluate the residual effects of single bedtime doses of zaleplon 10 mg, zopiclone 7.5 mg and placebo on psychomotor, memory and driving performance the next morning in the same subjects. Treatment periods were separated by a washout of at least 6 days. Treatment orders were balanced within both parts of the study. Six sequences of 5 treatments were made, using combinations of two orders in Part 1 and two 3x3 Latin squares in Part 2. Sequences were randomly assigned to subjects. All treatments were ingested in the presence of an investigator.

In Part 1, alcohol and alcohol-placebo were administered in the afternoon. Alcohol dosing was designed to obtain and sustain a BAC just under the legal limit for driving which is 0.5 g/L. This required subjects to drink an initial alcohol dose of 0.43 or 0.36 g/kg for men or women, respectively. A second, adjustable dose was administered following BAC measurement at the end of psychometric testing. Adjustable doses were between 30% and 50% of the initial dose for obtaining the desired BAC during the driving test. Alcohol treatment consisted of pure ethanol (99.8%) mixed with orange juice to a volume of 500 ml for the initial dose, and 250 ml for the second. Orange juice was flavored with Grand Marnier essence to serve as a taste mask. For the alcohol-placebo, subjects were given the same volumes of Grand Marnier flavored orange juice at the same times. Subjects had to consume the initial dose within 15 minutes and the second within 5 minutes while wearing a nose clip.

In Part 2, subjects ingested two gelatin capsules immediately before they retired for sleep in the evening. Treatments were zaleplon 10 mg, zopiclone 7.5 mg and placebo. Subjects were tested upon arising the next morning.

Procedure

Subjects were individually trained to perform all tests, including driving, in two practice sessions before participation in the first treatment period. Subjects' eligibility was verified in each treatment period upon their arrival at the Institute. Subjects were questioned about adverse events and the use of any systemic medication since their last visit. Vital signs were recorded and urine was assayed for the presence of cannabinoids. Pregnancy tests were performed for all women.

In Part 1, subjects fasted from 3 hours before to 40 minutes after ingestion of the first dose of alcohol or alcohol-placebo. Four subjects were treated and tested on the same day. Subjects proceeded in two pairs separated by a 1:15 hours interval. The first pair was given their initial alcohol dose at 11:45 a.m. From the start of ingestion, a period of 45 minutes was allowed for the alcohol to be fully absorbed. After this delay, subjects' BAC was estimated with a breath analyzer (Lion SD-400, Lion Laboratories Ltd., Barry, UK) and they were given a light meal (two low-fat sandwiches). Psychometric tests (word learning, critical tracking and divided attention) were administered between 12:35 and 1:15 p.m. Upon conclusion of the tests, BAC was measured again and subjects were given an adjustable dose of alcohol or alcohol-placebo. Thereafter they were transported to the start of the highway-driving test, which was conducted, between 2 and 3 p.m., i.e., between 40 and 100 minutes after the second alcohol dose. BACs were measured immediately before and after the driving test.

In the week separating Parts 1 and 2, subjects were habituated to sleeping for one night in the same residence facilities of the Institute where they would sleep during periods 3 to 5 (Part 2). The purpose of habituation was to overcome possible first-night sleep disturbances associated with sleeping in an unfamiliar environment. Four subjects whose sleep was disturbed were allowed a second habituation night on which all managed to sleep normally.

In Part 2, four subjects were treated on the same night and tested on the following day. Pairs proceeded with a one hour difference between their activities. The first pair arrived at 9 p.m. and retired to bed at 10:30 p.m. after ingestion of their medication. They were awakened 8 hours later and served a standardized breakfast. Word learning, critical tracking and divided attention tests were performed from 7:15 to 8 a.m. and the driving test from 8:30 to 9:30 a.m., i.e., 10 to 11 hours after receiving medication.

Assessments

The Driving Test was standardized in 1984 and has been applied for assessing drugs in more than 60 separate studies (Riedel et al., 1998). The subject drives a specially instrumented car over a 100-km (61 mile) primary highway circuit. A licensed driving instructor having access to dual controls accompanies him or her. The subject's task is to maintain a constant speed of 95 km/h (58 miles per hour) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. During the test the vehicle's speed and lateral position relative to the left lane delineation are continuously

recorded by systems described previously (O'Hanlon et al., 1982). These signals are edited off-line to remove data recorded during overtaking manoeuvres or disturbances caused by roadway or traffic situations. The remainder is then reduced to yield the Standard Deviation of Lateral Position (SDLP, in cm) and Standard Deviation of Speed (SDS, in km/h) for each successive 5-km segment and, as the square root of pooled variance over all segments, for the test as a whole. SDLP is the primary performance parameter. It is an index of road-tracking error or "weaving" and is a reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is $r = 0.85$. It has also proven sensitive to many sedating drugs and BACs as low as 0.35 g/L (Vuurman et al., 1996).

The Word Learning Test (Rey 1964) starts with sequential presentation of 15 common monosyllabic nouns. Each word is shown on a computer display for 2 seconds, and the subject is required to read it aloud. When the series ends, the subject is required to verbally recall as many words as possible. The same list is presented in the same way in five successive trials. The number of words correctly recalled is scored for each trial. The highest individual trial score is the Immediate Recall score. After a 30-minute delay, subjects are asked again to recall as many words as possible without prompting. The number correctly recalled is the Delayed Recall score. To correct for a failure in initial acquisition, delayed recall is also scored as a percentage of immediate recall, i.e., Relative Recall. Finally, the subjects are shown a series of 30 words on the computer display that included words from the original set and 15 new words. Subjects respond to each presentation by indicating as quickly as possible whether the given word is one of the original set. The number and speed of correct responses are recorded as the Recognition Score and Recognition Time (in ms), respectively.

The Critical Tracking Test (Jex et al., 1966) measures the ability to control an unstable error signal in a first-order compensatory tracking task. Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency of cursor deviations at which the subject loses control is the critical frequency. The final score (in rad/s) is determined from the average of all but the lowest and the highest scores in five trials.

The Divided Attention Test (Moskowitz 1973) measures the ability to divide attention between two tasks performed simultaneously. In one task, the subject performs the same tracking test described above but at a constant level of difficulty set at 50% of

his or her maximum capacity. In the other task, the subject monitors 24 peripheral displays in which single digits change asynchronously at 5-second intervals. The occurrence of the digit "2" is a signal for the subject to remove the foot from a pedal as rapidly as possible. Signals occur twice at every location, in random order, at intervals of 5 to 25 seconds. Mean Tracking Error (in mm) and average Reaction Time (in ms) are the performance measures.

The psychometric tests were administered in the following order in each period: immediate recall of the word list, critical tracking, divided attention, and finally delayed recall and recognition of the word list.

Subjective evaluations of sleep, mood and drug effects on driving performance were assessed using a series of visual analogue scales (100 mm). These assessments were used as exploratory measures. In the break between divided attention and delayed recall, subjects completed a 16-item mood scale from which three factors are derived: alertness, contentedness and calmness (Bond and Lader, 1974). Immediately before driving, the subjects indicated their anticipated degree of driving impairment, and upon conclusion of the test, both the subjects and the instructors rated the quality of the subjects' driving performance. The instructors also rated the subjects' apparent degree of drowsiness during the test. Additionally, after waking in Part 2, subjects estimated their sleep latency, frequency of nocturnal awakenings and sleep duration the preceding night. Finally, the subjects were asked what treatment they believed they had received at the end of each session, to check the treatment manipulations.

Statistical analysis

Performance parameters from Parts 1 and 2 of the study were analyzed separately, by using univariate repeated measures analysis of variance. The model included Subject as a random factor, and Period and Treatment as fixed factors. In Part 2, the overall Treatment effect was further analyzed, regardless of significance, by two drug-placebo contrasts with a standard Bonferroni adjustment, accepting significance at the $p < 0.025$ level.

RESULTS

Alcohol doses and BACs

In Part 1 of the study, mean ± SD adjustable alcohol dose administered after the laboratory tests was 0.16 ± 0.03 g/kg for both men and women, i.e., 36% and 44% of the initial dose, respectively. Mean (± SD) BAC declined from 0.40 ± 0.07 to 0.31 ± 0.03 g/L during psychometric testing, and from 0.37 ± 0.08 to 0.24 ± 0.08 g/L during the driving test. Mean BACs of the men were slightly, but not significantly, higher than those of the women. Twenty-eight (93%) subjects correctly indicated which drink they had received on each occasion, indicating that the alcohol conditions had not been effectively blinded.

Driving

The results of 150 driving tests were included in the complete data set: 5 (3.3%) of these were terminated prematurely for safety reasons by either the subjects or instructors. In Part 1 of the study two tests were terminated by the subjects and one test was terminated by the instructor after the subjects were administered alcohol. In addition, one test was terminated by the instructor after the subject was administered alcohol-placebo. In Part 2 the instructor terminated one test after zopiclone administration. Standard Deviation of Lateral Position (SDLP) values were adjusted for the early terminations by a planned last-value-carried-forward procedure; i.e., data collected during the last 5 km before the test was stopped were inserted for each of the unfinished segments.

In Part 1, mean ± SEM SDLP scores after alcohol-placebo and alcohol consumption were 17.7 ± 0.5 and 19.4 ± 0.7 cm, respectively (figure 6.1). Analysis showed that alcohol significantly impaired driving performance compared with alcohol-placebo ($F_{1,28}$ = 12.65, p = 0.001). The estimated mean ± SEM difference in SDLP was 1.7 (± 0.5) cm. In Part 2, mean ± SEM SDLP scores measured the morning after bedtime administration of placebo, zaleplon 10 mg and zopiclone 7.5 mg were 18.2 ± 0.5, 18.9 ± 0.6 and 21.6 ± 0.8 cm, respectively (figure 6.1). Analysis showed that the overall Treatment effect was highly significant ($F_{2,56}$ = 27.28, p < 0.001). Pairwise comparisons showed that this was due to zopiclone's residual effects being significantly different from those of both placebo and zaleplon (p < 0.001). The estimated mean (± SEM) difference in SDLP between zopiclone and placebo was 3.4 (± 0.5) cm , whereas it was only 0.7 (±

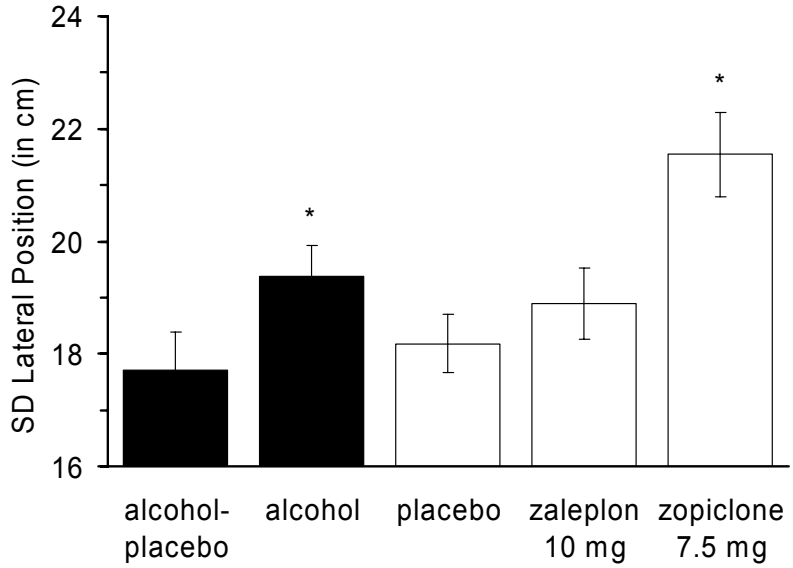

Figure 6.1 Mean (±SEM) Standard Deviation of Lateral Position (SDLP in cm) in the driving test in each treatment condition separately. Indicated are significant differences between active drugs and their respective placebo's (* $p < 0.001$).

0.5) cm between zaleplon and placebo (p = 0.143). Post hoc, a paired t-test comparing drug-placebo difference scores calculated for each subject showed that the mean the difference scores between zopiclone and placebo were significantly greater than that those between alcohol and alcohol-placebo ($t_{29} = -2.51$, $p = 0.018$),.

Though mean SDS scores showed a similar pattern of effects with alcohol, zopiclone and zaleplon, the differences from placebo were not significant ($F_{1,28} = 3.46$, $p = 0.073$, and $F_{2,56} = 1.98$, $p = 0.147$).

Word learning

Table 6.1 lists the mean ± SEM for performance measures in the word learning test and indicates the significant pairwise comparisons. Alcohol significantly impaired performance compared with alcohol-placebo in the word learning test. It significantly decreased delayed recall ($F_{1,28} = 10.23$, $p = 0.003$) and slowed reaction times in the recognition part of the test ($F_{1,28} = 4.45$, $p = 0.044$). Effects of alcohol on immediate recall, relative recall and recognition scores were in the expected direction, but were not

Table 6.1. Mean ±SEM of performance parameters in the word learning test for each treatment condition. Significant differences between active drugs and placebo are indicated as *** $p < 0.005$; ** $p < 0.025$; * $p < 0.05$.

	Immediate Recall (nr correct) Mean ± SEM	*Delayed Recall (nr correct)* Mean ± SEM	*Relative Recall (%)* Mean ± SEM	*Recognition (nr correct)* Mean ± SEM	*Recognition Speed (ms)* Mean ± SEM
Alcohol-placebo	12.8 ± 0.3	10.6 ± 0.5	82 ± 3	28.7 ± 0.3	810 ± 33
Alcohol	12.2 ± 0.3	9.4 ± 0.6 ***	76 ± 4	28.3 ± 0.3	853 ± 35 *
Placebo	13.8 ± 0.2	11.4 ± 0.6	82 ± 4	28.6 ± 0.3	793 ± 32
Zaleplon 10 mg	13.7 ± 0.2	11.3 ± 0.5	82 ± 3	28.7 ± 0.3	763 ± 27
Zopiclone 7.5 mg	12.7 ± 0.3 ***	9.5 ± 0.6 ***	74 ± 4 **	27.7 ± 0.4 **	868 ± 33 **

significantly different from those of alcohol-placebo ($F_{1,28}$ = 3.84, 4.41 and 1.75, p = 0.060, 0.051 and 0.196, respectively). In Part 2 of the study, overall Treatment effects were significant for all measurements ($F_{2,56} > 4.37$, $p \leq 0.017$), due to zopiclone's amnesic effects. Both immediate and delayed recall scores were significantly lower with zopiclone than with placebo or zaleplon ($p \leq 0.001$). Relative recall, recognition scores and recognition time were also significantly impaired by zopiclone as compared with placebo or zaleplon ($p \leq 0.021$). There were no significant differences between the effects of zaleplon and placebo on performance in the word learning test.

Critical tracking and divided attention

Table 6.2 lists the mean ± SEM for performance measures in the critical tracking and divided attention tests and indicates the significant pairwise comparisons. Alcohol significantly affected critical tracking performance ($F_{1,28}$ = 12.14, p = 0.002) as well as tracking error and reaction time in the divided attention test ($F_{1,28}$ = 20.26 and 16.17, respectively, $p < 0.001$). In Part 2 of the study, the overall Treatment effect was significant for tracking performance in the divided attention test ($F_{2,56}$ = 16.48, $p < 0.001$), but not for reaction time ($F_{2,56}$ = 2.75, p = 0.072) or critical tracking performance ($F_{2,56}$ = 2.45, p = 0.096). Drug-placebo comparisons showed that

Table 6.2 Mean ± SEM of performance parameters in the critical tracking and the divided attention tests test for each treatment condition. Significant differences between active drugs and placebo are indicated as *** $p < 0.005$

	Critical Tracking Test		*Divided Attention Test*	
	Critical Frequency (rad/s)		*Subcritical Tracking Error (mm)*	*Target Detection (ms)*
	Mean ±	*SEM*	*Mean* ± *SEM*	*Mean* ± *SEM*
Alcohol-placebo	3.81 ±	0.13	19.5 ± 1.0	1771 ± 53
Alcohol	3.61 ±	0.12 ***	21.6 ± 0.9 ***	1898 ± 60 ***
Placebo	3.81 ±	0.11	18.8 ± 0.9	1777 ± 66
Zaleplon 10 mg	3.89 ±	0.11	18.5 ± 0.9	1806 ± 78
Zopiclone 7.5 mg	3.74 ±	0.12	21.6 ± 0.9***	1897 ± 63

zopiclone significantly increased tracking error in the divided attention test ($p = 0.001$). Though the effects of zopiclone on reaction times were in the expected direction, they were not significant after Bonferroni correction ($p = 0.029$, $\alpha = 0.025$). There were no significant differences between the effects of zaleplon and placebo on performance in the critical tracking or divided attention tests.

Placebo and placebo-alcohol

Performance after placebo treatments was similar in Parts 1 and 2: none of the parameters showed a significant difference, and correlations were high, i.e., between 0.6 and 0.8 ($p \leq 0.001$), except for the recognition score, where $r = 0.4$ ($p = 0.033$). This suggests that performance in the tests used did not change significantly due to different times of day for testing in Part 1 and 2.

Subjective assessments

In Part 1, subjective assessments of driving performance were missing occasionally due to initial failures in completing the forms. Subjects rated their alertness and contentedness after alcohol intake as significantly less than that after alcohol-placebo ($F_{1,28} = 15.12$ and 5.40, $p = 0.001$ and 0.028, respectively) and they anticipated that alcohol would impair

their driving performance more than alcohol-placebo ($F_{1,25}$ = 7.54, p = 0.011). In contrast, the subjects did not evaluate the residual effects of zaleplon or zopiclone on mood or driving performance significantly different from placebo. Though they felt, on average, less alert after zopiclone, the difference from placebo was not significant after Bonferroni correction (p = 0.034, α = 0.025). In retrospect, subjects did not rate their driving to have been different from placebo after the administration of alcohol, zopiclone or zaleplon.

The driving instructors rated subjects as appearing significantly more sedated after alcohol ($F_{1,25}$ = 13.54, p = 0.001) and zopiclone (p = 0.019) administration than after alcohol-placebo and placebo, respectively. Though the instructors average rating of sedation with zaleplon was also higher than that with placebo, the difference was not significant after Bonferroni's correction (p = 0.029, α = 0.025). Treatment effects on subjects' driving quality were not rated significantly different

In Part 2 of the study, the subjects' evaluations of their sleep differed significantly between treatments. After placebo, zaleplon and zopiclone administration, they estimated their mean sleep latencies were 31, 19 and 18 minutes, respectively ($F_{2,56}$ = 6.72, p = 0.002); their mean number of awakenings 2.0, 1.9 and 0.7, respectively ($F_{2,56}$ = 6.03, p = 0.004); and their mean total sleep time 6.8, 7.1 and 7.4 hours, respectively ($F_{2,56}$ = 8.11, p = 0.001). Pairwise comparisons showed that after zopiclone administration, subjects' estimates of sleep latency were significantly shorter, number of awakenings were fewer, and total sleep times were longer as compared with placebo ($p \leq 0.005$). After zaleplon administration, only their estimates of sleep latency were significantly shorter than after placebo (p = 0.005). When asked whether they believed they had received an active hypnotic, 69% of the subjects responded positively after zopiclone administration versus 31% and 33% after placebo and zaleplon administration, respectively.

DISCUSSION

The results of this study support previous findings that zaleplon 10 mg taken at bedtime does not impair memory and driving performance the next morning (Vermeeren et al., 1998b). In addition, zaleplon was shown to be devoid of residual effects on critical tracking performance and divided attention. There were no significant differences between zaleplon 10 mg and placebo in residual effects on any of the tests used in the

present study, whereas the effects of zopiclone 7.5 mg and alcohol in most tests were significantly worse than those of their respective placebo's. The difference in residual effects between zaleplon and zopiclone is most likely due to pharmacokinetic factors. In contrast to zaleplon, whose elimination half-life is 1 hour, zopiclone's elimination half-life is longer, approximately 5 hours (Noble et al., 1998).

Zopiclone significantly affected driving, memory, and divided attention, but not critical tracking in the morning, 10 hours after bedtime administration. The results of the driving test are most relevant with respect to the drug's potentially hazardous effects on traffic safety. Mean SDLP was 3.4 cm greater with zopiclone than with placebo, whereas the mean difference in SDLP between alcohol-placebo and alcohol was 1.7 cm in subjects with an average BAC of 0.3 g/L (declining from 0.37 to 0.24 g/L). The effects of these BACs on SDLP correspond to that predicted from a dose-response curve established by Louwerens et al. (1987), indicating that the present group of subjects demonstrated normal sensitivity to the effects of a low dose of alcohol on driving.

The effects of zopiclone on sleep, memory and psychomotor performance in this study agree with those in previous reports (Griffiths et al., 1986; Julou et al., 1983) that the drug exhibits a pharmacological spectrum of activity that resembles that of benzodiazepines, yet with weaker muscle relaxant properties, as indicated by the lack of effect on critical tracking. Zopiclone clearly possesses residual amnestic effects, as shown by its impairment of immediate and delayed recall and at speed and accuracy of recognition in the word learning test. These effects were expected since we found the same in our previous study (Vermeeren et al., 1998b). However, at that time, only one other published study reported that zopiclone's amnestic effects persisted for as long as 11 hours (Fossen et al., 1983).

Previous studies of zopiclone's residual effects using laboratory tests of memory and psychomotor performance showed inconsistent results. A number of them demonstrated significant impairments (e.g., Lader and Denney, 1983), whereas others failed to detect any differences from placebo (e.g., Mamelak et al., 1987). In contrast, studies employing the same standardized highway-driving test used in this study invariably showed significant residual effects of zopiclone 7.5 mg on driving performance (this study; Vermeeren et al., 1998b; Volkerts and O'Hanlon, 1988). In a review of the studies published up to 1995, O'Hanlon (1995) explained the discrepancy as due to the use of small sample sizes or insensitive procedures, as indicated by simultaneous lack of effect of a positive control in most studies that reported no significant residual effects of zopiclone

7.5 mg. Our results support this conclusion. Moreover, results from a recent epidemiological study (Barbone et al., 1998) support the validity of results from experimental driving studies. Barbone et al. (1998) collected data from 19386 drivers in the United Kingdom involved in a first road-traffic accident, of which 1731 were users of a psychoactive prescription drug. These drugs included tricyclic antidepressants, selective serotonin reuptake inhibitors, benzodiazepines and zopiclone. Analyses showed that the odds having a road-traffic accident after use of zopiclone was 4 times that of having an accident when not using a psychoactive drug.

Alcohol, in mean blood concentrations between 0.24 and 0.40 g/L, had significant effects on driving, memory, critical tracking and divided attention, providing further evidence that social doses of alcohol can cause significant impairment in cognitive functioning and psychomotor skills to the extent that driving performance is compromised (Ferrara et al., 1994; Koelega 1995). Impairments observed in the critical tracking and divided attention tests are consistent with results from other studies showing that alcohol has adverse effects on perceptual motor control and attentional shifting (Jaaskelainen et al., 1999). Alcohol's effects on driving and memory were generally less marked than those of zopiclone. This finding may be related to the doses administered in this study. However, alcohol significantly impaired critical tracking, whereas zopiclone did not, supporting other findings that psychomotor performance is generally less resilient to the effects of alcohol than is cognitive functioning (Hindmarch et al., 1992).

Subjective evaluations of sleep showed that even though subjects were normal sleepers, they were sensitive to differences in the hypnotic effects of zaleplon, zopiclone and placebo. Results were consistent with each drug's pharmacokinetic profile; zaleplon shortened the time to sleep onset, whereas zopiclone also reduced nocturnal awakening and prolonged total sleep time, reflecting its longer duration of action. The finding that zaleplon had more effect on sleep onset than sleep maintenance, is consistent with results of clinical trials indicating that zaleplon 10 mg is particularly effective in the treatment of sleep onset insomnia (Walsh et al., 2000). Zopiclone's more pronounced sedative-hypnotic effects are also reflected by the finding that most subjects seemed aware of having received an active hypnotic after administration of zopiclone, but not zaleplon.

Subjects did not feel significantly less alert in the morning after zopiclone than after placebo. This could explain why they did not anticipate that the drug would impair their driving. In contrast, after the consumption of alcohol, they felt less alert and accordingly anticipated an impairment of their driving performance. However, subjective

feeling of alertness seemed not a good predictor of driving impairment, since contrary to the subjects' expectations the residual effects of zopiclone on driving were more impairing than the effects of alcohol. The underestimation of the effects of zopiclone might be due to a relative lack of knowledge. Most people are well informed about and are familiar with the adverse effects of alcohol, whereas they know relatively little about the residual effects of hypnotics. Our subjects did not believe that their driving would be affected after zopiclone, even though most of them were aware of having received an active hypnotic and were informed of the possible effects on driving by the written informed consent form. This clearly demonstrates the need for more explicit and adequate warning of patients about the potentially hazardous effects of drugs on driving performance.

In conclusion, the results of this study and the previous one (Vermeeren et al., 1998b) consistently demonstrate that zaleplon 10 mg does not impair performance in a highwayn over-the-road driving test 10 hours after bedtime administration. Moreover, results of these studies and others (Allen et al., 1993; Danjou et al., 1999; Troy et al., 2000) suggest that zaleplon 10 mg is unlikely to produce severe effects on patients' memory and psychomotor performance more than 3 hours after administration, due to its remarkably short elimination half-life. In contrast, zopiclone 7.5 mg taken at bedtime causes marked impairment of driving the next morning, 10 hours after intake. We therefore support Nicholson's (1998) recommendation that zopiclone 7.5 mg should be avoided by those patients whose activity the next morning involves skilled work and in whom impairment of performance, such as driving a car, could be a danger to themselves or others.

Chapter 7

Residual effects on actual car driving of evening dosing of chlorpheniramine 8 and 12 mg when used with terfenadine 60 mg in the morning

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ABSTRACT

The study was conducted according to a 4-way, observer- and subject-blind, cross-over design. Its purpose was to compare the repeated dose effects on actual driving performance of the following: the combination of chlorpheniramine 8 and 12 mg, in sustained release formulations, administered at bedtime and terfenadine 60 mg the following morning; flurazepam 30 mg at bedtime and placebo the following morning; and, placebo at both times. Subjects were 24 healthy female volunteers. Drug effects were assessed in two driving tests (Highway Driving and Car-Following) in the morning of the third treatment day. Results show no significant differences in driving performance between both chlorpheniramine/terfenadine treatments and placebo. Flurazepam significantly impaired driving in both tests.

INTRODUCTION

H1 receptor antagonists or antihistamines are widely used for treating a variety of allergic disorders. The older, first-generation antihistamines, such as diphenhydramine, triprolidine, hydroxizine or chlorpheniramine, are efficacious but lipophilic and readily cross the blood brain barrier to penetrate the CNS. There they block histaminergic neurotransmission which plays a major role in sustaining wakefulness (Lin et al., 1996). Consequently they produce sedation and associated performance impairment. Regulatory warnings concerning these effects are therefore applied to all first-generation antihistamines. Newer, second-generation antihistamines, such as cetirizine, loratadine, terfenadine and fexofenadine, are less lipophilic and therefore penetrate the brain more slowly. They are better tolerated than their predecessors and relatively nonsedating when given in recommended, therapeutic doses. Consequently patients prefer these so-called "nonsedating" antihistamines. However owing to their recency, they are more expensive than older antihistamines on the basis of comparable daily dosing costs. Health maintenance organizations and their participating physicians are aware of the similar efficacies of old and new antihistamines but also of the differences in their respective costs and side-effects. In an effort to comply with their patients' wishes but at the same time avoid the full costs of the new antihistamines, a unique dosing regimen is being used. It involves an alternating p.m./a.m. combination of sedating and nonsedating

antihistamines, the former to be taken at bedtime and the latter upon arising. The respective drugs are chlorpheniramine 8 or 12 mg, in sustained release formulations, and terfenadine 60 mg.

Though chlorpheniramine is generally not considered to be a highly sedating antihistamine, it does possess a long elimination half-life (ca 30 hours). The possibility therefore exists that its brain concentration the morning following nocturnal dosing will be high enough to cause residual sedation and performance impairment. There are hardly any published data concerning the duration of such effects after single and repeated doses of chlorpheniramine. An early study by Hindmarch and Parrot (1978) showed that chlorpheniramine 4 mg t.i.d. had significant residual effects on the morning of the fifth day of treatment: as compared to baseline, subjects had more difficulty awakening, felt less alert and their critical flicker/fusion frequency threshold was lowered, indicating slower information processing.

This study was designed to determine whether the combinations of chlorpheniramine 8 and 12 mg (sustained release formulations) administered at bedtime followed by terfenadine 60 mg the next morning have residual sedative effects capable of impairing performance at times when patients can be expected to engage in potentially dangerous activities such as car driving. Therefore the effects of chlorpheniramine/ terfenadine treatments were measured in two driving tests conducted in actual traffic, and compared with those of placebo and flurazepam 30 mg, a hypnotic previously shown to exert severe residual effects on driving (Volkerts and O'Hanlon, 1985; Brookhuis et al., 1990). Subjects were all women, since results from previous studies suggest that they have smaller safety margins than men with respect to the impairing effects of antihistamines on driving performance (Robbe and O'Hanlon, 1990; Ramaekers et al., 1992b; Volkerts et al., 1992b; Ramaekers and O'Hanlon, 1994; Vuurman et al., 1994).

METHODS

Subjects

Twenty-four healthy female volunteers, aged 22 to 45 years, were recruited via newspaper advertisements. Subjects were screened by a medical history questionnaire and in a physical examination. The latter included a 12-lead electrocardiogram, blood chemistry and hematology assessments, and urinalysis for β-HCG and drugs of abuse. Exclusion

criteria included pregnancy; any history or current evidence of severe gastrointestinal, hepatic, renal, cardiovascular (QTc > 400 ms), neurological or mental disorders, alcohol or drug abuse; requirement for chronic use of systemic medication except oral contraceptives; excessive smoking (> 10 cigarettes/day) or consumption of caffeine-containing beverages (> 5 cups/day). All subjects possessed a driving license and drove at least 5,000 kilometer per year for the previous three years. They agreed not to use any drugs of abuse or oral medication, except contraceptives, for one week prior to and during treatments. Subjects were prohibited from consuming alcohol for 24 hours before treatments. On test days, their consumption of caffeine containing beverages was limited to one cup of tea at breakfast. Smoking was prohibited for at least 30 minutes prior to, and during testing. Subjects were treated in accordance with the Declaration of Helsinki and all its amendments through Hong Kong, 1989. The study was approved by the standing Ethics Review Committee of Maastricht University.

One subject dropped out after the second treatment period for reasons unrelated to treatment. A total of 23 completed the study. Their mean ± SD age was 29.0 ± 6.1 years, and their mean ± SD heights and weights were 170 ± 6 cm and 64.5 ± 6.6 kg.

Design

Drugs and placebo were administered according to a 4-way, observer- and subject-blind, cross-over design. The four treatments were: chlorpheniramine 8 mg at bedtime followed by terfenadine 60 mg in the morning; chlorpheniramine 12 mg at bedtime followed by terfenadine 60 mg in the morning; flurazepam 30 mg at bedtime followed by placebo in the morning; and, placebo at both times. Treatments started on the evening of day 1 and ended on the morning of day 3. Half of the subjects received drugs and placebo at 9.30 p.m. and 7.00 a.m., and half at 11.00 p.m. and 8.30 a.m. Driving tests were undertaken on day 3 of each treatment period, beginning 30 minutes after the last morning dose i.e. 10 hours after their last evening dose. Treatment orders were balanced and assigned to subjects by exhaustive, random selection of 24 possible permutations of the four treatment conditions. Washout periods were at least 12 days.

Study drugs were supplied in commercially available formulations: chlorpheniramine as Chlor-Trimeton® Repetabs, timed release allergy tablets, 8 and 12 mg; terfenadine as Seldane® (Triludan®) 60 mg capsules, and flurazepam as Dalmane® (Dalmadorm®) 30 mg capsules. Placebo was provided in capsules. A study nurse, responsible for drug administration, was the only person with access to the randomization

code. She was unblinded to each subject's treatment at the time of dosing. Subjects closed their eyes before the nurse placed the appropriate medication at their tongue, to avoid identification of treatments by color of respective tablets and capsules. The nurse did not communicate the nature of the treatments to the subjects or the investigators during the data collection phase.

Procedures

Subjects were individually trained to perform both driving tests before the first treatment period. Subsets of four subjects received the first treatment dose on Thursday or Friday night, and the final treatment dose on the morning of Saturday or Sunday, respectively. On the latter days, beginning 30 minutes after the last morning dose, subjects performed two driving tests. Each treatment period, subjects slept in a residence facility on both nights prior to day 3. In the evening of day 1 two pairs of subjects were transported to this facility and retired to bed at 10 or 11.30 p.m., i.e. 30 minutes after the first treatment dose. They were awakened exactly 8 hours later and after administration of the morning medication they were transported to their homes. That evening they were transported to this facility again and treated in the same manner as the night before. After morning doses on day 3, subjects were transported to the origin of the driving tests which started at 7.30 or 9.00 a.m., i.e. 10 hours after the second evening dose. Half the subjects started with a highway driving test, and the other half with a car-following test. Each subject followed the same order of tests through all treatment periods. After finishing the tests subjects were transported home.

Highway Driving Test

The highway driving test was originally developed during the 1970's for driver fatigue research in the USA. It was standardized for drug screening purposes in 1982 and it has been used in more than 50 separate studies for measuring drug effects on driving performance (O'Hanlon and Ramaekers, 1995; O'Hanlon et al., 1995). The subject drives a specially instrumented car over a 100 kilometer (61 miles) primary highway circuit. She is accompanied by a licensed driving instructor, having access to dual controls. The subject's task is to maintain a constant speed of 95 kilometers (58 miles) per hour and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle's speed and lateral position relative to the left lane delineation are continuously recorded. These signals are digitally sampled at 4 Hz and edited, off-line, to remove data

recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remainder is then reduced to yield the standard deviation of lateral position (SDLP in cm) and standard deviation of speed (SDSP in km/h) for each successive 5-kilometer segment, and as the square-root of pooled variance over all segments, for the test as a whole. The primary variable is SDLP, an index of road tracking error or "weaving". It is a very reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is r = 0.85. It has also proven sensitive to many sedating agents including alcohol in blood concentrations as low as 0.35 g/L (Ramaekers et al., 1992b; Vuurman et al., 1994; Vermeeren and O'Hanlon, 1998).

Car-Following Test

In this test two vehicles travel in tandem over a 25 kilometer section of a 2-lane, undivided, secondary highway at 95 kilometer (58 miles) per hour. An investigator drives the leading car and the subject, in the second car, is instructed to follow at a distance between 25 and 35 meter. Subjects are further instructed to constantly attend the leading car since it may slow down or speed up at unpredictable times. They are required to follow the leading car's speed movements, i.e. maintain the initial headway by matching the velocity of her car to the other's. During the test, the speed of the leading car is automatically controlled by a modified "cruise control" system. At the beginning it is set to maintain a constant speed of 95 kilometer per hour and, by activating a microprocessor, the investigator can start sinusoidal speed changes reaching an amplitude of -10 or -20 kilometer per hour and returning to the starting level of 95 kilometer per hour within 50 seconds. This maneuver is repeated 10-12 times. The leading car's speed and signals indicating the beginning of the maneuver are transmitted via telemetry to be recorded in the following vehicle together with the following vehicle's speed. Phase-delay converted to a measure of the subject's average reaction time to the movement of the leading vehicle (RT) was taken as the primary dependent variable in this test. Headway was recorded by a laser distance sensor and served as a control variable. Earlier and similar versions of this test have been applied in previous studies and were shown sensitive to the effects of antihistamines and anxiolytics (Ramaekers and O'Hanlon, 1994; Ramaekers et al., 1995; O'Hanlon et al., 1995).

Statistical analysis

SDLP, SDSP and RT were analyzed preliminary using analysis of variance (ANOVA) with Subject, Period, Treatment and first-order Carryover as factors. Failure to detect a significant Carryover effect caused the analysis to be repeated without it. Five planned mean pair comparisons were accomplished by t-tests using pooled error variance for the three drugs versus placebo and each of the two antihistamine combinations versus flurazepam. All statistical tests were conducted using SAS (version 6.09).

RESULTS

Failure to complete the driving tests

Two subjects were stopped by the driving instructor during the Highway Driving Test after treatment with flurazepam. These subjects had been driving with SDLP's exceeding the normal limit (i.e. 35 cm) and were on the verge of falling asleep when the decision to terminate the test occurred. Both subjects had successfully finished the Car-Following Test prior to the Highway-Driving Test.

Highway Driving

Figure 7.1 presents mean ± SE Standard Deviations of Lateral Position (SDLP) recorded in every treatment condition. Preliminary analysis revealed no significant Period effect ($p = 0.4783$), a highly significant Treatment effect ($p < 0.0001$), but also a nearly significant Carryover effect ($p = 0.0504$). ANOVA after dropping Carryover showed a highly significant Treatment effect ($F_{3,63} = 39.33$; $p < 0.0001$). Mean pair comparisons showed that this was due to a severely impairing effect of flurazepam. SDLP was significantly increased following flurazepam as compared to placebo and both chlorpheniramine/terfenadine treatments ($F(1,63) = 87.75$, 67.91 and 78.39; all $p < 0.001$). Differences between both chlorpheniramine/terfenadine treatments and placebo were not significant ($F(1,63) = 1.27$ and 0.26; $p = 0.2641$ and 0.6094, for 8 and 12 mg, respectively).

The indication of a Carryover effect from analysis of data obtained in a cross-over study is always ambiguous and often spurious owing to the confounding of that factor with the effects of Treatment, Period and their interaction (Senn, 1993). The indication in

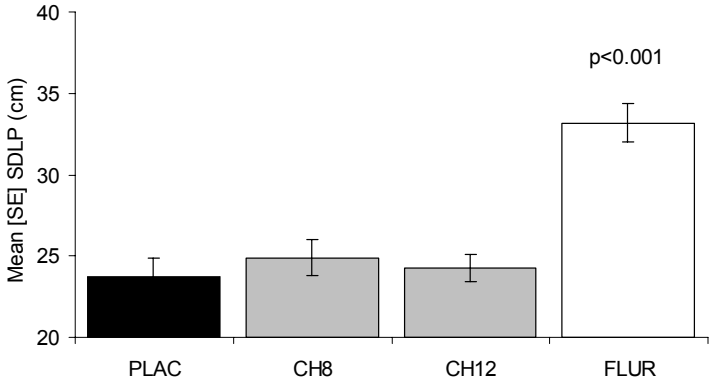

Figure 7.1 Mean ±SE Standard Deviation of Lateral Position (SDLP) in the Highway Driving Test for placebo (PLAC), chlorpheniramine 8 mg/ terfenadine 60 mg (CH8), chlorpheniramine 12 mg/terfenadine 60 mg (CH12), and flurazepam 30 mg (FLUR) treatment. Indicated are significant drug-placebo contrasts.

this case was examined in two ways. The first was simply to inspect the mean SDLP values recorded in all conditions combined after the following preceding treatments: none, placebo, chlorpheniramine 8 and 12 mg and flurazepam. These means ± SE were 24.9 ± 1.0 (n = 23), 28.6 ± 1.6 (n = 18), 27.4 ± 1.3 (n = 17), 29.2 ± 1.9 (n = 17) and 23.0 ± 1.3 (n = 17), respectively. They clearly show that mean SDLP was lowest when the preceding treatment was flurazepam, next lowest following 'none', and much higher following both chlorpheniramine doses and placebo. Interpretation of these findings is reserved for the discussion. The second approach was to reanalyze the data without Carryover, but including the Treatment by Period interaction. If a robust Carryover effect were present, it should make both the main effect of Period and the Treatment by Period interaction significant. This is because the absence of carryover effect in the first period would make the data there different from those in all subsequent periods, where the effect is present; and, the effect of the treatment causing the carryover would be constant over periods, whereas the effects of the others would vary depending on whether they precede or follow the treatment causing carryover. The results of this analysis showed neither a significant Period effect ($p = 0.0910$) nor a significant Treatment by Period interaction ($p = 0.4171$), but again a highly significant Treatment effect ($p < 0.0001$). The data entering this analysis are represented by mean and SE values in table 7.1.

Table 7.1 Mean SDLP (SE and N) for treatments, periods, and treatments by periods separately

Treatment		*Period*				
		1	*2*	*3*	*4*	*All*
placebo	Mean	21.6	23.3	25.9	24.2	23.7
	SE	1.5	2.9	2.3	2.7	1.2
	N	6	6	6	5	23
chlorpheniramine 8 mg /terfenadine 60 mg	Mean	23.2	25.3	24.0	27.0	24.9
	SE	1.9	2.2	2.0	2.6	1.1
	N	6	6	5	6	23
chlorpheniramine 12 mg /terfenadine 60 mg	Mean	26.3	23.3	22.1	25.3	24.3
	SE	2.0	1.8	1.2	1.4	0.8
	N	6	5	6	6	23
flurazepam 30 mg	Mean	29.1	35.0	34.1	34.0	33.2
	SE	1.8	3.3	2.3	1.6	1.2
	N	5	6	6	6	23
Total	Mean	24.9	26.9	26.6	27.8	
	SE	1.0	1.6	1.4	1.3	
	N	23	23	23	23	

Mean Standard Deviations of Speed (SDSP) were 2.43, 2.51, 2.41 and 2.78 kilometer per hour (all SE = 0.10) following placebo, chlorpheniramine 8 mg/terfenadine, chlorpheniramine 12 mg/terfenadine, and flurazepam, respectively. Preliminary analysis revealed no significant Period or Carryover effects (p = 0.3548 and 0.7039, respectively). ANOVA after dropping Carryover showed a significant Treatment effect ($F_{3,63}$ = 4.42; p = 0.0069). Mean pair comparisons revealed that this was due to a significant increase in speed variability following flurazepam. SDSP was significantly increased following flurazepam as compared to placebo and both chlorpheniramine/terfenadine treatments ($F_{1,63}$ = 9.67, 5.34 and 10.13; p = 0.0028, 0.0241 and 0.0023, respectively). Differences between both chlorpheniramine/terfenadine treatments and placebo were not significant (both $F < 1$).

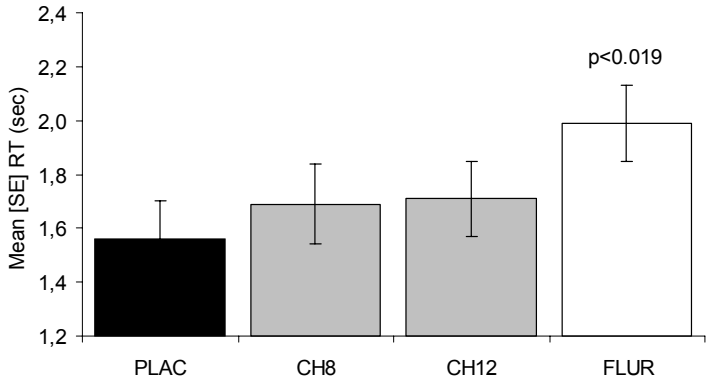

Figure 7.2 Mean ±SE Reaction Time in the car-following test for placebo (PLAC), chlorpheniramine 8 mg/ terfenadine (CH8), chlorpheniramine 12 mg/terfenadine (CH12), and flurazepam (FLUR) treatment. Indicated are significant drug-placebo contrasts.

Car-following

Mean ± SE Reaction Times in the car-following test were 1.56 ± 0.14, 1.68 ± 0.15, 1.71 ± 0.14 and 1.99 ± 0.14 seconds following placebo, chlorpheniramine 8 mg/terfenadine, chlorpheniramine 12 mg/terfenadine, and flurazepam, respectively (figure 7.2). Preliminary analysis revealed no significant Period, Treatment and Carryover effects (p = 0.2733, 0.1404 and 0.4492, respectively). ANOVA after dropping the Carryover showed a significant Period effect ($F_{3,63}$ = 4.71, p = 0.0050) but no significant Treatment effect ($F_{3,63}$ = 2.05, p = 0.1160). Mean pair comparisons, however, showed that RT was significantly increased following flurazepam as compared to placebo ($F_{1,63}$ = 5.78; p = 0.0191), but not as compared to both chlorpheniramine/terfenadine treatments (F = 2.74 and 2.53; p= 0.1027 and 0.1170, for 8 and 12 mg, respectively). The differences between both chlorpheniramine/terfenadine treatments and placebo were not significant (both F < 1).

DISCUSSION

Residual effects of flurazepam

The residual effects of flurazepam on highway driving performance confirmed previous results obtained by Volkerts and O'Hanlon (1985) using the same methodology and study

procedures. In their study, evening doses of flurazepam 30 mg produced an increment in mean SDLP of about 7 cm relative to placebo, when tested in the morning between 10-11 hours after drug administration, in a group of 24 women who had previously used hypnotics for the treatment of subjective insomnia. Though some improvement occurred over the day, subjects' performance was still markedly impaired in a repetition of the test, between 16-17 hours after drug administration. In the present study, flurazepam's effect on subject's driving performance was only assessed in the morning, between 10-11.5 hours after drug administration. Compared to placebo it produced a significant change in mean SDLP of about 9.5 cm. This is among the largest mean changes seen in over 60 studies performed in The Netherlands for measuring the effects of anxiolytics, hypnotics, antidepressants and antihistamines on driving performance. Some of these drugs, such as triazolam 0.5 mg, lorazepam 0.5 mg t.i.d., and mianserin 10 mg t.i.d., were found to produce severe driving impairment in healthy volunteers as indicated by a mean change in SDLP between 6 and 8 cm (Riedel et al., 1988; O'Hanlon et al., 1995; Ramaekers et al., 1992a). A comparable rise in mean SDLP of nearly 9 cm was found in a study by Louwerens et al. (1987) for blood alcohol concentrations of 1.2 g/L in a group of female "social drinkers". The residual effects of flurazepam on driving performance in the Car-Following Test have never been assessed before. As it turned out, flurazapam significantly increased mean RT to speed change maneuvers of the leading vehicle by 0.43 seconds. This finding supports the results obtained in the Highway Driving Test and was largely expected given the long half-life of flurazepam's active metabolite, N-desalkylflurazepam (i.e. between 50 and 100 hours).

It is clear from the current results that subjects using flurazepam should be informed about its potentially dangerous effects on driving the morning after nocturnal intake and even be advised to avoid operating any vehicle, or hazardous machinery during treatment until tolerance to the sedative action of flurazepam is complete. It is known from epidemiological research (Neutel, 1995) that patients receiving a prescription for a hypnotic (i.e. flurazepam and triazolam) are at increased risk of becoming involved in an injurious traffic accident within 4 weeks after their first prescription. Patients drove with a risk that was 9 times higher than that of unmedicated controls during the first week after their prescription were filled. After 4 weeks the relative risk had decreased to a value of 3.

The indication of a Carryover effect on SDLP from results of the preliminary analysis was judged spurious. That indication was clearly attributable to the enormous flurazepam effect, but in exactly the opposite way that might have been the most likely

pharmacological Carryover effect; the slow elimination of flurazepam's metabolite, N-desalkylflurazepam, causing residual effects extending throughout washout periods and into the next treatment period. Yet, mean SDLP was lowest in periods following flurazepam, indicating best average driving performance. The reason is simply that none of the treatments administered in those periods i.e. placebo and both chlorpheniramine doses, produced comparable impairing effects. The next lowest mean SDLP was measured in the first period, when there was no preceding treatment, wherein less than a quarter (5 out of 23) received flurazepam. Highest mean SDLPs were measured following both chlorpheniramine and placebo treatments, wherein more than one third (6 out of 17 or 18) received flurazepam. Moreover, there were no significant effects of either Period or Treatment by Period on SDLP, which presumably would have been the case in the presence of a robust Carryover effect.

Residual effects of chlorpheniramine

It was anticipated that administration of chlorpheniramine 8 and 12 mg at bedtime would affect the volunteers' driving performance the next morning. This expectation was mainly based on the fact that its elimination half-life is long enough to sustain its pharmacological activity for a considerable period. The failure of the chlorpheniramine/terfenadine combinations to impair performance in any of the driving test was therefore unexpected.

Results from a study by Lee et al. (1988) suggest that the use of sustained release formulations may have attenuated chlorpheniramine's suspected residual effects. These investigators assessed the effects of single doses of prolonged release formulations of dimenthindene 2.5 mg and chlorpheniramine 12 mg on a battery of physiological, performance and subjective measures in a crossover study with 12 healthy volunteers. Subjects were tested before, and at 2, 4, 6 and 8 h after drug administration. Effects were complex and often marginal, Yet, the authors' conclusion is that 'sustained release preparations seem a useful advance on standard formulations with respect to obviating central sedative effects and are preferable when sedation is unacceptable'.

Further explanation may come from a study by Roehrs et al. (1993) on the interaction of sleep and performance effects of triazolam and diphenhydramine in healthy volunteers. Though both drugs initially impaired performance, only triazolam continued to do so after a 60-minute nap. The nap reversed diphenhydramine's effects on performance. These data indicate that diphenhydramine specifically activates sleep

mechanisms that may be reversed by a nap, whereas triazolam induces a non-specific, global reduction in arousal unrelated to sleep. In the current study, sleeping periods might have reversed chlorpheniramine's suspected effects on driving in a similar way. The mechanism by which it occurs is still largely unknown, but might be mediated by restoring the balance between histamine release and synthesis. Histamine release (without reuptake) is highest during waking and decreases abruptly with the onset of sleep (Schwartz et al., 1994). If histamine availability at the postsynaptic H1 receptors is greatest shortly after awakening, antihistamines would be less likely to block histaminergic transmission at this time than others.

The results of this study seem to contradict those recently reported by Kay et al. (1997). They administered the same two chlorpheniramine/terfenadine regimens to parallel groups of healthy volunteers, and placebo to a third, for 4 nights and days, all preceded by a placebo baseline night and day. Residual sedation was assessed by the Stanford Sleepiness Scale and in the Multiple Sleep Latency Test (MSLT), on days following the first and fourth bedtime doses (days 2 and 5, respectively). Subjective estimates of sleepiness and mean latencies to stage 1 sleep in the MSLT showed significant differences between drugs and placebo groups on both days. Mean sleep latencies on the baseline day and days 2 and 5 were for the placebo group 9.2, 10.9 and 10.8 minutes; for the chlorpheniramine 8 mg group 7.4, 6.3 and 10.0 minutes; and, for the chlorpheniramine 12 mg group 8.4, 6.9 and 8.1 minutes, respectively. These data indicate that there was already a small, though nonsignificant, difference between groups on the baseline day. Moreover, examination of changes from baseline over days within each chlorpheniramine group show that 8 and 12 mg doses decreased sleep latencies the day following the first dose, but these residual effects seem to have disappeared after 4 consecutive nights of treatment. Mean sleep latencies on day 5 have returned to or exceeded baseline values in the chlorpheniramine groups. So some tolerance seems to develop between the first and the fourth dose of treatment. This may partly explain the disparity between Kay et al. results and our own. If tolerance develops rapidly, chlorpheniramine's residual effects following the first and second consecutive doses, can be expected to wane. In addition, it is by no means certain that the MSLT and driving tests measure the same thing. Instructions to the subjects in the MSLT are to attempt to fall asleep in an environment conducive to its occurrence. Obviously this is not the case for the driving tests. Doubtless the MSLT is extremely sensitive to drug induced increases in daytime sleepiness, but it can not indicate whether the degree of daytime sleepiness is

sufficient to offset the stimulating effects of a normal environment and overcome compensatory effort to avoid the consequences of performance failures in performing potentially dangerous tasks such as driving. For the moment the best resolution of the apparent conflict between the two studies results is to assume validity of both. Evening dosing of chlorpheniramine 8 and 12 mg can have effects on daytime sleepiness the next morning that are visible in the MSLT, particularly following the first dose. Quite possibly these effects would degrade performance in intrinsically unstimulating tasks. However, they do not seem sufficient to impair performance in more arousing tasks resembling those employed in the present study. Whether patients following these alternating chlorpheniramine/terfenadine dosing regimens would ever experience residual sedation to the point of compromising their driving safety can only be answered by further research.

In conclusion, the results of this study confirm that flurazepam severely impairs driving performance the morning after bedtime administration. This drug constitutes an important traffic safety hazard and its users should be warned accordingly. Chlorpheniramine 8 and 12 mg administered at bedtime did not affect performance in any of the driving tests the next morning and seems safe for use in combination with a morning dose of terfenadine or, by implication, any other equally nonsedating antihistamine.

Chapter 8

Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance

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ABSTRACT

Background: Fexofenadine is the hydrochloride salt of terfenadine's active metabolite.
Objective: The drug's effects on performance were assessed in this study for the purpose of determining its safety of use by patients who engage in potentially dangerous activities, especially car driving.
Methods: Fexofenadine was administered in daily doses of 120 mg or 240 mg, each in single and divided units given over 5 days. Clemastine 2 mg b.i.d. and placebo were given in similar series. Twenty-four healthy volunteers (12 male, 12 female, aged 21-45 y) participated in a double blind 6-way crossover study. Psychomotor tests (critical tracking, choice reaction time and sustained attention) and a standardized actual driving test were undertaken between 1.5-4 hours post a.m. dosing on days 1, 4 and 5 of each series. On day 5, subjects were challenged with a moderate alcohol dose prior to testing.
Results: Fexofenadine did not impair driving performance. On the contrary, driving performance was consistently better during twice daily treatment with 120 mg fexofenadine 120 mg than during treatment with placebo, significantly so on day 4. Both of the 240 mg/day regimens significantly attenuated alcohol's adverse effect on driving on day 5. Effects in psychomotor tests were not significant, with the exception of the critical tracking test in which the first single doses of fexofenadine, 120 and 240 mg, had significantly impairing effects.
Conclusion: It was concluded that fexofenadine has no effect on performance after being taken in the recommended dosage of 60 mg b.i.d.

INTRODUCTION

Fexofenadine was recently approved by the FDA in the dosage of 60 mg b.i.d. for the indication of seasonal allergic rhinitis. Its structure is identical to terfenadine's active metabolite, except that fexofenadine is the hydrochloride salt. Fexofenadine is a selective H1-receptor antagonist, and it is not known to possess any other clinically relevant pharmacological activity after normal doses (HMR, 1995). Following oral administration it is rapidly absorbed, with t*max* occurring within 1 to 2 hours (Lippert et al., 1995). Elimination half-life ranges from 13 to 16 hours. Single oral doses of 40 mg, and above, achieve more than 80% maximum inhibition of both wheal and flare. The

pharmacological effect starts 1-2 hours post dose and is sustained over a period of 24 hours (Day et al., 1996). Fexofenadine has been administered to human volunteers in repeated doses up to 690 mg twice daily for 28.5 days. It was well tolerated and produced no serious side effects. Clinical trials demonstrated effective treatment of modest to severe symptoms of ragweed or fall seasonal allergic rhinitis between 60 and 240 mg b.i.d. (Bernstein et al., 1996; Tinkelman et al., 1996) Unlike terfenadine, fexofenadine is devoid of quinidine-like effects on myocardial conductivity. The most commonly reported side effect of fexofenadine in clinical trials was headache. The incidence of fatigue, drowsiness and nausea were comparable to those in patients receiving placebo. It was therefore expected that fexofenadine would have little or no behaviorally impairing side effects after normal doses and would therefore be safe for use by patients who drive.

The present study was designed to test whether fexofenadine impairs psychomotor performance, especially during car driving in a standardized test. To provide information on the safety margins or the severity of any effects with increasing dose levels fexofenadine was administered in 1x and 2x the normal daily dose. The effects were compared to those of placebo and a normal therapeutic dose of clemastine (i.e. 2 mg b.i.d.), which was shown previously to possess moderately impairing properties (Vuurman et al., 1994). A secondary purpose was to assess possible pharmacokinetic or dynamic interactions between fexofenadine and alcohol that could affect driving, since many patients using antihistamines occasionally drink and drive.

MATERIALS AND METHODS

Subjects

Twenty-five healthy male and female volunteers (age range 22-44 y) were recruited via newspaper advertisements and paid for participating in this experiment. Subjects were screened by a medical history questionnaire and in a physical examination. The latter included a 12-lead electrocardiogram evaluation, blood chemistry and hematology assessments, and urinary tests for βHCG and drugs of abuse. Exclusion criteria included pregnancy, any history or current evidence of severe physical or mental disorder, alcohol or drug abuse; serious gastrointestinal, hepatic, renal, cardiovascular or neurological disorders; allergies requiring possible treatment with systemic antihistamines; consumption of more than 10 beverages containing caffeine per day, smoking more than

20 cigarettes per day, and drinking more than 28 glasses of alcohol containing beverages per week; or, participation in any other clinical trial within the previous 4 months. All subjects possessed a valid driving licence and reported having driven between 5,000 and 35,000 km per year (mean, 10,000 km/y) during the preceding 3 years. They agreed not to use any drugs of abuse or oral medication, except oral contraceptives, aspirin and acetaminophen, for one week prior to and during treatments. They restricted alcohol consumption to a maximum of 2 glasses wine or beer with a meal during treatment periods, and on test days their consumption of caffeine containing beverages was limited to one cup of tea at breakfast. Smoking was prohibited for at least 30 min prior to, and during testing. Subjects were instructed to sleep normally on nights before testing.

One subject dropped out after the first treatment period for reasons unrelated to treatment. A total of 24 subjects (12 male, 12 female) completed the study. Their mean ± SD age was 31.5 ± 8.5 y. Height and weight of the men was 180.5 ± 5.7 cm, 75.1 ± 10.4 kg, and of the women 167.8 ± 7.0 cm, 65.5 ± 8.2 kg. Men reported consuming 9.5 ± 5.8 alcoholic beverages per week, and women, 6.0 ± 6.0. Nine subjects were smokers of 2-20 cigarettes per day.

The study was conducted in accordance with the Declaration of Helsinki (Hong Kong Modification 1989). Subjects were informed of the study's goal, procedures and possible adverse effects, in writing, and they indicated their informed consent, in writing. The study was approved by the standing Ethics Review Committee of Maastricht University.

Study design and drug/alcohol administration

The study was conducted according to a double blind, placebo and active drug controlled, 6-way crossover design. Treatments were fexofenadine 120 mg q.a.m., 60 mg b.i.d., 240 mg q.a.m., 120 mg b.i.d., clemastine 2 mg b.i.d. and placebo b.i.d. Treatment periods lasted five days, starting on the evening before the 1st day and ending the morning of the 5th day. Study medication was supplied in identical appearing gelatine capsules. Quarters of the subjects ingested their medication at 8:15, 9:30, 10:45 and 12:00 a.m and p.m. Treatment orders were randomly assigned from those residing in 4 replications of a 6x6 Williams Square. Washout periods were at least 6 days.

Subjects were treated with an alcohol challenge on the fifth day of each period. The alcohol dosing regimen was developed for achieving and sustaining a blood alcohol concentration (BAC) just under the local legal limit for drivers; i.e. 0.5 g/L. It normally

comprised the administration of 7 constant 5.6 g doses at 15 min intervals from the time of drug or placebo ingestion until the beginning of laboratory performance testing; a larger (10 g) dose before the longest (45 min) laboratory test; and, two more adjustable doses, occurring 30 min and immediately before the driving test. Pure alcohol (99.8%) was mixed with orange juice. BAC was estimated from concentrations in expired alveolar air before the 2nd and subsequent doses using a Lion Alcolmeter SD-400. Adjustable doses were set for achieving the desired BAC during the driving test. Adjustments started earlier in some individual cases when BAC was increasing too rapidly or too slowly to achieve that objective.

Procedure

Subjects were individually trained to perform the psychomotor tests and rehearsed the driving test before the first treatment period. Psychomotor and driving tests were undertaken on days 1, 4 and 5 of each treatment period. Subjects fasted between 3 hours prior to and 1 hour following ingestion of the morning dose. Thereafter they were a given a light meal. Critical tracking, choice reaction time and sustained attention tests were performed from 12 to 22 hours after dosing and the driving test 3-4 hours after dosing.

The critical tracking test measures the ability to control an unstable error signal in a first-order compensatory tracking task (Jex et al., 1966). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. The frequency of cursor deviations, i.e. cursor instability (λ), increases as a stochastic, linear function of time, and thus the required velocity of corrections increases. The frequency at which the subject loses control is the critical instability frequency (λc, in rad/s). The test includes five trials of which the lowest and the highest score were removed; the average of the remaining scores is taken as the final score.

Average choice reaction time (in ms) of correct responses was measured in the presence of distracting cues. The task is to react to the appearance of the words *left* and *right* by pressing corresponding buttons. Half of the words are displayed at compatible and half at incompatible (left or right) sides of a screen.

The sustained attention test is a variant of the classic Mackworth "Clock Test" (Mackworth 1950). The subject is seated in front of a computer screen displaying a circular arrangement of 60 grey dots simulating the second marks on a clock. The luminance of each dot briefly increases in clockwise rotation at a rate of 2/sec.

Occasionally, the rotation proceeds with a "double jump" by skipping one of the dots in the normal sequence. The dependent variable is the number of correct detections. Test duration is 45 minutes and 10 signals occur within each successive 15-min period.

The driving test was originally developed during the 1970's for driver fatigue research in the USA. It was standardized for drug screening purposes in 1982 and it has been used in more than 50 separate studies for measuring drug effects on driving performance (O'Hanlon and Ramaekers 1995; O'Hanlon et al., 1995) The subject drives a specially instrumented car over a 100 km (61 mi) primary highway circuit. He/she is accompanied by a licensed driving instructor, having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle's speed and lateral position relative to the left lane-line delineation are continuously recorded. These signals are digitally sampled at 4 Hz and edited, off-line, to remove parts where data are disturbed by extraneous events (e.g. passing maneuvers). The remainder is then reduced by successive 5 km segments of the ride. Means and standard deviations of both variables are calculated for the entire test, the latter parameters by taking the square root of variances pooled over all segments. Standard Deviation of Lateral Position (SDLP) is the primary outcome variable. SDLP is an index of road tracking error or allowed "weaving". It is a very reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is $r = 0.85$. It has also proven sensitive many sedating agents including alcohol in blood concentrations as low as .0.35 g/L (Ramaekers et al., 1992b; Vuurman et al., 1996).

Statistical analysis

Psychomotor and driving performance parameters were analyzed separately for days 1, 4 and 5, using univariate repeated measures analysis of variance. Statistical tests were conducted using the SAS (6.09) General Linear Models procedure, with sequential (Type I) sums of squares. Main effects included in the model were Subjects, Gender, Period, Treatment and Treatment by Period and Treatment by Gender interactions. Drug-placebo differences were tested using the Least Squares Means procedure.

RESULTS

Alcohol doses and blood alcohol concentrations

Mean ± SD cumulative alcohol doses (in g/kg) and BACs (in g/L) at the beginning of the driving tests were practically the same in every condition: i.e. 0.80 ± 0.08, 0.81 ± 0.10, 0.82 ± 0.09, 0.79 ± 0.09, 0.80 ± 0.09, and 0.79 ± 0.09 g/kg; and 0.45 ± 0.07, 0.45 ± 0.07, 0.47 ± 0.05, 0.49 ± 0.07, 0.45 ± 0.07 and 0.48 ± 0.05 g/L for placebo, clemastine, and fexofenadine 120 mg q.a.m., 60 mg b.i.d., 240 mg q.a.m., and 120 mg b.i.d., respectively.

Driving performance

Seventeen driving tests (3.9% out of a total of 432) were terminated before scheduled completion because the subject (in 3 tests) or driving instructor (in 14 tests) judged that it would be unsafe to continue (table 8.1). Calculation of Standard Deviation of Lateral Position (SDLP) values for subjects whose rides were terminated before scheduled completion were adjusted according to a planned last-value-carried-forward procedure. That is, the data collected during the last 5 km segment before stopping were inserted for each of the unfinished segments. Mean (± SE) SDLP scores on day's 1, 4 and 5 of each treatment series are presented in figure 8.1.

Table 8.1. Failures to complete driving tests, by treatment and day of treatment.

		Day 1	*Day 4*	*Day 5 (with alcohol)*
		I/S	*I/S*	*I/S*
Placebo	b.i.d.	-	1/1	-
Fexofenadine	120 mg q.a.m.	1/0	2/0	1/0
	60 mg b.i.d.	1/0	-	1/1
	240 mg q.a.m.	-	-	2/0
	120 mg b.i.d.	-	-	-
Clemastine	2 mg b.i.d.	0/1	1/0	4/0

I Rides terminated by decision of the driving instructor; S rides terminated by decisions of the subject; b.i.d. twice daily; q.a.m. once daily in the morning

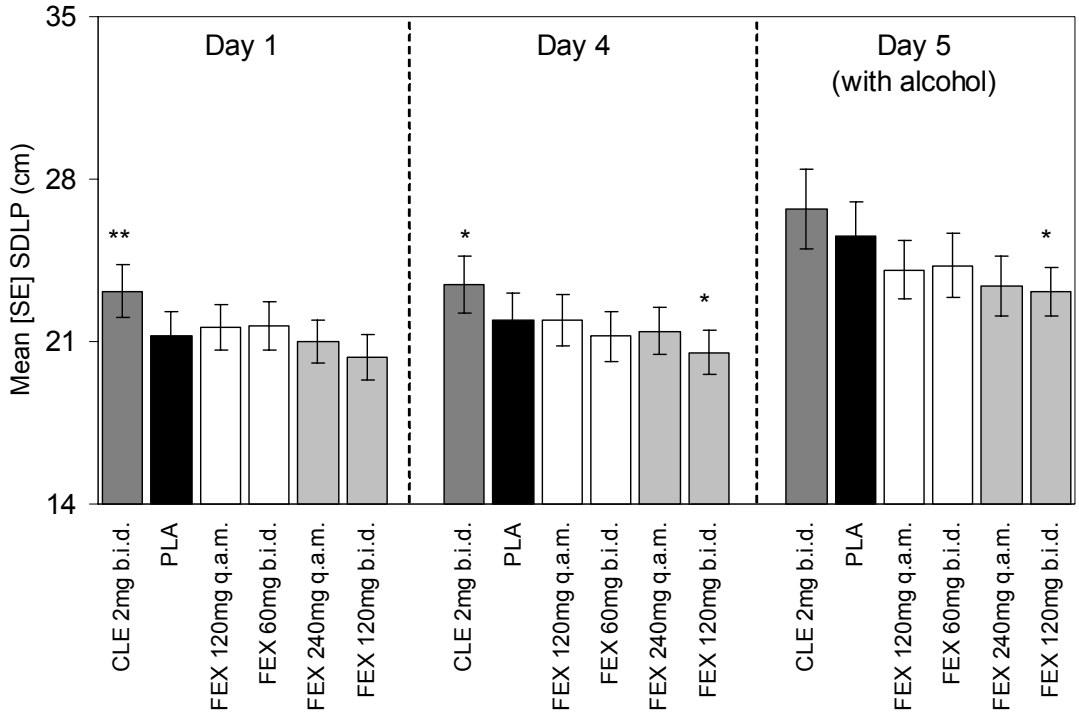

Figure 8.1 Mean (±SE) SDLP per treatment and days within treatment. Treatments are clemastine (CLE) 2 mg b.i.d., placebo (PLA) and fexofenadine (FEX) in daily doses of 120 and 240 mg in unitary (q.a.m.) and divided dosing (b.i.d.) regimens. Asterisks over bars indicate level of significance for drug-placebo differences as * ($p < 0.05$) and ** ($p < 0.01$).

Significant overall effects of Treatment were found on both day 1 and 4 ($F_{5,85} = 6.05$, $p = 0.0001$; $F_{5,85} = 3.93$, $p = 0.003$, respectively). Mean drug-placebo comparisons showed that clemastine significantly impaired driving performance on both days ($p= 0.0006$ and 0.0309). On day 1, no fexofenadine dose had effects on driving performance that differed significantly from placebo's. Yet on day 4, mean SDLP in the fexofenadine 120 mg b.i.d. condition was nearly significantly ($p = 0.0504$) lower (i.e. better) than in the placebo condition. Though mean SDLP changes in the other fexofenadine conditions on day 4 were in the same direction, none was significant.

Comparison of SDLP scores on day 4 and day 5 indicated that alcohol significantly impaired driving performance ($F_{1,212}= 52.82$, $p = 0.0001$). Analysis of SDLP scores on day 5 also showed a significant Treatment effect ($F_{5,85} = 2.94$, $p = 0.017$). Mean drug-placebo comparisons revealed that this effect was not attributable to clemastine, but rather to the higher daily doses of fexofenadine: the combined effect of alcohol and

fexofenadine 120 mg b.i.d. was significantly (p = 0.0376) less impairing than that of alcohol alone, and the similar effect of fexofenadine 240 mg q.a.m. closely approached significance (p = 0.0606). The effects of both lower fexofenadine doses and clemastine in combination with alcohol were not significantly different from those of alcohol alone. There were no significant Gender effects or Gender by Treatment interactions, indicating that there were no differences in driving performance between men and women in general or in any particular treatment condition.

Critical Tracking

Analyses showed a significant effect of Treatment on critical tracking frequency (λc) on day 1, but not on day 4 ($F_{5,85}$ = 2.55, p = 0.0337; $F_{5,85}$ = 1.36, n.s). The effect on day 1 was attributable to significant impairment of tracking performance by clemastine, and also by fexofenadine 120 mg q.a.m. and 240 mg q.a.m. (means ± SE = 3.82 ± 0.17, 3.82 ± 0.16 and 3.81 ± 0.17; p = 0.0367, 0.0304 and 0.0219, respectively) as compared to placebo (mean ± SE= 4.00 ± 0.17). The effects of fexofenadine 60 mg b.i.d. and 120 mg b.i.d. were not significantly different from placebo's (means ± SE = 3.94 ± 0.16 and 4.01 ± 0.16). Tracking performance was significantly impaired by alcohol ($F_{1,212}$ = 18.20, p = 0.0001). Analysis of λc scores on day 5 showed a significant Treatment effect ($F_{5,85}$ = 3.52, p = 0.0061). Both fexofenadine 240 mg q.a.m. and clemastine 2 mg b.i.d. in combination with alcohol had significantly more impairing effects on tracking than alcohol alone (means ± SE = 3.66 ± 0.19 and 3.63 ± 0.18 and 3.83 ± 0.19; p= 0.0349 and 0.0145, respectively). The effects of fexofenadine 60 mg b.i.d., 120 mg q.a.m. and 120 mg b.i.d. in combination with alcohol (means ± SE = 3.78 ±0.18, 3.72 ± 0.17 and 3.90 ± 0.18, respectively) were not significantly different from those of alcohol alone. Significant Gender effects on day 1, 4 and 5 ($F_{1,85}$ = 15.06, 27.89, 41.50, $p \leq$ 0.0002, indicated that tracking performance of men was better than of women.

Choice Reaction Time

Analyses showed no significant effects of Treatment on choice reaction time on day 1, 4 and 5, yet alcohol significantly ($F_{1,212}$ = 27.81, p = 0.0001) prolonged mean reaction times. Significant Gender effects on day 1, 4 and 5 ($F_{1,85}$ = 7.24, 4.52, 5.29, $p \leq$ 0.0086, 0.0364, 0.0239, respectively) indicated that men were generally faster.

Sustained Attention

Analyses showed that the Treatment effect on number of correct detections in the sustained attention test only approached significance on day 1, and was not significant on day 4 ($F_{5,85}$ = 1.95, p = 0.0942; $F_{5,85}$ = 1.02, n.s.). Mean drug-placebo comparisons revealed a tendency towards impaired performance on the first day of clemastine treatment as compared to placebo (means ± SE = 19.9 ± 1.5 and 22.1 ± 1.2; p = 0.0749), which was no longer present on day 4. Fexofenadine had no effects on sustained attention. Alcohol, however, significantly impaired sustained attention ($F_{1,179}$ = 51.13, p = 0.0001). Analysis of correct detections on day 5 showed a significant Treatment effect ($F_{5,80}$ = 3.59, p = 0.0056). Mean drug-placebo comparisons showed that this effect was mainly due to a significantly impairing effect of clemastine in combination with alcohol as compared to alcohol alone (means ± SE = 15.3 ± 1.7 and 18.3 ± 1.7; p = 0.0201). The effects of alcohol in combination with fexofenadine in this test did not differ significantly from those of alcohol alone (means ± SE = 19.2 ± 1.4, 17.4 ± 1.7, 20.0 ± 1.4 and 18.3 ± 1.7 for fexofenadine 60 mg b.i.d, 120 mg q.a.m., 120 mg b.i.d. and 240 mg q.a.m. respectively). Significant Gender effects on day 4 and 5 ($F_{1,85}$ = 5.78, p = 0.0184; $F_{1,80}$ = 6.94, p = 0.0101) indicated that women generally detected more signals then men.

DISCUSSION

Fexofenadine, given over five days in separate dosing regimens of 60 mg b.i.d., 120 mg q.a.m., 120 mg b.i.d. and 240 mg q.a.m., did not by itself impair driving performance and did not add to the impairment produced by alcohol in a blood concentration of approximately 0.4 g/L. On the contrary, the higher divided dose, by itself, significantly improved driving performance on day 4, and both of 240 mg/d regimens significantly or almost significantly reduced alcohol's effect on driving performance on day 5. Neither of the 120 mg/d regimens had significant effects on driving. However, both of the lower doses attenuated the alcohol effect to approximately the same extent, about half as much as the higher doses, giving the impression that fexofenadine's capacity to antagonize that effect is dose-related. Clemastine 2 mg b.i.d., the active control, significantly impaired driving performance on days 1 and 4 to confirm the test's sensitivity to sedative effects of

antihistamines. The combination of clemastine plus alcohol impaired driving performance to a greater degree than placebo plus alcohol but the difference was not significant.

Fexofenadine did not affect performance significantly in any laboratory test, except critical tracking. In this test, after the first 120 and 240 mg doses on day 1, and again after 240 mg in combination with alcohol, the drug reduced the critical tracking frequency, λc. Clemastine in combination with alcohol did the same. The question is therefore how two drugs having similar effects on λc could have opposite effects on road tracking performance as measured by SDLP. One answer may be implicit in the fundamental engineering model of compensatory manual tracking performance (McRuer and Jex 1967; McRuer and Krendel 1959). That model, and all that have evolved from it, use mathematical expressions to describe the relationship between the system's deviance from a desired norm (i.e. "error") and the operator's controlling response. These models contain at least two parameters, termed delay and gain, representing human operating characteristics. In neuropsychological terms, delay represents the time elapsing between the sensory transduction of an error signal and the beginning of a compensatory motor response. It is the continuous analog of discrete reaction time. An individual's delay can lengthen under the influence of any factor that slows neurotransmission, resulting in a decrease in the maximum error frequency an operator can control, which was estimated by λc in the present study. Gain in the engineering model is simply the observed ratio of the motor output to the given error input, but within a biological system that ratio must be related to the number of neural units recruited in expediting the motor response. The more there are, the stronger the motor reaction. Differences in gain determine individual response style. People operating with high gain react very vigorously to the perceived error, which after the delay, enables them to rapidly restore the controlled system to the desired state when error develops slowly, but at the cost of overshooting the mark, particularly when the error develops rapidly. Those with low gain react sluggishly. They allow slowly developing errors to accumulate further before correction but do not over-react to faster ones. Gain may vary within an individual with his or her level of CNS activation.

It is possible to explain clemastine's as well as fexofenadine's effects according to this model. Clemastine is known to be sedating and is likely to increase delay by slowing neurotransmission. The findings that it impairs road tracking (i.e. increases SDLP) as well as laboratory tracking (i.e. decreases λc), appears to confirm this hypothesis. In contrast, fexofenadine either improved road tracking (i.e. diminished SDLP), or impaired

laboratory tracking (i.e. reduced λc), or did both simultaneously. These effects are theoretically those of an agent that increases gain (i.e. better low frequency error compensation in road tracking with a greater tendency to overreact to high frequency error in laboratory tracking). Pharmacologically, these effects are what one might expect from a mild stimulant that raises brain activation as a whole and the excitability of neurons within the motor cortex in particular. Yet, the profile displayed by fexofenadine is different from those of the classic psychostimulants such as amphetamines, caffeine and nicotine. The latter enhance signal detection performance in vigilance tests (Koelega 1995), whereas in this study fexofenadine did not.

The present indication that fexofenadine might posses mildly activating properties is supported by occasional findings in studies with its metabolic precursor, terfenadine. Significant signs of activation were found on subjective alertness, psychomotor performance, and vehicle handling in closed-course driving tests while on terfenadine therapy (Betts et al., 1989; Clarke and Nicholson 1978; Moskowitz and Burns 1988). Congruent but nonsignificant effects on have also been demonstrated on event-related electroencephalographic potentials and SDLP, measured according to the same procedures as employed in the present study (Ramaekers and O'Hanlon, 1994; Riedel et al., 1989; Simons et al., 1996; Volkerts et al., 1992b). Signs of performance improving effects have also been reported for a very similar piperidine antihistamine, ebastine (Brookhuis et al., 1993; Mattila et al., 1992).

Almost the entire terfenadine dose is normally transformed during 1st-pass metabolism into fexofenadine and azacyclonol, an inactive compound, at a ratio of 2:1 (Ling et al., 1995). Thus fexofenadine was probably responsible for the effects formerly attributable to its parent. Moreover, assuming equal absorption, one should expect greater effects from the same oral doses of fexofenadine than terfenadine, because the former forms no inactive metabolites.

Pharmacological mechanisms whereby antihistamines could affect behavior in the manner fexofenadine appeared to in this study have been previously proposed (Simons 1994). One that should theoretically enhance arousal-dependent performance is the inhibition of the enzyme responsible for histamine's extraneuronal catabolism; i.e. histamine N-methyltransferase. It is unknown whether fexofenadine possesses that or any other property capable of increasing CNS arousal. But before initiating a search for the mechanism it would be well to inquire whether the drug penetrates the brain after being given in doses equivalent to those in this study. It would appear that it does from the

results of an attempt to measure terfenadine's passage through the blood-brain barrier in mice (Rose et al., 1982). Separate groups of 3-6 animals were given single doses of terfenadine, 2 - 100 mg/kg, and 1 h later, [3H] mepyramine, i.p. Inhibition of radioligand binding at cortical H1 receptors was measured for determining the extent to which terfenadine or its active metabolite occupied those sites. Terfenadine 2 and 3 mg/kg respectively resulted in about 16 and 24% mean receptor occupancy. Occupancy increased exponentially with higher dose until almost complete inhibition of radioligand binding occurred above 75 mg/kg. The two lowest doses were the equivalent of 140 and 210 mg in a 70 kg human. Even though the former occupied much lower percentages of cortical H1 receptors than did equivalent doses of lipophilic antihistamines (e.g. triprolidine and d-chlorpheniramine, 70%), it is clear that all drugs had more or less crossed the blood-brain barrier. The implication of these results was subsequently noted by Manning and Gengo (1993): chronic daily dosing with terfenadine and presumably other 2nd generation antihistamines might eventually result in brain concentrations capable of affecting behavior.

In conclusion, fexofenadine in doses up to 240 mg/d should be safe for use by patients who drive. Doses up to 120 mg/d apparently have no effect on driving performance. Doses of 240 mg/d given consecutively for 4/5 days may affect driving performance in a manner that appears beneficial. We attribute this to some activating effect of the drug within the CNS. That effect may also be beneficial in drivers whose performance would otherwise be deficient due to fatigue. Further studies are required to confirm our explanation and to elucidate fexofenadine's mechanism of action.

Chapter 9

Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females

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ABSTRACT

Emedastine is registered in its country of origin (Japan) as an antihistamine for the indication of seasonal allergic rhinitis. Further research on the drug's sedating properties was needed to secure its registration elsewhere. The present study was designed to compare the effects of emedastine 2 and 4 mg twice daily after single and repeated doses, on actual driving performance versus those of cetirizine 10 mg once daily and placebo; and to determine how repeated doses of each drug interact with alcohol to affect driving. Each treatment was administered for 5 days to 19 healthy volunteers (9 men, 10 women, age range 21 to 45 year) according to a 4-period double blind crossover design. Driving performance was measured in a standardised test between 3 and 4 hours after administration of the morning dose on days 1, 4 and 5. Alcohol, sufficient for achieving a blood alcohol concentration of 0.5 g/L was given before driving on day 5 of each period. Both emedastine doses similarly and significantly impaired driving in every test. Cetirizine's effects were less. They were significant over days 1 and 4 combined, though not separately. Women were more impaired by both drugs. Alcohol increased driving impairment similarly in every condition. Subjects were only able to discriminate the sedating and impairing effects of the first dose of emedastine 4 mg from placebo. Emedastine, in oral doses of 2 and 4 mg twice daily, is sedating and impairs driving. The drug could therefore constitute a traffic hazard and its users should be warned accordingly.

INTRODUCTION

Emedastine difumarate (KG-2413, Kanebo Pharmaceuticals, Japan) is a new benzimidazole derivative which has the clinical profile of an antihistamine drug. It is currently used in Japan for the indications of seasonal and perennial allergic rhinitis and urticaria. The recommended dose is 2 mg twice daily.

Emedastine is a highly potent and selective H1 receptor antagonist (Fukuda et al., 1984; Sharif et al., 1994). Following oral administration in Caucasian volunteers, emedastine is well absorbed, with average t*max* occurring between 3 and 4 hours (Jansen et al., 2000). It was shown to be converted by oxidative biotransformation by the cytochrome P450 isoforms, primarily by CYP450 1A2 and CYP 2E1, but also by CYP

3A4, to far less active metabolites (Ishida et al., 1997). Elimination occurs mainly via the kidney, with a half-life of about 6-7 hours (Jansen et al., 2000; Herranz et al., 2001). Steady state is reached after the third oral dose in a repeated 2 mg twice daily dosing regimen (Joukhadar et al., 2001).

For many people, sedation is of primary concern when considering the adverse effects of antihistamines. Older, first-generation anti-histamines, such as clemastine, chlorpheniramine, diphenhydramine and promethazine, are lipophilic and readily cross the blood brain barrier to penetrate the CNS. There they block histaminergic neurotransmission, often in combination with blockade of cholinergic, serotonergic, or adrenergic neurotransmission, all of which have been shown to play significant roles in regulating cortical arousal (Lin et al., 1996; Robbins, 1997). Consequently these drugs produce sedation and associated performance impairment. In addition, they potentiate the impairing effects of alcohol on performance. Therefore, regulatory warnings concerning the use of alcohol and the drugs' effects on operation of automobiles and other potentially dangerous machinery are applied to all first generation antihistamines. Newer, second generation antihistamines, such as acrivastine, astemizole, cetirizine, desloratadine, ebastine, fexofenadine, loratadine, mizolastine and terfenadine, due to their physico-chemical properties, penetrate the brain to a lower extent (Ter Laak et al., 1994). They are generally better tolerated than their predecessors, relatively nonsedating when given in recommended, therapeutic, doses and they have not been shown to potentiate the effects of alcohol. Consequently regulatory warnings concerning use of alcohol and driving for these drugs are waived. One exception is cetirizine, whose label includes the precautions typical of sedating antihistamines.

Questions concerning emedastine's sedating properties have recently become an issue because the drug is rapidly approaching registration in European countries. On the one hand, there are reasons to expect that emedastine may have relatively minor sedative effects. First, emedastine's chemical structure closely resembles those of two relatively nonsedating benzimidazole antihistamines, astemizole and mizolastine. If emedastine's rate of passing through the blood brain barrier is similarly slow, it may also be relatively nonsedating. Second, animal studies have shown that emedastine has less marked effects on the CNS than the first generation antihistamines chlorpheniramine, diphenhydramine and promethazine. On the other hand, clinical trials have shown that the most commonly reported side effects were related to sedative CNS activity; sleepiness (16%), malaise (1.3%) and dryness of mouth (0.8%). Side effects were more frequent during the first

week of treatment and declined with continued drug use. Recently Jansen et al. (2000) administered emedastine 4 mg once daily, emedastine 2 mg twice daily, cetirizine 10 mg once daily and placebo for 5 days to sixteen healthy young Caucasian males in a double blind, crossover study. They found that 12, 9, 7, and 5 subjects, respectively, reported drowsiness. Though these are subjective evaluations of the drug's effects, they do suggest that emedastine may have sedative and performance impairing effect. Yet, as far as we know, there are no published data concerning its effects on psychomotor performance and its effects on driving, alone or in combination with alcohol.

The present study was therefore primarily designed to determine whether emedastine 2 and 4 mg twice daily has impairing effects on car driving. The effects were to be compared to those of placebo and cetirizine 10 mg once daily. The secondary purpose of the study was to evaluate these drugs' interactions with alcohol with respect to driving performance, since many patients using antihistamines occasionally drink and drive.

Cetirizine 10 mg, once daily in the morning, was included in the study to serve as a standard for judging the safety of emedastine's effects on driving. Even though cetirizine's sedating activity is definitely less than that of first generation antihistamines, the Food and Drug Administration and other national drug regulatory authorities have refused to waive its warning. The reason is that, even though most studies designed to measure cetirizine's effects on psychomotor performance have yielded non-significant results (Rombaut and Hindmarch, 1994; Volkerts and Van Laar, 1995), others have occasionally shown mildly impairing effects (Nicholson and Turner, 1998; Ramaekers et al., 1992b; Patat et al., 1995). Moreover, patients receiving the drug in clinical trials have reported a higher incidence of somnolence than placebo controls (PDR, 1999; Howarth et al., 1999). A recent post-marketing surveillance study by Mann et al. (2000) showed that, although number of reports of sedation were low, patients receiving cetirizine were more likely to report sedation than those receiving acrivastine, loratadine or fexofenadine (odds ratios were 3.5, 2.8, 1.0 and 0.6, respectively). It would therefore appear that cetirizine 10 mg has just enough sedating activity to serve as a standard for judging the safety of other antihistamines' effects on driving. If emedastine produces the same or greater effects it would logically qualify for the same warning concerning possible effects on operation of automobiles and other potentially dangerous machinery.

The further inclusion of an unquestionable impairing antihistamine for demonstrating sensitivity of the test and procedures would have been ideal, but was

precluded for practical reasons. Moreover, this seemed unnecessary for demonstrating sensitivity of the standard driving test. That test has been applied in nine separate investigations of antihistamines' effects on driving performance. As described in a review by O'Hanlon and Ramaekers (1995) the test has always detected impairing effects of antihistamines regarded as sedating, and lesser, yet still significant, effects of nominally nonsedating drugs following their administration in doses that were either at or only twice the currently recommended levels, such as acrivastine 16 mg, cetirizine 10 mg, and mizolastine 20 mg, and terfenadine 120 mg twice daily. The possibility was recognised that some undetected methodological failure might systematically reduce the test's sensitivity in the present investigation. However, in that case, diminished sensitivity would be revealed by the failure to measure any effects of the mild alcohol challenge given on day 5 of each treatment period.

MATERIALS AND METHODS

Subjects

Twenty-one male and female volunteers (ages, 21 to 45 years) were recruited through newspaper advertisements. Inclusion criteria were good health and a driving experience of more than 6,000 km per year over the preceding three years. Volunteers were screened by a medical history questionnaire and a physical examination. The latter included a 12-lead electrocardiogram, blood chemistry and haematology, and urinary tests for β-human chorionic gonadotropin and drugs of abuse. Volunteers were excluded for any of the following: pregnancy or lactation; history of severe physical or mental disorders, alcoholism or drug abuse; use of systemic medication within the previous two weeks, except oral contraceptives; blood donation or participation in any other clinical trial within the previous three months; weight beyond (15% of the Metropolitan Life Insurance Company norms; excessive consumption of caffeine, (more than 10 cups per day), nicotine (more than 20 cigarettes per day) or alcohol (more than 40 gram per day); and, total alcohol abstinence. Qualified volunteers were accepted as subjects after agreeing not to use drugs of abuse or systemic medication (except oral contraceptives, aspirin and acetaminophen) from two weeks before treatments until their conclusion. Alcohol was prohibited for 24 hours before each treatment period and during it. Caffeine

was prohibited on test days. Smoking was prohibited for 30 minutes before tests until their conclusions.

Two subjects dropped out for reasons unrelated to treatment, leaving 9 men and 10 women to complete the study. Their mean ± SD age was 34.4 ± 7.5 years. The men's height and weight were 183 ± 5.5 cm and 83.3 ± 11.6 kg, and the women's, 168.6 ± 6.5 cm and 66.1 ± 10.3 kg. Four subjects, all females, were smokers of 5 to 13 cigarettes per day.

The study was conducted in accordance with the Declaration of Helsinki with amendments through Hong Kong, 1989. The protocol and consent form were approved by the Ethics Review Committee of Maastricht University. Written informed consent was obtained from each subject before enrolment.

Study design and drug/alcohol administration

The study followed a randomised, double blind, 4-period crossover design. Treatments were emedastine 2 and 4 mg twice daily, cetirizine 10 mg in the morning followed by placebo in the evening, and placebo twice daily. Medication was supplied in identical appearing gelatine capsules. Treatment orders were randomly assigned from those residing in five, 4x4 Williams Squares. Treatment periods lasted 5 days and were separated by washout periods of at least 6 days. Half of the group ingested capsules each day at 08:00 and 20:00 hour, the others, 90 minutes later. On test days subjects ingested their morning medication in the presence of an investigator. Compliance at other times was determined from subjects' diaries containing self-recorded ingestion times, daily telephone contacts with the investigators and the return of unused material at the end of treatment periods. On test days subjects fasted from 3 hours before until 1 hour after ingestion of the morning dose to keep absorption rate and t*max* before the driving tests constant.

Subjects were treated with an alcohol challenge on the fifth day of each period, 2 hours after morning medication. The alcohol dose was determined beforehand for each individual separately. For this subjects drank a weight and gender calibrated dose of alcohol: i.e. 0.43 and 0.36 gram per kilogram bodyweight for males and females, respectively. Pure alcohol (99.8%) was mixed with orange juice. Doses were selected to produce a blood alcohol concentration (BAC) after 60 minutes, i.e. the scheduled start of the driving test on day 5, as close to, but just under, the legal limit for drivers, i.e. 0.5 g/L. Each subjects' rate of alcohol absorption and metabolism was measured at 15 minute intervals for 2.5 hours by estimating BAC from expired alveolar air samples using a Lion

Alcolmeter SD-400 (Lion Laboratories lpc). Data were used to adjust individual alcohol doses proportionately when BAC's measured after 60 minutes were above 0.6 g/L or below 0.4 g/L.

On test days, subjects consumed the same individualised alcohol dose two hours after morning medication on day 5 of each treatment period. Subjects fasted from 5 hours before until 30 minutes after alcohol consumption. BACs were measured one and two hour after drinking, i.e. shortly before and after the driving test. Subjects failing to achieve a BAC of 0.45 g/L or 0.3 g/L after one hour were given an additional 4 or 6 gram dose of alcohol, respectively.

Procedure

Driving tests were undertaken on days 1, 4 and 5 of each treatment period. Subjects rehearsed the test a week before the first period. On mornings of test days subjects were interviewed by the medical supervisor to determine compliance and occurrence of adverse events since the last visit. They ingested their medication and vital signs were recorded one hour later, where after on day 1 and day 4 they were served a standardised breakfast. On day 5, breakfast was consumed 30 minutes after alcohol dosing, i.e. 23/4 hours after drug administration. Driving tests were performed between 3 and 4 hours after ingestion, i.e. approximately at emedastine's t*max*. On day 1 of each period subjects were given diaries for recording times of subsequent self-medication and any adverse events that might occur.

Assessments

The driving test was standardised in 1984 and has been applied for assessing drugs in more than 60 separate studies (O'Hanlon and Ramaekers, 1995; O'Hanlon et al., 1995). The subject drives a specially instrumented car over a 100 km (61 miles) primary highway circuit. A licensed driving instructor having access to dual controls accompanies him or her. The subject's task is to maintain a constant speed of 95 km/h (58 miles per hour) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle's lateral position relative to the left lane delineation is continuously recorded. This signal is digitally sampled at 4 Hz and edited off-line to remove data recorded during overtaking manoeuvres or disturbances caused by roadway or traffic situations. The remainder is then reduced to yield the standard deviation of lateral position (SDLP, in cm) for each successive 5-km segment and, as the square root of pooled variance over all

segments, for the test as a whole. SDLP is an index of road tracking error or "weaving" and is a reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is r = 0.85. It has also proven sensitive to many sedating drugs and alcohol in blood concentrations as low as 0.035 % (Vuurman et al., 1996)

Subjective evaluations of mood and effects of treatments on driving were assessed using a series of visual analogue scales (100 mm). Before the start of the driving test subjects completed a 16-item mood scale from which three factors are derived: alertness, contentedness and calmness (Bond and Lader, 1974). Subjects also indicated the degree to which they expected the medication to affect their driving ability, and on day 5 they indicated the same for additional effects of alcohol. Immediately upon conclusion of the driving test, subjects and instructor rated the quality of the formers driving performance. Finally, the instructor rated the subjects' apparent degrees of drowsiness during the test.

Subjects recorded any abnormal mental or physical feeling they experienced on days 1 to 4 of each treatment period in their diaries.

Statistical analysis

Analyses were confined to data from the nineteen subjects who completed the study. SDLP, the primary outcome variable, was analysed in three stages using the SAS (SAS Institute, Inc.), (6.09) General Linear Model univariate analysis of variance, with Subject as a random factor and sequential (Type III) sums of squares. First, driving data obtained on day 1, 4 and 5 were combined in a 4-way analysis of variance using a model including Subject (19 levels), Period (4 levels), Treatment (4 levels), Day (3 levels), and Treatment by Day. Main effects of Treatment were further analysed by 3 drug-placebo contrasts, and effects of Day by contrasts between day 4 and 1, and day 4 and 5, to compare acute and subchronic drug effects, and effects of alcohol. Second driving data obtained on day 1, 4 and 5 were analysed separately using 3-way analyses of variance to test main effects of Subject, Period and Treatment. Treatment effects were further analysed by three drug-placebo contrasts using sequential Bonferroni adjustment, i.e., the α-criterion (α_c) for determining significance was 0.017 (= 0.05/3) for the smallest, 0.025 (= 0.05/2) for the second smallest and 0.05 for the largest *p* value in each set (Overall and Rhoades, 1987). Third, the effects of Gender on driving performance were analysed post hoc, using a model including Subject, Period, Treatment, Gender and Gender by Treatment for each day separately.

Subjective parameters were analysed per day of treatment with sequential Bonferroni correction, as in the second stage of that for SDLP.

RESULTS

Alcohol doses and BACs

Mean ± SD alcohol doses were 37.7 ± 4.8 gram for men and 28.0 ± 3.0 gram for women, producing mean ± SD BACs of 0.43 ± 0.09 and 0.41 ± 0.10 g/L before tests, and 0.26 ± 0.10 and 0.21 ± 0.08 g/L afterward, respectively. Mean BAC values did not differ significantly between treatment conditions before (0.41 - 0.43 g/L, $F3,51) = 0.52$) and after the driving tests (0.22 - 0.25 g/L, $F3,51) = 1.68$).

Driving performance

Twenty-one tests (9.2% of a total 228) were stopped for safety reasons by the subjects or instructor (table 9.1). One subject chose to stop in the placebo condition and two were stopped in the cetirizine condition. In contrast, seven subjects stopped or were stopped a total of nine times in each emedastine condition. SDLP values were adjusted for the early terminations by a planned last-value-carried-forward procedure; i.e., data collected during the last 5 km before stopping were inserted for each of the unfinished segments.Mean

Table 9.1 Failures to complete driving tests, by treatment and day of treatment.

	Day 1	*Day 4*	*Day 5 (with alcohol)*
	I/S	*I/S*	*I/S*
placebo b.i.d.	-	0/1	-
cetirizine 10 mg q.a.m.	1/0	0/1	1/0
emedastine 2 mg b.i.d.	2/2	1/0	2/2
emedastine 4 mg b.i.d.	0/1	1/0	4/0

I Rides terminated by decision of the driving instructor; S rides terminated by decisions of the subject; b.i.d. twice daily; q.a.m. once daily in the morning

Table 9.2 Standard deviation of lateral position (SDLP, in cm) in the driving test by treatment and day of treatment.

	Day 1		*Day 4*		*Day 5 (with alcohol)*	
	Mean	*(SEM)*	*Mean*	*(SEM)*	*Mean*	*(SEM)*
Placebo b.i.d.	20.01	(0.82)	19.18	(0.68)	22.34	(0.90)
Cetirizine 10 mg q.a.m.	21.36	(0.99)	20.50	(0.97)	23.24	(1.42)
Emedastine 2 mg b.i.d.	24.21	(1.59) *	22.24	(1.25) *	24.06	(1.30)
Emedastine 4 mg b.i.d.	24.60	(1.20) *	23.03	(1.11) *	24.24	(1.21)

* significant drug-placebo difference; b.i.d., twice daily; q.a.m., once daily in the morning

(SEM) SDLP values on days 1, 4 and 5 of each treatment condition are given in table 9.2. Analysis of variance showed significant main effects of Treatment ($F_{3,195} = 18.67$, $p < 0.001$) and Day ($F_{2,195} = 12.08$, $p < 0.001$), but not of Period ($F_{3,195} = 1.98$, $p = 0.118$) or an interaction between Treatment and Day ($F_{6,195} = 1.19$, $p = 0.311$).

Pair-wise comparisons between drugs and placebo showed that SDLP was significantly increased during treatment with emedastine 2 and 4 mg ($p < 0.001$) and with cetirizine ($p = 0.028$). Contrasts between days showed that SDLP declined from day 1 to day 4 ($p = 0.005$), and increased from day 4 to 5 ($p < 0.001$), indicating that some tolerance to drugs' effects developed over four days of treatment, and that alcohol significantly impaired driving on day 5.

Day by day analyses showed no significant Period effects. Treatment effects were significant on days 1 and 4 ($F_{3,51} = 11.11$ and 7.89; $p < 0.001$), but not on day 5 ($F_{3,51} = 1.58$). Emedastine's effects were significantly greater than placebo's on day 1 and day 4 (2 mg – $F_{1,51} = 19.75$ and 12.71; $p < 0.001$: 4 mg – $F_{1,51} = 23.52$ and 19.07; $p < 0.001$). Cetirizine's effect was not significant on either day separately ($F_{1,51} = 1.94$ & 2.17). The lack of a significant Treatment effect on day 5 indicates that there were no differential effects of drugs and placebo in combination with alcohol.

Figure 9.1 shows mean (± SEM) SDLP for the men and women by days and conditions. Men drove with a lower mean SDLP than women did. Day by day analyses showed that differences due to Gender were significant ($F_{1,48} \leq 7.48$; $p < 0.009$).

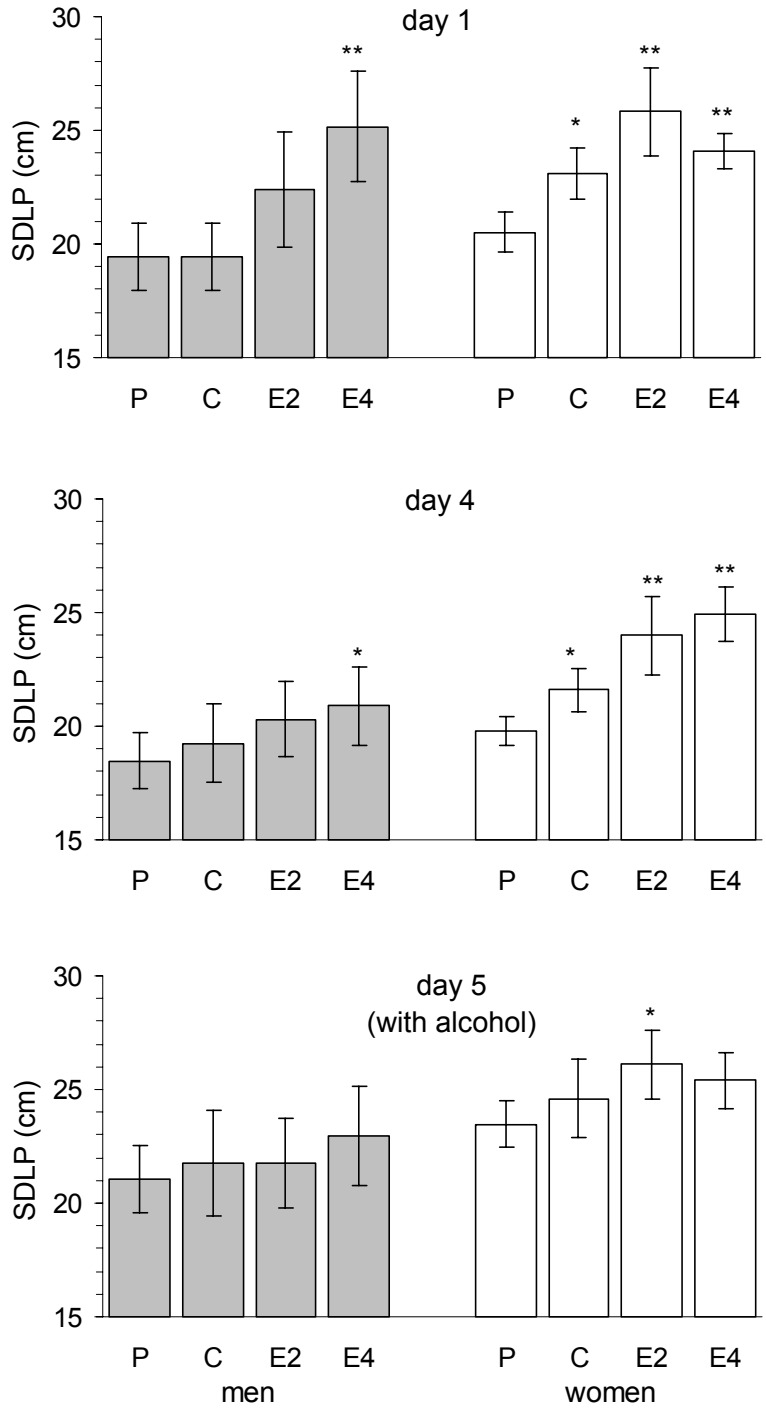

Figure 9.1 Mean (±SEM) Standard Deviation of Lateral Position (SDLP in cm) in the driving test on days 1, 4 and 5 of each treatment series for men (n= 9) and women (n= 10) separately. Treatments are: placebo (P), cetirizine 10 mg once daily in the morning (C), and emedastine 2 and 4 mg twice daily (E2 and E4). Asterisks over bars indicate level of significance for drug-placebo differences: * $p < 0.050$ (not significant after sequential Bonferroni correction), ** $p < 0.005$

Because the interaction of Gender by Treatment was significant on day 1 ($F_{3,48}$ = 2.98; p < 0.041), Treatment effects were analysed for men and women separately. The men's driving performance was only impaired by emedastine 4 mg ($F_{1,21}$ = 14.75; p < 0.001), whereas the women's was impaired by emedastine 2 and 4 mg as well as cetirizine ($F_{1,21}$ = 17.99, 9.97 and 5.83; p < 0.001, 0.005 and 0.024, α_c = 0.017, 0.025 and 0.050, respectively). Though the pattern of significant drug-placebo differences was the same on day 4, the interaction was not significant ($F_{3,48}$ = 1.24). The combinations of drugs and alcohol did not produce significantly greater impairment than alcohol alone for either gender, at least not when judged by the adjusted α-criterion.

To determine whether women's greater sensitivity to antihistamine's sedating and impairing effects might be the consequence of a smaller volume of distribution resulting in slightly higher plasma concentrations, we correlated performance changes with bodyweight. It was expected that there would be a negative correlation between performance change (drug minus placebo) and bodyweight. However, correlations for the group as a whole and for men and women separately were all zero or positive on all days. For the group as a whole correlations on day 1 were 0.22, 0.48 (p = 0.037), and 0.0 for emedastine 2 and 4 mg, and cetirizine, respectively.

Subjective Assessments

Mean (SEM) and results of analysis of overall Treatment effects on subjective evaluations of mood and effects of treatments on driving are given in table 9.3. Treatment effects on alertness were significant on days 1 and 4. At these times, subjects rated their alertness following emedastine 4 mg as significantly lower than placebo ($F_{1,51}$) = 10.91 and 9.29, p < 0.002 and 0.004). They likewise felt significantly less content after emedastine 4 mg but only on day 1 ($F_{1,51}$ = 10.98, p < 0.002). Otherwise, they failed to discriminate significantly between drug and placebo effects on mood.

Subjects' ratings of their capability to drive before rides were significantly affected by Treatments on day 1 only. At this time, they anticipated driving worse after emedastine 4 mg than placebo ($F_{1,50}$ = 9.40, p < 0.004). Otherwise, the subjects expected to drive normally after every drug and combination of drug and alcohol.

Subjects' ratings of their driving quality after rides were affected in a similar manner. The overall Treatment effect was significant on day 1, as was the emedastine 4 mg-placebo contrast ($F_{1,51}$ = 12.03, p < 0.002). Otherwise, the subjects rated their driving

Table 9.3 Summary of results from subjective evaluations of mood and effects of treatments on driving using 100 mm visual analogue scales. Treatment are: placebo (P), cetirizine 10 mg once daily in the morning (C), and emedastine 2 and 4 mg twice daily (E2 and E4).

		Mean ± SEM rating (in mm) per Treatment and Day of treatment				*Treatment Effect*	
		P	*C*	*E2*	*E4*	*F3,51=*	p =
Alertness	Day 1	71 ± 5	65 ± 5	64 ± 6	56 ± 6 **	3.76	0.016
	Day 4	73 ± 5	70 ± 5	67 ± 5	63 ± 5 **	3.32	0.027
	Day 5	62 ± 5	67 ± 5	61 ± 4	55 ± 5	2.89	0.044
Contentedness	Day 1	78 ± 4	72 ± 4	76 ± 4	69 ± 4 **	4.13	0.011
	Day 4	77 ± 4	76 ± 4	73 ± 4	75 ± 4	1.86	*NS*
	Day 5	78 ± 4	78 ± 4	74 ± 4	75 ± 4	1.85	*NS*
Calmness	Day 1	76 ± 4	76 ± 4	83 ± 3	74 ± 4	2.53	0.066
	Day 4	79 ± 4	75 ± 5	77 ± 4	78 ± 4	0.66	*NS*
	Day 5	75 ± 4	69 ± 5	73 ± 4	73 ± 4	0.96	*NS*
Anticipated effects of medication on driving	Day 1	26 ± 5	34 ± 6	35 ± 7	46 ± 6 **	3.17	0.033
	Day 4	37 ± 7	27 ± 5	43 ± 6	41 ± 7	1.57	*NS*
	Day 5	39 ± 7	25 ± 5	43 ± 7	40 ± 7	2.06	*NS*
Anticipated effects of alcohol on driving	Day 5	66 ± 5	53 ± 6	55 ± 5	63 ± 6	2.49	*NS*
Subject rating of driving quality	Day 1	62 ± 5	58 ± 5	51 ± 5	43 ± 5 **	4.66	0.006
	Day 4	69 ± 4	69 ± 4	59 ± 6	59 ± 6	1.95	*NS*
	Day 5	66 ± 3	60 ± 6	57 ± 6	56 ± 5	1.64	*NS*
Instructor rating of driving quality	Day 1	80 ± 2	75 ± 4	66 ± 5 **	64 ± 5 **	4.75	0.006
	Day 4	85 ± 3	79 ± 3	76 ± 4 *	75 ± 4 **	2.59	0.064
	Day 5	75 ± 3	70 ± 4	69 ± 5	65 ± 4	1.83	*NS*
Instructor rating of subjects' apparent sedation	Day 1	20 ± 4	27 ± 6	42 ± 6 **	47 ± 6 **	8.95	0.001
	Day 4	12 ± 3	21 ± 3	31 ± 5 **	31 ± 5 **	6.05	0.002
	Day 5	30 ± 4	38 ± 6	39 ± 6	44 ± 5	2.28	*NS*

Asterisks indicate drug-placebo contrasts significant after sequential Bonferroni correction

** $p < 0.017$; * $p < 0.025$; *NS* $p \geq 0.01$.

quality as no worse after drug, or combined drug/alcohol treatments than following the respective placebo.

The instructor significantly discriminated between treatment effects on day 1 and almost significantly on day 4. On both, he rated the subjects' performance worse after both emedastine 2 and 4 mg than placebo (lower dose – $F1,51) = 8.54$ and 5.31, $p \leq 0.006$ and 0.025, $\alpha_c = 0.025$; higher dose – $F1,51) = 10.43$ and 6.28, $p = 0.003$ and 0.016, $\alpha_c = 0.017$). The instructor's ratings of the subjects' apparent sedation paralleled those of driving performance. The same overall Treatment effects and drug-placebo comparisons were all significant beyond the $p = 0.001$ level.

Safety

There were no serious adverse events. Somnolence (unusual drowsiness and or fatigue) was reported on days 1 to 4 by 24, 38, 53 and 70% of the subjects in the placebo, cetirizine, emedastine 2 mg and emedastine 4 mg conditions, respectively. Other frequently reported adverse events headache (10, 19, 11 and 15% respectively) and dizziness (5, 10, 16 and 0%, respectively). Dry eyes, dry mouth, moody, nausea, photophobia, itching, stomach disorder, "strange" feeling, and heavy feeling in extremities were reported by single subjects. All adverse events were resolved by the end of the study.

DISCUSSION

Emedastine's acute effects on the subjects' driving performance were as severe as any produced by relatively high doses of older antihistamines in previous studies employing the standard driving test; i.e., clemastine 2 mg (Vuurman et al., 1994; Vermeeren and O'Hanlon, 1998), diphenhydramine 50 mg (Ramaekers and O'Hanlon, 1994), and triprolidine 5 mg (Riedel et al., 1989; Volkerts et al., 1992b). Moreover, for the female subjects at least, there was little difference between the impairing effects of emedastine 2 mg and 4 mg twice daily, and little change in those effects from the first to the fourth day of continual dosing. It would appear from the lack of a dose effect that emedastine not only penetrated the blood brain barrier after both doses, but that it did so to degrees that occupied similarly large proportions of central H1 receptors.

Further deterioration in the subjects' performance occurred after the alcohol challenge on the fifth day while their average BACs declined from 0.42 to 0.24 g/L. However, emedastine did not add significantly alcohol's effect, relative to the combination of alcohol and placebo. It may be that behavioural and/or pharmacological tolerance finally attenuated the sedative effect or that the subjects exerted greater effort in anticipation of alcohol's better known effects. Yet, it can not be said that the emedastine's activity was completely over on the fifth day: mean drug-placebo differences approached significance ($p < 0.080$) after both doses and almost as many rides had to be stopped for safety reasons as on day 1.

The subjects were to some extent aware of emedastine's sedating effects on their driving ability, particularly after 4 mg doses. They rated their alertness as significantly lower than normal before every driving test and the majority spontaneously reported somnolence on days 1 and 4. Yet, they only expected the first 4 mg dose to affect their driving performance. Furthermore, they judged the quality of their performance to have been significantly worse after emedastine 4 mg than placebo. Subjects were less able to anticipate and accurately assess the effects of the 2 mg dose. They never felt significantly less alert or capable of driving and never judged the quality of their performance to have been worse after emedastine 2 mg than placebo. In contrast, the instructor rated the subjects' performance and appearance as reflecting sedation after both doses of emedastine on days 1 and 4.

Expectations about emedastine's nonsedating properties were primarily founded on the drug's structural resemblance to other benzimidazole antihistamines that are widely regarded as nonsedating when taken in recommended doses; i.e., astemizole 10 mg and mizolastine 10 mg. However, it is not entirely clear that the latter are truly nonsedating and there is ample evidence to indicate that emedastine differs from both in important ways. Astemizole and its active metabolites accumulate in plasma, and presumably brain, for more than a month of continual daily dosing. However, it seems that no one has ever assessed the drug's effects on performance at steady state. The reported lack of astemizole's effects after much shorter intervals of repeated dosing or single doses up to 20 mg can not be taken as evidence that the same would be found at steady state (De Gier et al., 1986; Hindmarch et al., 1987). Mizolastine was shown to increasingly impair volunteers' driving performance in the standard driving test after single doses from 5 to 40 mg (Vuurman et al., 1995). In another study, volunteers were treated with repeated 10 mg doses for seven days and tested on the last (Patat et al., 1995). The drug significantly

impaired their divided attention and tracking performance. None of the aforementioned performance decrements was particularly large but their occurrence indicates that mizolastine penetrates the blood brain barrier after administration in 10 mg doses. Mizolastine and emedastine have similar pharmacokinetic and -dynamic properties. Both drugs are absorbed within 2 hours and their elimination proceeds with mean monoexponential half-lives of about 14 and 7 hours, respectively (Rosenzweig et al., 1992; Jansen et al., 2000). Both are highly selective H1 antagonists. However, a comparison of results from two similar radioligand displacement studies shows that they differ markedly with respect to H1 binding affinity. Benavides and associates (1995) showed that mizolastine displaced [3H-]pyrilamine in guinea pig cerebellar sections with a Ki of 17 nmol/l, whereas the Ki of pyrilamine was 0.88 nmol/l in the same test. In contrast, using competitive binding with [3H-]pyrilamine in guinea pig forebrain homogenates, Sharif et al.(1994) found emedastine's Ki to be about equal to pyrilamine's, 1.3 and 0.8 nM, respectively. Thus, it appears that emedastine possesses minimally a tenfold higher affinity for H1 receptors than mizolastine. Assuming equal brain penetration, emedastine's sedating activity after 2 and 4 mg doses should therefore be at least the same as mizolastine's after 20 and 40 mg doses, i.e., far above the minimum for causing driving impairment.

The results of this study may explain why the two previous investigations of cetirizine 10 mg's effects on driving performance yielded contradictory results. The one showing no effect employed male subjects exclusively (Volkerts et al., 1992b). The men in this study also failed to respond to the drug. The other showing a small but significant effect employed males and females in equal proportions (Ramaekers et al., 1992b). In the present study, the women responded by driving with significantly elevated SDLPs on both on the 1st and 4th days of treatment. Other studies have demonstrated women's greater sensitivity to the impairing effects of different antihistamines on driving performance; i.e. clemastine 2 mg and mizolastine 5-40 mg (Vuurman et al., 1994) and acrivastine 8 mg (Robbe and O'Hanlon, 1990; Ramaekers and O'Hanlon, 1994). Women's greater sensitivity to antihistamine's sedating and impairing effects is often assumed to be the consequence of a smaller volume of distribution resulting in slightly higher plasma concentrations. However, neither in this study nor any reported earlier was there a significant correlation between individuals' bodyweights and their performance impairment. Thus, the gender difference in response to antihistamines remains an intriguing mystery for further investigation. Future studies determining the effects of

antihistamines on performance should employ either mixed-gender subject samples or those comprised exclusively of the gender which presently seems the more sensitive.

In conclusion, emedastine, in doses of 2 and 4 mg twice daily, impairs driving performance for at least four days of continual dosing. Patients taking the drug in either dosage should be advised to avoid driving. In contrast, cetirizine 10 mg once daily has only mild, yet measurable, effects on driving. Our data support the hypothesis that women might be more susceptible to antihistamine-induced sedation.

Chapter 10

Concluding Remarks

The aim of this dissertation was to provide more information regarding the impairing effects of hypnotics and antihistamines on cognitive functions and driving performance and on factors that modulate these effects. In this final chapter an attempt is made to put the results of the studies presented in this dissertation into the realm of their broader meanings, both practical and theoretical. What are the determinants and modulating factors for the effects of hypnotics and antihistamines on performance as they emerge from the studies presented here? How can this information be of use for those involved in the development, use and regulation of these drugs?

Hypnotics

Results from the experimental studies described in *chapter 4 through 7* and those reviewed in *chapter 3* clearly indicate hypnotics can have residual effects the day after bedtime use. Increasing epidemiological evidence confirms the clinical relevance of the deficits in psychomotor and driving performance. The consequences of the residual effects hypnotics on memory and cognition, as revealed in experimental studies, have not yet been corroborated by epidemiological research. It can be assumed, however, that it does reduce patients' ability to function adequately at home or at work, and lead to variety of problems that are less discrete or identifiable than injurious accidents, such as forgetting what one was doing before being interrupted by telephone call.

What makes a hypnotic safe for use by patients who drive? Apart from the obvious low dose; the factor that is most often referred to first is rapid elimination.

However, things are more complicated than that. Rapid absorption is another prerequisite. Patients expect hypnotics to have a rapid onset of action, i.e., induce sleep within approximately 30 minutes. This is best accomplished by hypnotics that are almost completely absorbed within about 60 minutes after ingestion. Those that are not may create a special problem. That problem was illustrated in a study assessing the residual effects of loprazolam on performance in the highway driving test when the effects were much greater than anticipated on the basis of the drug's half-life (Volkerts and O'Hanlon, 1986). Loprazolam does not reach peak plasma concentrations for 5 hours after ingestion on average. To induce a more rapid onset of action higher doses can be given, so that the rising plasma concentration exceeds the hypnotic threshold within the desired time interval. This means that the concentration continues to rise for some time after the person has fallen asleep. When it finally declines, the concentration stays above the hypnotic threshold for some time and may just fall below at the time of awakening. What remains is still sedating and capable of impairing driving performance.

A similar mechanism may explain the residual effects of triazolam 0.5 mg and zopiclone 7.5 mg. These drugs and doses were also found to have moderate to severe residual effects on driving performance that were initially not anticipated on the basis of their short half-lives (*chapters 3, 5 and 6*; Riedel et al., 1988). Although these drugs' mean times to peak plasma concentrations are much faster than that of loprazolam, there are large individual variations. Some individuals do not reach peak plasma concentrations for 4-5 hours after ingestion. To ensure a fast onset of sleep in everyone, however, the recommended doses may have been set too high. That of triazolam has already been lowered considerably, but that of zopiclone has not. Perhaps Nicholson's (1998) suggestion regarding zopiclone that "there is a case for the introduction of a 5.0 mg tablet for patients whose performance the next day is critical", should be reconsidered by the manufacturer in the light of recent evidence confirming that 7.5 mg has detrimental effects on driving (*chapter 5 and 6*) and epidemiological evidence that the use of zopiclone is associated with a fourfold increase in the risk for traffic accidents (Barbone et al., 1998).

A third pharmacokinetic factor that influences the duration and severity of effects is redistribution. Drugs that are rapidly and extensively redistributed have a relatively short duration of action in the brain. This may explain why temazepam SGC 20 mg produced no residual effects on performance in the highway driving test 10 hours after administration in spite of its intermediate half-life of 11 (±6) hours, and why the effects of flunitrazepam 2 mg were significant and persistent, but less severe than expected based

on the drugs half-life of 15 (±5) hours. Concentrations of temazepam and flunitrazepam in plasma fall in a biphasic manner. After absorption concentrations first fall very rapidly to rather low levels due to redistribution, and than much slower while being excreted.

In summary, hypnotics that are rapidly absorbed and rapidly redistributed or eliminated could be safe for driving depending on the dose taken. Besides the pharmacokinetic profile of the drug, however, there are several other factors related to the its user that determine whether a particular drug and dose will have residual effects, such as pharmacokinetic, pharmacodynamic and behavioral tolerance, hepatic and renal function, and use of co-medication. Selection of a "safe" drug and dose offers no guarantee that an individual user will not be affected.

Antihistamines

Results from the study with chlorpheniramine (*chapter 7*) raise the question whether sedating antihistamines are safe hypnotics for patients who need to drive. Sedating antihistamines are one of the classes of drugs that have been used over the years to treat insomnia. They were already used for this purpose, before the introduction of barbiturates and benzodiazepines as hypnotics, and they are still very popular (Monti and Monti 2000). One of them, diphenhydramine is the primary active ingredient in various proprietary preparations for insomnia that are currently sold over-the-counter in many countries. However, their efficacy may be limited. In a review of the literature on the usefulness of H1 antagonists in the treatment of insomnia it is concluded that their use is not supported by available objective evidence (Monti and Monti 2000). One of the problems is the development of acute tolerance to the sedative effects that has been shown to occur by the third or fourth day. This is illustrated by results from our study with clemastine (*chapter 8*) and several previous studies assessing the effects of first generation antihistamines on driving (O'Hanlon and Ramaekers 1995). It would seem that the sedating antihistamines are only helpful for occasional use.

Another intriguing aspect of the effects of antihistamines is the gender difference in sensitivity. As shown in *chapter 9* women seem more sensitive to the sedating effects of emedastine and cetirizine. Similar effects were found for acrivastine (Ramaekers and O'Hanlon, 1994; Robbe and O'Hanlon, 1990) and clemastine (Vuurman et al., 1994). Since no significant correlation with bodyweight was found in the study with emedastine, some other mechanism might be responsible. Interestingly, histaminergic neurons in the

tuberomammilary nucleus express estrogen receptors that modulate their activity [Fekete et al., 1999]. The neurons become more active as estradiol increases during the follicular phase and very active just before ovulation. They project to luteinizing hormone–releasing hormone neurons and are responsible for the LH surge causing ovulation. The following fall in estradiol may diminish histaminergic activity, in general, making all the effects of H1 antagonists more prominent. It would be interesting to test this hypothesis by measuring the effects of H1 antagonists across the menstrual cycle.

A most remarkable finding was the slight improvement of driving performance associated with the use of fexofenadine, suggesting that the drug has weak stimulating effects (*chapter 8*). Although unexpected, it was in line with the previous finding for terfenadine and ebastine. At this time, the metabolites of two other successful antihistamines, desloratadine and levocetirizine, have been tested using the same highway driving test (Verster 2002; Vuurman et al. submitted). Neither was found to have any adverse effects on driving performance, as expected. But it was highly remarkable that the metabolite of loratadine, desloratadine, was also found to improve driving performance slightly in a car following task. Although these effects are all very weak, they do support the hypothesis that H1 antagonist can produce weak stimulating effects, depending on the dose. The underlying mechanism is unclear. Two possible mechanisms are suggested by results from animal studies. One is that antihistamines inhibit dopamine reuptake. For example, Matsunaga et al. (1998) examined the effects of 10 antihistamines on dopamine uptake in synaptosomes. They found that ebastine most potently inhibited dopamine reuptake, followed by terfenadine, oxatomide and astemizole. Emedastine showed little effect. There are also several studies in rats providing behavioral evidence that some antihistamines stimulate dopaminergic transmission. For example, Suzuki et al. (1999) using a place preference paradigm with rats, showed that chlorpheniramine and tripelennamine produced rewarding effects that followed a bell shaped dose response curve. The effects were abolished by pretreatment with a D1 antagonist. Recently Korotkova et al. (2002) provided evidence that there may be a second mechanism by which antihistamines enhance dopaminergic transmission. They showed that histamine in the substantia nigra pars reticulata stimulates GABAergic neurons. The latter tonically inhibit dopamine neurons in the substantia nigra pars compacta. Histamine did the same in the ventral tegmental area. The effects seemed to be mediated by H1 receptors. These results from these studies suggest that H1 antagonists can stimulate dopaminergic neurotransmission by reducing GABAergic inhibition of dopamine pathways and by

blocking dopamine reuptake. The bell shaped dose-response curve found by Suzuki et al. (1999). Might explain why the effects only occur at certain doses.

Methodology

The methodological guidelines described in *chapter 2* have been accepted and advanced by the International Council for Alcohol Drugs and Traffic Safety (ICADTS 1999). It was agreed that the final evidence that a drug is safe for driving or hazardous to a specified degree should be based on the combined results of a program of research, that proceeds from conventional laboratory testing to sophisticated driving simulators and finally include actual driving. In line with this the European Medicines Evaluation Agency (EMEA), the pan-European equivalent of the U.S. Food and Drug Administration, recognized that short laboratory psychomotor tests may be used for initial assessment of the residual effects of a hypnotic, but cannot provide unequivocal evidence that impairments will not emerge in more complex real-life activities that extend over hours (O'Hanlon 2002). The EMEA therefore recommends the application of more realistic tests lasting a minimum of one hour, in their guidelines for the development of hypnotic drugs (Angst et al., 1995).

These guidelines should stimulate the design of studies using more similar test procedures to assess the effects of different drugs and doses. It is expected that this will facilitate future attempts to compare results from different studies and draw firm conclusions about the effects of different drugs, doses and formulations.

Healthy volunteers and patients

Most experimental studies presented in this dissertation employed healthy volunteers as subjects. It is often questioned whether the results found in healthy volunteers are predictive for patients. It is assumed that anxious, depressed and insomniac patients are already impaired in psychological performance because of the disorders themselves. It is than argued that by reducing the anxiety, depression or sleep problem, the drugs tend to improve psychological performance. This improvement is supposed to outweigh any drug-related impairment, except when high doses are given or in elderly (Lader 2001). These assumptions have not been properly tested.

Although there are studies indicating that anxious, depressed and insomniac patients have cognitive problems, the effects of these disorders on psychomotor performance and driving are less clear (e.g., Akerstedt et al., 2002; Austin et al., 2001; Cushman et al., 1990; Leger 2000; Sateia et al., 2000). Yet, studies using the highway driving test suggest that driving performance of insomniac, anxious and depressed patients is similar to that of healthy volunteers and can be impaired by drugs.

The effects of anxiolytics on driving performance of patients were assessed in two studies (Van Laar et al., 1992; Vermeeren et al., 1994). Results show driving performance at baseline did not differ from those of normal controls. Moreover, patients treated with placebo continued to drive in a normal manner and their performance did not improve even though their anxiety diminished (Vermeeren et al., 1994). In contrast, driving performance of patients treated with anxiolytics (diazepam 5 mg t.i.d., lorazepam 2 b.i.d., and alpidem 50 mg b.i.d.) deteriorated while their feelings of anxiety diminished. The degree of impairment found in these patients was equivalent to that found in studies with healthy volunteers, suggesting no attenuation of the side effects due to improved symptoms (O'Hanlon et al., 1995).

The effects of antidepressants on driving performance of depressed outpatients were assessed in a study comparing the effects of moclobemide and fluoxetine (Ramaekers et al., 1997). Results showed that driving performance of these patients on baseline was on average only slightly worse than that of healthy volunteers. Yet, similar to the findings in anxious patients, remission of depressive symptoms during drug treatment was not accompanied by an improvement of driving performance.

The effects of hypnotics on driving performance of insomniac patients were assessed in six studies (see *chapter 3 and 4*). The study described in *chapter 4* was the only one that used polysomnography to assess sleep, however. This revealed that subjects in this study had no objectively measurable sleep disturbance. Nevertheless, it is likely that these subjects are representative for at least a group of hypnotic users, since most physicians will not apply polysomnography to diagnose insomnia before prescribing a hypnotic. Since these persons do not suffer from an objective lack of sleep, this cannot impair their performance. Consequently, the use of hypnotics cannot improve their performance. The residual sedation can only impair it.

As mentioned before these studies suggest that driving performance of patients is largely similar to that of healthy volunteers and can be impaired by drugs. The results from healthy volunteer studies are therefore expected to be predictive for the effects of

drugs on driving performance of patients. This is confirmed by epidemiological studies showing that use benzodiazepines and antidepressants is associated with increased risks for traffic accidents. Nevertheless more information is needed on the interaction of unwanted side-effects and the therapeutic effects of drugs.

Conclusion

It should be clear from the preceding chapters that hypnotics and antihistamines can impair cognitive functions and driving performance. Epidemiological studies confirm that the use of such impairing drugs is associated with increased risk of domestic and traffic accidents. Fortunately, the development and use of less impairing alternatives has already reduced the burden posed by such drug related accidents. Nevertheless, pharmaceutical industries should continue to develop safer, less behaviorally toxic, drugs. Each new drug should be tested using experimental studies, for its effects on cognitive and psychomotor performance, in particular driving. The final evidence that a drug is safe for driving or hazardous to a specified degree should be based on the combined results of a program of research that follow the guidelines endorsed by the International Council on Alcohol Drugs and Traffic Safety (ICADTS 1999). Such research should facilitate independent reviews or meta-analyses should make the results more readily available for use by health care providers. Patients should be better informed about the specific effects of a drug and dose by the prescribing physician and through more specific warnings on the package insert.

Over the years the systematic and scientific study of the effects of medicinal drugs on driving performance, using the same standardized driving test and similar designs and procedures, has proven a fruitful way of compiling a large set of data that can be used to compare the effects of various drugs and doses between studies and identify factors that modulate such effects. This dissertation has shown both the practical and theoretical value of such research.

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Summary

Centrally acting or 'psychoactive' drugs are widely used in the treatment of psychological, psychiatric or neurological problems, such as anxiety, depression, schizophrenia, epilepsy and Parkinson's disease. Yet, like all medicinal drugs, these substances not only have therapeutic effects, but also a variety of side effects on mental and behavioural functions. They may cause sedation and associated slowing of reactions and attentional deficits, memory disturbances, or emotional and motivational changes. In patients using these drugs such effects can have severe adverse effects on their quality of life and safety of activities of daily living. One of the most important daily activities in industrialized societies is car driving. Yet it is also one of the most hazardous, as shown by injury and mortality statistics. According to conservative estimates, an average of 10% of the adult population in the Europe drives under the influence of medicinal drugs with twice the risk of becoming involved in a traffic accident. If so, these drugs caused 4,500 deaths, 135,000 injuries and 6.3 billion Euro in property damage and medical care per year.

There are two ways to lower the rate of drug-related accidents: *prevention* by reducing the use of performance impairiung drugs and *restriction*, for example by legally prohibiting driving while under the influence of performance impairing drugs. Prevention is of course preferred and can be achieved by stimulating the development and prescription of drugs that are unlikely to produce performance impairment. The latter is possible since large differences exist between the effects of different drugs within the same therapeutic class. Either way information is needed regarding the impairing effects of many different drugs and doses and on factors that may modulate these effects.

Chapter 2 - The European Community's Committee for Proprietary and Medicinal Products (CPMP) has accepted a 3-tier warning system for identifying the driving hazard potential of every drug as part of the pan-European registration process. The information should be included in package inserts in all Member States as of January 1st 1994.

Determination of the degree of impairing effects of a drug/dose, or categorization according to this system, should be based on information provided by the field of human psychopharmacology. It was demonstrated that drugs can be categorized on the basis of expert consensus. Yet, the experts' task would have been much simpler if different investigators had employed similar methodologies. Differences between studies with respect to experimental design, performance tests, drug doses and subjects make it extremely difficult to reach any firm conclusions concerning the degree of behavioral impairment attributable to particular drugs. We surveyed a number of international experts in the field of drugs and driving with the objective of providing a preliminary set of guidelines based on a consensus of scientific opinion, regarding methodology for experimental research on medicinal drugs affecting driving performance.

Chapter 3 - The risk of "hangover effects", i.e., residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration, is one of the main problems associated with the use of hypnotics. Epidemiology shows that use of hypnotics increases patients' risk for injurious accidents. It seems that risks generally increase with increasing half-life. Yet, use of hypnotics with short half-lives, such as triazolam and zopiclone and zolpidem, was also occasionally found to be associated with increased risks. Information on duration and severity of residual effects of 11 hypnotics (flunitrazepam, flurazepam, loprazolam, lormetazepam, midazolam, nitrazepam, temazepam, triazolam, zaleplon, zolpidem, zopiclone) is derived from expert ratings, a meta-analysis and actual driving studies. The summary table provided in this chapter (table 3.8) should enable prescribing clinicians to select the drug and dose considered most favorable in this respect, within the range of possibilities of the individual patient. This table should also enable clinicians to inform patients more easily and adequately about the expected degree and duration of residual effects of the hypnotic dose they are prescribing.

Chapter 4 - Zolpidem is the first of new class of hypnotics, the imidazopyridines, which are structurally unrelated to the benzodiazepines. It preferentially binds to $\omega 1$ receptors, i.e., GABA-A receptors containing an $\alpha 1$ subunit. The study described in this chapter intended to determine whether the imidazopyridine zolpidem and the benzodiazepine flunitrazepam differentially affect sleep architecture, and whether zolpidem had any residual effects on driving performance or memory functions the morning after nightly

drug administration. These effects were compared with flunitrazepam, partial sleep deprivation and placebo.

Seventeen women who complained of chronic sleep disturbances underwent four experimental sessions on separate nights at weekly intervals – initially partial sleep deprivation, and thereafter zolpidem 10 mg, flunitrazepam 2 mg and placebo administered according to a double-blind, crossover design. Polysomnographic recordings were made each night, and a word learning test and the highway driving test were performed the following morning. Subjective assessments of sleep quality, daytime sleepiness and activation, effort to perform the tests and driving quality were determined by questionnaires.

Polysomnographic recording showed that zolpidem and flunitrazepam significantly shortened sleep onset latency. Zolpidem respected the overall sleep architecture, whereas flunitrazepam significantly decreased REM sleep over the whole night. Subjectively, flunitrazepam improved sleep quality and duration, but subjects reported feeling drowsier and less active in the morning. In addition, flunitrazepam significant impaired memory performance, whereas zolpidem did not. Driving performance was not disturbed by any drug treatment or partial sleep deprivation. It was concluded that zolpidem 10 mg is an effective hypnotic that causes no psychometric dysfunction the next day.

Chapter 5 - Zaleplon is a new pyrazolopyrimidine hypnotic. Similar to zolpidem it preferentially binds to GABA-A receptors containing an α1 subunit, and has low affinity for GABA-A receptors containing α2 and α3 subunits. It possesses an unusually rapid rate of elimination (t1/2 1 hour), which may allow patients to take the drug later in the night and be free of residual effects the next morning. The study described in this chapter was designed to measure the residual effects of zaleplon 10 and 20 mg after bedtime and middle-of-the-night administration, on memory functions and actual driving performance.

Twenty-eight healthy volunteers (14 men, 14 women, aged 21-40 y) participated in a double-blind, 7-way, crossover study. They ingested capsules twice on each treatment night; once before initiating sleep and again after being briefly awakened 5 hours later. Treatments were: placebo at both times, zaleplon 10 or 20 mg, or zopiclone 7.5 mg at bedtime followed by placebo, or placebo first and a hypnotic in the middle of the night. Subjects arose 3 hours after the second dose. One hour later, sleep quality and mood were

assessed by questionnaires and balance and memory in a test battery, comprising word learning, spatial memory, semantic verification and syntactic reasoning tests. A standardized actual driving test was undertaken between 5 and 6 hours after the second dose.

Zaleplon had no residual effects on driving regardless of dose and time of administration. The only significant effects measured after zaleplon administration were minor impairments of delayed recall in the word learning test following middle of the night administration of both doses. Zopiclone's effects on driving were adverse. Even when the drug was administered 10 h before the test it produced an effect equivalent to that of alcohol in a study with 24 "social drinkers" who undertook the test while having a blood alcohol concentration of about 1.0 g/L. Zopiclone's effects were far worse after middle-of-the-night administration. The amnestic effects zopiclone were obvious in every test after middle-of-the-night doses, while the evening doses still impaired delayed recall 11.5 h after its administration. It was concluded that zaleplon 10 and 20 mg can be taken up to 5 hours before driving with little risk of serious impairment. Use of zopiclone 7.5 mg should be avoided by patients who need to be alert the morning after bedtime administration.

Chapter 6 - The primary objective of the study described in this chapter was to replicate our previous finding that zaleplon, taken in the recommended dose of 10 mg at bedtime, has no residual effects the next morning on car driving performance, memory or psychomotor skills related to driving. More supporting evidence was required, before concluding that zaleplon 10 mg is safe enough for unsupervised use by individual patients who drive. The secondary objective was to compare the residual effects of zaleplon 10 mg and zopiclone 7.5 mg with those of alcohol at a peak BAC of 0.5 g/L on the same tests and in the same subjects.

Thirty healthy volunteers (15 men and 15 women, aged 21 to 45 yrs) participated in a two-part placebo controlled, crossover design. In Part 1 alcohol and alcohol-placebo drinks were administered single blind around noon. In Part 2 single oral doses of zaleplon 10 mg, zopiclone 7.5 mg and placebo were administered double blind at bedtime. Tests included a highway driving test, laboratory tests of word learning, critical tracking and divided attention, and subjective assessments of sleep, mood and effects of treatments on driving. Driving started 40 minutes after alcohol consumption in Part 1, and 10 hours after drug intake in Part 2.

The results demonstrated that alcohol, at average plasma concentrations of approximately 0.3 g/L, significantly impaired performance in all tests. Zaleplon's residual effects did not differ significantly from those of placebo in any test. In contrast, zopiclone had significant residual effects on driving, divided attention and memory. The magnitude of impairment in the driving test observed the morning after zopiclone 7.5 mg was twice that observed with alcohol in the same subjects. In contrast to results from objective tests, subjects did not feel less alert the morning after zopiclone and did not anticipate that the drug would affect their driving performance. They did notice and anticipate the effects of alcohol though.

Chapter 7 - Owing to their recency, second generation antihistamines are more expensive than older antihistamines. Health maintenance organizations and their participating physicians are aware of the similar efficacies of old and new antihistamines, but also of the differences in their respective costs and side-effects. In an effort to reduce the burden of side effects produced by old antihistamines and the financial burden of new antihistamines, a unique dosing regimen is being used. It involves an alternating PM/a.m. combination of sedating and nonsedating antihistamines, the former to be taken at bedtime and the latter upon arising. The study described in this chapter was designed to determine whether such a dosing regimen, using the combinations of the sedating antihistamine chlorpheniramine 8 and 12 mg (sustained release formulations) administered at bedtime followed by the nonsedating antihistamine terfenadine 60 mg the next morning would have residual sedative effects capable of impairing driving performance.

Antihistamines effects were measured in two driving tests conducted in actual traffic (Highway Driving and Car-Following), and compared with those of placebo and the hypnotic flurazepam 30 mg using a 4-way, observer- and subject-blind, cross-over design. Drug effects were assessed in the morning of the third treatment day. Subjects were all (n= 24) women, since results from previous studies suggested that they have smaller safety margins than men with respect to the impairing effects of antihistamines on driving performance.

It was anticipated that administration of chlorpheniramine 8 and 12 mg at bedtime would affect the volunteers' driving performance the next morning, based on the fact that its elimination half-life is long enough to sustain its pharmacological activity for a considerable period. However, neither dose of chlorpheniramine had significant effects

on performance in any of the driving tests the next morning. The use of sustained release formulations may have attenuated the residual effects. In contrast, flurazepam 30 mg had significant residual effects on highway driving and car following performance. Its effects in the highway driving test were comparable to of alcohol in a group of female "social drinkers" while their average blood alcohol concentrations were 1.2 g/L. It is clear that subjects using flurazepam 30 mg should be informed about its potentially dangerous effects on driving the morning after nocturnal intake and even be advised to avoid operating any vehicle, or hazardous machinery during treatment

Chapter 8 - The study described in this chapter was designed to test whether fexofenadine, a selective H1-receptor antagonist, impairs psychomotor performance and car driving. Fexofenadine's structure is identical to terfenadine's active metabolite, except that fexofenadine is the hydrochloride salt. Since terfenadine was devoid of sedative effects when administered in normal therapeutic doses, fexofenadine was expected to be similarly free of behaviorally impairing side effects after normal doses. A secondary purpose was to assess possible pharmacokinetic or dynamic interactions between fexofenadine and alcohol that could affect driving, since many patients using antihistamines occasionally drink and drive.

Twenty-four healthy volunteers (12 male, 12 female, aged 21-45 y) participated in a double-blind 6-way crossover study. Fexofenadine was administered over five days in separate dosing regimens of 60 mg b.i.d., 120 mg q.a.m., 120 mg b.i.d. and 240 mg q.a.m. The effects were compared to those of placebo and a normal therapeutic dose of clemastine (i.e. 2 mg b.i.d.). Psychomotor tests (critical tracking, choice reaction time and sustained attention) and a standardized actual driving test were undertaken between 1.5-4 hours post a.m. dosing on days 1, 4 and 5 of each series. On day 5, subjects were challenged with a moderate alcohol dose prior to testing.

Results showed that fexofenadine did not by itself impair driving performance and did not add to the impairment produced by alcohol. On the contrary, the 120 mg b.i.d. dose, by itself, significantly improved driving performance on day 4, and both of 240 mg/d regimens significantly or almost significantly reduced alcohol's effect on driving performance on day 5. Both of the lower doses attenuated the alcohol effect about half as much as the higher doses, giving the impression that fexofenadine's capacity to antagonize that effect is dose-related. Pharmacologically, these effects are what one might expect from a mild stimulant that raises brain activation as a whole and the excitability of

neurons within the motor cortex in particular. Yet, the profile displayed by fexofenadine is different from those of the classic psychostimulants such as amphetamines, caffeine and nicotine. The latter enhance signal detection performance in vigilance tests whereas in this study fexofenadine did not. Further studies are required to confirm our explanation and to elucidate fexofenadine's mechanism of action. Clemastine 2 mg b.i.d., the active control, significantly impaired driving performance on days 1 and 4 to confirm the test's sensitivity to sedative effects of antihistamines. The combination of clemastine plus alcohol impaired driving performance to a greater degree than placebo plus alcohol but the difference was not significant.

Chapter 9 - The study described in this chapter was designed to determine whether a new highly potent, H1-selective antihistamine, emedastine, has impairing effects on driving and to evaluate its interactions with alcohol. Although its chemical structure resembles those of two relatively nonsedating antihistamines, and animal studies had shown that it had less effects on the CNS than the first generation antihistamines, its most commonly reported side effects in clinical trials was sleepiness.

Nineteen healthy volunteers (9 men, 10 women, age range 21 to 45 year) participated in a 4-way double-blind, crossover design. Treatments were emedastine 2 and 4 mg twice daily, cetirizine 10 mg once daily and placebo. Each treatment was administered for 5 days. Driving performance was measured using the highway driving test between 3 and 4 hours after administration of the morning dose on days 1, 4 and 5. Alcohol, sufficient for achieving a blood alcohol concentration of 0.5 g/L was given before driving on day 5 of each period.

Both emedastine doses similarly and significantly impaired driving in every test. The acute effects were as severe as any produced by relatively high doses of older antihistamines in previous studies employing the same highway driving test. Cetirizine's effects were less. They were significant over days 1 and 4 combined, though not separately. Alcohol increased driving impairment similarly in every condition. Women were more impaired by both antihistamines than men. Their greater sensitivity is often assumed to be the consequence of a smaller volume of distribution resulting in slightly higher plasma concentrations. However, there was no significant correlation between individuals' bodyweights and their performance impairment. Thus, the gender difference in response to antihistamines remains an intriguing mystery for further investigation. Future studies determining the effects of antihistamines on performance should employ

either mixed-gender subject samples or those comprised exclusively of the gender that presently seems the more sensitive.

Chapter 10 - This chapter comprises some concluding remarks on the factors determining whether a hypnotic is safe for use by patients who drive; the use of antihistamines as hypnotics; the gender difference in sensitivity to antihistamines; the stimulating effect of antihistamines; the propagation of methodological guidelines; and the question whether results from healthy volunteers are predictive for patients.

Samenvatting

Centraal werkende, z.g. "psychoactieve" geneesmiddelen worden veel gebruikt bij de behandeling van psychische, psychiatrische of neurologische aandoeningen, zoals angst- en paniekstoornissen, depressiviteit, schizofrenie, epilepsie en de ziekte van Parkinson. Net als andere geneesmiddelen, kunnen deze middelen naast het therapeutische effect ook bijwerkingen geven op mentaal functioneren en gedrag, zoals sedatie en daaraan gerelateerd vermindering van het reactievermogen, aandachtsstoornissen, geheugenstoornissen, en veranderingen in stemming en motivatie. Deze effecten kunnen ernstige gevolgen hebben voor de kwaliteit van leven van patienten en voor hun veiligheid bij dagelijkse bezigheden, zoals werk en deelname aan het verkeer. Het laatste is volgens de ongevallenstatistieken ook één van de meest risicovolle bezigheden. Volgens voorzichtige schattingen rijdt gemiddeld tien procent van de Europeanen onder invloed van centraal werkende geneesmiddelen. Hun risico om bij een ongeval betrokken te raken is tweemaal zo groot als normaal. Volgens deze schattingen veroorzaakten geneesmiddelen per jaar 4.500 doden, 135.000 gewonden en 6.3 miljard Euro aan materiële schade en medische kosten.

Er zijn twee manieren waarop het aantal medicijngerelateerde ongevallen kan worden verminderd: *preventie* door het terugdringen van het gebruik van geneesmiddelen die het functioneren verminderen en *restrictie* door bijv. een verbod op rijden onder invloed van rijgevaarlijke geneesmiddelen. Preventie heeft vanzelfsprekend de voorkeur en kan o.a. worden bereikt door geneesmiddelen te ontwikkelen en voor te schrijven die het functioneren niet nadelig beïnvloeden. Dit laatste is mogelijk aangezien er grote verschillen blijken te bestaan tussen de centrale bijwerkingen van geneesmiddelen binnen eenzelfde therapeutische klasse. Hoe dan ook is er informatie nodig over de mate waarin verschillende geneesmiddelen en doseringen het dagelijks functioneren van patienten beinvloeden en over de factoren hier een invloed op hebben.

Hoofdstuk 2 - De EG-commissie voor Proprietary and Medicinal Products (CPMP) heeft, als onderdeel van de Europese geneesmiddelregistratie een waarschuwingssysteem aangenomen, waarin elk geneesmiddel in een van drie klassen kan worden ingedeeld, afhankelijk van de mate waarin het de rijvaardigheid beïnvloedt. Deze informatie zou vanaf 1 januari 1994 moeten worden opgenomen in patiëntenbijsluiters in alle landen van de Europese Gemeenschap.

De classificatie van geneesmiddelen in verschillende doseringen binnen dit systeem zou gebaseerd moeten zijn op informatie afkomstig van humaan psychofarmacologisch onderzoek. Het is gebleken dat geneesmiddelen op basis hiervan goed in dit systeem zijn in te delen door middel van een consensus onder experts. De opdracht van de experts zou echter eenvoudiger zijn geweest als verschillende onderzoekers meer vergelijkbare onderzoeksmethoden hadden toegepast. Verschillen in onderzoeksopzet, keuze van testen, doseringen en proefpersonen maken het bijzonder lastig eenduidige conclusies te trekken over de mate waarin specifieke medicijnen de prestaties beïnvloeden. Dientengevolge is het idee ontstaan om richtlijnen op te stellen voor deze onderzoeksmethodologie. Om deze richtlijnen te baseren op wetenschappelijke consensus hebben wij een enquête gehouden onder experts op dit onderzoeksterrein.

Hoofdstuk 3 - Het risico op "kater effecten", d.w.z. residuele slaperigheid overdag en achteruitgang van psychomotore en cognitieve functies de dag na inname, is een van de belangrijkste problemen bij het gebruik van slaapmiddelen. De epidemiologie geeft aanwijzingen dat slaapmiddelgebruik gepaard gaat met een verhoging van het risico op ongevallen met lichamelijk letsel. Het blijkt dat risico's over het algemeen toenemen naarmate de halfwaardetijden langer zijn. Echter, gebruik van slaapmiddelen met korte halfwaardetijden, zoals triazolam, zopiclone en zolpidem, blijkt soms ook gepaard te gaan met verhoogde risico's. Informatie over de duur en ernst van de resteffecten van 11 slaapmiddelen (flunitrazepam, flurazepam, loprazolam, lormetazepam, midazolam, nitrazepam, temazepam, triazolam, zaleplon, zolpidem, zopiclone) is afgeleid van classificaties door experts, een meta-analyse van experimentele studies en rijvaardigheidsstudies. De tabel waarin deze informatie wordt samengevat (tabel 3.8) is bedoeld om clinici die deze middelen voorschrijven in staat te stellen een keuze te maken voor een middel en dosering die in dit opzicht het meest voordelig is gezien de mogelijkheden van een individuele patiënt. Deze tabel zou artsen ook in staat moeten

stellen patiënten snel en adequaat voor te lichten over de verwachte ernst en duur van de resteffecten van het slaapmiddel dat zij voorschrijven.

Hoofdstuk 4 - Zolpidem is de eerste van een nieuwe klasse slaapmiddelen, de imidazopyridines, die structureel verschillen van de benzodiazepines. Zolpidem bindt bij voorkeur aan ω1 receptoren, d.w.z. GABA-A receptoren die een α1 element bevatten. Het in dit hoofdstuk beschreven onderzoek beeoogde vast te stellen of de imidazopyridine zolpidem en de benzodiazepine flunitrazepam verschillende effecten hebben op slaaparchitectuur en beoogde te bepalen of zolpidem resteffecten heeft op rijvaardigheid en geheugenfuncties de ochtend na inname voor het slapen. Deze effecten werden vergeleken met die van flunitrazepam, partiele slaap deprivatie en placebo.

Zeventien vrouwen met klachten over chronische slaapproblemen ondergingen vier experimentele sessies in verschillende nachten met telkens een week er tussen – als eerste partiele slaap deprivatie en daarna zolpidem 10 mg, flunitrazepam 2 mg en placebo volgens een dubbelblind, gekruist design. Gedurende de nachten werden er polysomnografische registraties gemaakt en in de ochtenden werden er telkens een geheugentest en een rijvaardigheidstest afgenomen. Met vragenlijsten werden subjectieve beoordelingen gemeten van slaapkwaliteit, slaperigheid, activatie overdag en mentale inspanning om de testen uit te voeren.

Polysomnografische registraties toonden aan dat zolpidem en flunitrazepam de inslaaptijd significant verkortten. Zolpidem liet de algemene slaaparchitectuur onveranderd, terwijl flunitrazepam de hoeveelheid REM slaap significant verminderde in vergelijking met placebo. Subjectief verbeterde flunitrazepam de kwaliteit en duur van de slaap, maar de proefpersonen voelden zich 's ochtends ook iets suffer en minder actief. Daarbij verslechterde flunitrazepam de geheugenprestaties, terwijl zolpidem dat niet deed. De rijvaardigheid was niet anders dan normaal na gebruik van een van de slaapmiddelen of na partiele slaapdeprivatie. De conclusie was dat zolpidem een effectief slaapmiddel is dat de volgende dag geen psychometrische disfunctie veroorzaakt.

Hoofdstuk 5 - Zaleplon is een nieuw pyrazolopyrimidine slaapmiddel. Net als zolpidem bindt het bij voorkeur aan GABA-A receptoren met een α1 element en heeft het een lage affiniteit voor GABA-A receptoren die α2 of α3 elementen bevatten. Zaleplon wordt ongewoon snel afgebroken (t½ 1 uur), waardoor patiënten het later in de nacht kunnen innemen zonder de volgende ochtend last te hebben van resteffecten. Het in dit

hoofdstuk beschreven onderzoek was opgezet om de resteffecten van zaleplon 10 en 20 mg op rijvaardigheid en geheugen functies te bepalen, na inname 's avonds voor het slapen en na inname midden in de nacht.

Achtentwintig gezonde vrijwilligers (14 mannen en 14 vrouwen tussen 21 en 40 jaar oud) namen deel aan een dubbelblind, 7-wegs, gekruist onderzoek. Zij namen tweemaal per nacht twee capsules in; eenmaal 's avonds voor het slapen en 5 uur later nog een keer, terwijl ze even wakker werden gemaakt. De behandelingen waren: placebo op beide tijdstippen, zaleplon 10 mg, zaleplon 20 mg of zopiclone 7,5 mg 's avonds gevolgd door placebo of eerst placebo en midden in de nacht een slaapmiddel. Proefpersonen stonden 3 uur na de nachtelijke dosering op. Nog een uur later werden subjectieve slaapkwaliteit en stemming gemeten m.b.v. vragenlijsten en werd evenwicht en geheugen gemeten m.b.v. een testbatterij, waarin een woordenleertaak, een ruimtelijke geheugentaak, een semantische verificatietaak, een syntactische redeneertaak waren opgenomen. Tussen 5 en 6 uur na de nachtelijke dosering werd een gestandaardiseerde rijvaardigheidstest afgenomen.

Zaleplon had geen resteffecten op rijvaardigheid, onafhankelijk van dosis en tijd na inname. De enige significante effecten die van zaleplon werden gevonden waren geringe verslechteringen van uitgestelde herinnering (delayed recall) in de woordenleertaak na beide nachtelijke doseringen. Zopiclone had nadelige effecten op rijvaardigheid. Zelfs wanneer het middel 10 uur voor het rijden was ingenomen had het nog effecten die vergelijkbaar waren met die van alcohol, zoals gemeten in een studie met 24 "sociale drinkers" die dezelfde rijvaardigheidstest deden terwijl ze een gemiddelde bloed alcohol concentratie hadden van 1,0 promille (g/L). Zopiclone's effecten op rijvaardigheid na de nachtelijke dosering waren nog sterker. De geheugenverslechterende effecten van zopiclone waren duidelijk aanwezig in alle geheugentesten na de nachtelijke doseringen, terwijl de avonddosering 11,5 uur na inname ook nog effecten op geheugen had. De conclusie was dat zaleplon 10 en 20 mg tot 5 uur voor het rijden kan worden ingenomen met weinig risico dat het de rijvaardigheid ernstig zal schaden. Gebruik van zopiclone 7,5 mg voor het slapen zou vermeden moeten worden door patiënten die de volgende ochtend alert moeten zijn.

Hoofdstuk 6 - Het primaire doel van de in dit hoofdstuk beschreven studie was de bevindingen van ons vorige onderzoek te repliceren, n.l. dat zaleplon in de aanbevolen dosering van 10 mg voor het slapen, de volgende ochtend geen rest-effecten heeft op

rijvaardigheid, geheugen en psychomotore vaardigheden gerelateerd aan rijvaardigheid. Meer ondersteunend bewijs was nodig voordat geconcludeerd kon worden dat zaleplon 10 mg veilig genoeg is om ongecontroleerd gebruikt te kunnen worden door individuele patiënten die autorijden. Het secundaire doel van de studie was om de resteffecten van zaleplon 10 mg en zopiclone 7,5 mg te vergelijken met de effecten van alcohol in maximale concentraties van 0,5 g/L op dezelfde testen en bij dezelfde proefpersonen.

Dertig gezonde vrijwilligers (15 mannen en 15 vrouwen, tussen 21 en 45 jaar oud) namen deel aan een tweeledig, placebo gecontroleerd, gekruist onderzoek. In deel 1 werden alcohol en alcohol-placebo drankjes enkelblind toegediend rond het middaguur. In deel 2 werden eenmalige orale doses zaleplon 10 mg, zopiclone 7,5 mg en placebo dubbelblind toegediend voor het slapen. De testen bestonden uit een snelwegrit, laboratoriumtesten voor verbaal geheugen, psychomotoriek en verdeelde aandacht, en subjectieve maten van slaap, stemming en de effecten van medicatie op rijvaardigheid. De rijtest begon 40 minuten na alcoholconsumptie in deel 1 en 10 uur na inname van medicatie in deel 2.

De resultaten toonden aan dat alcohol, bij een gemiddeld plasmaconcentratie van 0,3 g/L, de prestatie in alle testen significant verslechterde. Zaleplon's resteffecten verschilden in geen van de testen significant van placebo, terwijl zopiclone wel significante resteffecten had op rijvaardigheid, verdeelde aandacht en geheugen. De mate waarin zopiclone de rijvaardigheid verminderde was tweemaal zo groot als die van alcohol in dezelfde groep proefpersonen. In tegenstelling tot de resultaten van objectieve testen, voelden proefpersonen zich niet minder alert de ochtend na gebruik van zopiclone en verwachten dan ook niet dat het middel hun rijvaardigheid zou verminderen. Zij merkten en verwachten echter wel effecten van alcohol.

Hoofdstuk 7 - Omdat ze nieuwer zijn, zijn tweede generatie antihistaminica duurder dan oudere middelen. Organisaties voor gezondheidszorg en de aangesloten artsen zijn zich bewust van het feit dat oude en nieuwe antihistaminica even effectief zijn, maar ook dat de kosten van deze middelen verschillen. Daarom wordt een uniek doseringsschema gebruikt in een poging de lasten van bijwerkingen van oudere middelen en de kosten van nieuwere middelen te verminderen. Dat schema houdt in dat er 's avonds en 's ochtends afwisselend een sederend en een niet-sederend antihistaminicum wordt gebruikt. Het sederende middel wordt voor het slapen genomen en het niet-sederende 's ochtends na het opstaan. Het in dit hoofdstuk beschreven onderzoek was opgezet om te bepalen of

een dergelijk doseringsschema, waarin 's avonds het sederende antihistaminicum chloorfeniramine 8 en 12 mg (in een formulering voor vertraagde afgifte) wordt gegeven, 's ochtends gevolgd door het niet-sederende antihistaminicum terfenadine 60 mg, rest-effecten zou hebben die de rijvaardigheid zouden kunnen beïnvloeden.

De effecten van antihistaminica werden gemeten met twee rijvaardigheidstesten in het normale verkeer (een snelwegrit en een 'car-following' taak) en vergeleken met die van placebo en het slaapmiddel flurazepam 30 mg, in een 4-wegs, dubbelblind, gekruist onderzoek. De effecten van medicatie werden gemeten in de ochtend van de derde behandeldag. De proefpersonen waren allemaal (n= 24) vrouwen, aangezien de resultaten van vorige studies suggereerden dat vrouwen geringere veiligheidsmarges hebben dan mannen m.b.t. de nadelige effecten van antihistaminica op rijvaardigheid.

De verwachting was dat toediening van chloorfeniramine 8 en 12 mg voor het slapen de rijvaardigheid van de vrijwilligers de volgende ochtend zou verminderen, omdat de halfwaardetijd van dit middel zo lang is dat het gedurende een aanzienlijke periode farmacologisch actief blijft. Echter, geen van beide doseringen chloorfeniramine had significante effecten op rijvaardigheid de volgende ochtend. Het gebruik van de formulering voor vertraagde afgifte kan de resteffecten afgezwakt hebben. Flurazepam 30 mg had daarentegen wel significante effecten op prestatie tijdens de snelwegrit en de car-following taak. De effecten van dit slaapmiddel in de snelwegrit waren vergelijkbaar met die van alcohol in een groep 'sociale drinkers' met bloed-alcohol-concentraties van gemiddeld 1,2 g/L. Het is duidelijk dat mensen die flurazepam 30 mg gebruiken geïnformeerd moeten worden over de mogelijke gevaarlijke effecten op rijvaardigheid de ochtend na inname en misschien moet hen zelfs aangeraden worden geen auto te besturen of gevaarlijke machines te bedienen tijdens de behandeling .

Hoofdstuk 8 - De in dit hoofdstuk beschreven studie was opgezet om te bepalen of fexofenadine, een selectieve H1-antagonist, psychomotore functies en rijvaardigheid nadelig beïnvloedt. De chemische structuur vande base van fexofenadine is gelijk aan die van de actieve metaboliet van terfenadine. Aangezien terfenadine vrij is gebeleken van sedatieve effecten wanneer het in de normale therapeutische dosering werd gegeven, werd verwacht dat fexofenadine in een normale dosering eveneens vrij zou zijn van nadelig effecten op gedrag. Een ander doel van deze studie was de mogelijke farmacokinetische of dynamische interactie van fexofenadine en alcohol op rijvaardigheid te bepalen, omdat

veel patiënten die antihistaminica gebruiken bij gelegenheid ook alcohol gebruiken en dan autorijden.

Vierentwintig gezonde vrijwilligers (12 mannen en 12 vrouwen, tussen 21 en 45 jaar oud) namen deel aan een dubbelblind, gekruist onderzoek. Fexofenadine werd steeds 5 dagen gegeven in doseringen van 60 mg tweemaal daags, 120 mg eenmaal daags, 120 mg tweemaal daags, en 240 mg eenmaal daags. Deze effecten werden vergeleken met die van placebo en een therapeutische dosering clemastine (2 mg tweemaal daags). Psychomotore testen (tracking, keuzereactietijd en volgehouden aandacht) en een rijvaardigheidstest werden tussen 1,5 en 4 uur na de ochtenddosering uitgevoerd op dag 1, 4 en 5 van behandeling. Op dag 5 kregen de proefpersonen bovendien nog een matige dosis alcohol voorafgaand aan de testen.

De resultaten gaven aan dat fexofenadine op zichzelf geen nadelige effecten op rijvaardigheid had en dat het niets toevoegde aan de nadelige effecten van alcohol. In tegendeel, de dosering van 120 mg tweemaal daags verbeterde de rijvaardigheid significant op dag 4 en beide doseringen van 240 mg per dag verminderden op dag 5 de effecten van alcohol op rijvaardigheid op significante of bijna significant wijze. De beide lagere doseringen verminderden de effecten van alcohol half zoveel als de hogere doseringen, waardoor het likt alsof het vermogen van fexofenadine om deze effecten tegen te gaan dosis-afhankelijk is. Farmacologische lijken deze effecten op wat is te verwachten van een licht stimulerend middel, dat de globale hersenactiviteit en vooral de gevoeligheid van neuronen in de motorcortex verhoogt. Echter, het profiel dat fexofenadine laat zien verschilt van dat van klassieke stimulantia zoals amfetaminen, cafeïne en nicotine. Deze middelen verbeteren signaal-detectie in vigilantietaken, terwijl fexofenadine dat in deze studie niet deed. Er zijn meer studies nodig om onze verklaring te bevestigen en meer licht te werpen op het werkingsmechanisme van fexofenadine. Clemastine 2 mg tweemaal daags, de actieve controle, verminderde de rijvaardigheid significant op dag 1 en 4, wat bevestigt dat de test gevoelig is voor de sedatieve effecten van antihistaminica. De combinatie van clemastine en alcohol verminderde de rijvaardigheid in nog sterkere mate, maar het verschil was niet significant.

Hoofdstuk 9 - De in dit hoofdstuk beschreven studie was opgezet om te bepalen of een nieuwe, zeer potent H1-selectief antihistaminicum, emedastine, nadelige effecten heeft op rijvaardigheid en om de interactie van dit middel met alcohol te evalueren. Hoewel emedastine's chemische structuur lijkt op die van twee relatief niet-sederende

antihistaminica en dierstudies hebben aangetoond dat het minder effecten had op het centrale zenuwstelsel dan eerste generatie antihistaminica, was slaperigheid de meest frequent gerapporteerde bijwerking in klinische studies.

Negentien gezonde vrijwilligers (9 mannen en 10 vrouwen, tussen 21 en 45 jaar oud) namen deel aan een 4-wegs, dubbelblind, gekruist onderzoek. Behandelingen waren emedastine 2 en 4 mg tweemaal daags, cetirizine 10 mg eenmaal daags en placebo. Elke behandeling duurde vijf dagen. Rijvaardigheid werd gemeten met de rijtest over de snelweg tussen 3 en 4 uur na inname van de ochtenddosering op dag 1, 4 en 5 van behandeling. Op dag 5 van iedere behandelperiode werd een hoeveelheid alcohol gegeven die voldoende was om een maximale bloed-alcohol-concentratie van 0,5 g/L te veroorzaken.

Beide doseringen emedastine hadden vergelijkbare en significant nadelige effecten op rijvaardigheid in elk van de testen. De acute effecten waren even ernstig als die veroorzaakt door relatief hoge doseringen van oudere antihistaminica in voorgaande studies waarin dezelfde rijvaardigheidstest werd gebruikt. Cetirizine had minder effecten. Gecombineerd over dag 1 en 4 waren ze significant, maar niet op een van beide dagen afzonderlijk. Alcohol verergerde de nadelige effecten op rijvaardigheid in iedere condities even sterk. De rijvaardigheid van de vrouwen verminderde sterker ten gevolge het gebruik van antihistaminica dan die van mannen. Er wordt vaak verondersteld dat de grotere gevoeligheid van vrouwen voor de effecten van farmaca het gevolg is van hun kleinere verdelingsvolume, waardoor hun plasma-concentraties iets groter zijn. Er was in dit geval echter geen significante correlatie tussen lichaamsgewicht en prestatievermindering. Het sekseverschil in reactie op antihistaminica blijft daarom een intrigerend mysterie voor verder onderzoek. Toekomstige studies naar de effecten van antihistaminica op prestatie zouden ofwel gemengde steekproeven moeten gebruiken ofwel een steekproef die uitsluitend bestaat uit de sekse die op dit moment het meest gevoelig lijkt.

Hoofdstuk 10 - Dit hoofdstuk bevat een aantal afsluitende opmerkingen met betrekking tot factoren die bepalen of een slaapmiddel veilig is voor gebruik door patiënten die autorijden; het gebruik van antihistaminica als slaapmiddel; sekseverschillen in de gevoeligheid voor de effecten van antihistaminica; het stimulerend effect van antihistaminica; de verspreiding van methodologische richtlijnen; en de vraag of resultaten van onderzoek met gezonde vrijwilligers predictief zijn voor patiënten.

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Curriculum Vitae

Annemiek Vermeeren werd op 28 oktober 1959 geboren in Groningen. In 1978 behaalde zij het VWO diploma aan het Praedinius Gymnasium in diezelfde stad. Aansluitend begon zij met haar studie Psychologie aan de Rijksuniversiteit Groningen. Tijdens haar studie was zij als student bij de vakgroep Functieleer enige jaren betrokken bij onderzoek naar temporele informatie verwerking o.l.v. van dr. J.L. Jackson. Vervolgens was zij in 1984 en 1985 als studentassistent werkzaam bij het Verkeerskundig Studiecentrum in het kader van een onderzoek naar de dienst-, rij- en rusttijden van internationale vrachtwagenchauffeurs, onder supervisie van Prof. dr. J.F. O'Hanlon. In februari 1987 vertrok zij naar Maastricht voor een stageonderzoek aan het Instituut voor Geneesmiddelen, Veiligheid en Gedrag (IGVG), een onderzoeksinstituut in 1986 door dr. O'Hanlon opgericht aan de Rijksuniversiteit Limburg. Haar onderzoek richtte zich op de effecten van een benzodiazepine antagonist bij slaapgedepriveerde vrijwilligers. Hierdoor raakte zij geïnteresseerd in psychofarmacologisch onderzoek en in het bijzonder in slaap en het GABAerge systeem. Na haar afstuderen in de psychologische functieleer in februari 1988, was zij tot januari 1998 werkzaam aan het Instituut voor Humane Psychofarmacologie (voorheen IGVG). Daar heeft zij onderzoek verricht naar de effecten van geneesmiddelen op cognitieve functies en rijvaardigheid en naar de methodologie van dergelijk onderzoek. Vanaf 1996 was zij tevens als parttime universitair docent verbonden aan de Faculteit der Psychologie van de Universiteit Maastricht. Sinds 1 januari 1998 bekleedt zij deze functie voltijds.

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