Issues in Pharmacopsychology

Modeling effects in Driving and Cognition

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Modeling effects in Driving and Cognition

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Paranimfen

Marja Hortulanus
Frans Schreurs
Joost Gadiot †

Voor Rita

If 'manners maketh' man as someone said
Then he's the hero of the day
It takes a man to suffer ignorance and smile
Be yourself no matter what they say

From: Sting, 'An Englishman in New York'

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Chapter 1

Introduction

1.1 Background

For thousands of years and in all cultures humans have used drugs for medicinal, recreational and religious purposes. The substances best known in Europe were opium, hashish and hellebore, while rauwolfia has been used in the traditional medicine of most Asian countries (Caldwell 1993). Alraun (Mandragora), henbane (Hyoscyamus niger) and belladonna (Atropa belladonna) were popular among the ingredients of witches' ointments and potions.

A first major landmark in controlled drug development was the advancement of chemistry in the 19th century, which made it possible to synthesize new compounds with curative potentials. Many new compounds were marketed as a drug with little or no basic testing regarding safety or efficacy. After a few drug-related disasters such as the death in 1937 of over 100 children taking sulfanilamide dissolved in diethylene glycol, a toxic solvent (Geiling 1939), prescription and development became subject to regulation.

The second landmark was the development and use of drugs with specific psychoactive properties. Chlorpromazine was the first drug to be systematically studied as a psychoactive compound and described as useful in the treatment of mental disorders (Delay and Deniker 1952). This marked the birth of *psychopharmacology* as a rapidly growing scientific discipline in the early 1950's. From the beginning it has been interwoven with the disciplines of psychiatry and psychology, relying on behavioral models developed within those disciplines to define observed behavioral effects and to determine clinical end-points.

History

As knowledge about human behavior advanced, new models emerged to explain behavioral changes induced by psychoactive drugs. Besides an interest in clinical efficacy of new drugs is, attention was now also given to the accompanying unintended or 'side-effects' of drugs. Evaluation of effects of new drugs on behavior, mood and cognition were more carried out routinely in the process of drug development, both for CNS and non-CNS drugs. In the 1950's and early 1960's of the last century drug testing had its roots in behaviorism, being the mainstream of psychological research in those days (Skinner 1937,1971). In the 1970's behavioral research shifted towards a more cognitive oriented approach that considered the human as an information processing entity. This shift marked

the division of psychopharmacology into two lines of research as the cognitive approach of behavior was no longer solely embedded in neurophysiology:

> *Psychopharmacology* which sets out to understand the neurochemical action of drugs that yield a specific behavioral effect and had a biological approach.
> *Pharmacopsychology*, that focuses more on the psychological effects and behavioral consequences of drugs.

Both lines of research use similar tests and behavioral measures. The main differences is that in psychopharmacology the drug is considered as a *dependent* variable while in pharmacopsychology it is an *independent* variable. Often studies in this field are difficult to classify into either of the two as the hypothesis stated are not clear cut on the status of the drug as a dependent or independent measure. More often than not investigators fail to elaborate on the behavioral model that comprises the basis of their study. Tests and evaluations are described in functional units as 'Working memory', 'Vigilance' or 'Divided Attention'. Without knowledge of the underlying (neuro)psychological model one has little insight in the actual mechanism of action the drug is supposed to work by.

The problem to be addressed in this thesis

In pharmacopsychology behavior is the dependant variable which is influenced by the known properties of some drug. Because it focuses on behavior and not on the drug itself, a much more refined study of the behavioral effects can be made and evaluated within an existing psychological theory or (neuro)psychological framework. Therefore, given a drug with a known chemical profile one should be able to predict the effects on distinct behavioral functions. Contrary to the psychopharmacological approach, behavioral effects can be *predicted* in pharmacopsychology. However, this requires a fundamental understanding of human behavior and its neurochemical basis. Over the last decades much progress has been made in this domain but knowledge is still far from complete. The theoretical background for it has been developed in cognitive psychology in the 70's and 80's of the last century. Aided by the expanding knowledge of neurotransmitter systems and using new neuroimaging techniques, models were developed linking biological functioning with overt behavior.

Although a few sound behavioral models exist, only the minority of drug studies actually use them to predict and explain drug effects on behavior. Given the complexity of behavior in general and the general lack of specificity of most drugs this is understandable but also regrettable. Nevertheless well described behavioral domains should be open to this psychopharmacological approach. This thesis describes a series of eight experimental studies that investigate the feasibility of this approach in two distinct but specific behavioral domains: motor

and cognitive performance. Motor performance in these studies is operationaliszed in terms of car driving in a specially instrumented vehicle. Cognitive performance is studied in 'learning', operationaliszed as performance in a well controlled classroom situation. Before presenting the methods and results of the individual studies in this thesis more information on the theoretical background of pharmacopsychology is presented in the following paragraphs.

1.2 Issues in this thesis

Theoretical versus applied pharmacopsychology

Pharmacopsychology goes back to the experimental work of Kraepelin (1892) in Leipzig, a student of Wundt (1832-1920) who is often referred to as the 'Father of Experimental Psychology'. In a series of experiments with healthy volunteers, Kraepelin studied the effects of alcohol on behavior as well as then known CNS active substances like morphine, paraldehyde, chloral hydrate and ether. Although without much sophistication, he used essentially the same methods and objective tests still used in experimental psychology today: reaction times, reading speed estimation and basic memory functions (Dimascio & Shader 1967). His work could be distinguished from early (psycho)pharmacology in that his interest lay in behavior as the dependent variable. At present, pharmacopsychology involves the study of both the mental functions that can be modified with drugs and the experimental designs and methods by which these can be detected (O'Hanlon and Freeman 1995).

Research in the field can be divided in two main areas. The first, theoretical pharmacopsychology uses drugs as tools to study basic psychological and psychomotor processes (Leonard 2001, Sanders 1984). Not the drug, but the behavior is the main object of study. The other main area of research, applied pharmacopsychology, seeks to elucidate the profile of CNS action of new drugs in terms of (un)wanted changes in behavior (Cole 1968, Hindmarch & Kerr 1992). This is achieved by conducting studies in which healthy volunteers perform a variety of psychomotor and cognitive tests once or repeatedly after taking either an investigational drug, a reference drug with well known properties or a placebo (an inactive compound) and comparing the results (Volkerts 1995). In this manuscript the main focus will be on the latter area, that of **applied pharmacopsychology** with a focus on behavioral safety of medicinal drugs.

On drug safety and testing

In the process of developing new drugs strict requirements are made as to the 'biological' safety of a drug, with validated procedures and predefined clinical endpoints. Contrary to this the process of defining the 'behavioral' safety of a drug is much less clear (Ferrara 1992). This is because behavioral tests usually

measure a surrogate end point and the relevance of the measured effects will ultimately depend on the relationship to daily life tasks or on their predictive value for an increased risk of accidents (Sanders 1988). Accidents should not only be seen as direct clear incidents like automobile crashes, but also as the unfavorable outcome of longer lasting processes like impaired memory function or learning ability, restricting full cognitive deployment of an individual. The best known example of this 'behavioral toxicity' (Ramaekers 1998) is the increased risk of an accident caused by drugs that impair driving a car. While traffic accidents happen on a daily basis and are accepted as a risk of engaging in traffic per se, the use of psychoactive drugs is considered to be a prominent contributing factor (Robertson 1994, Alvarez 1994, Starmer 1992, O'Hanlon 1984, Irving 1992).

Although the law does not specifically prohibit the use of any medicinal drug and leaves this responsibility to the individual patient, it does issue a warning on drugs that are suspected to interfere with 'reaction speed' and should therefore not be used while operating potentially dangerous machinery and car driving. The situation is much less clear for drug effects on cognition or learning. Although individual cognitive functions can be evaluated by neuropsychological tests, establishing detrimental effects in daily life is much more difficult. Besides that and contrary to the case of psychomotor impairment it is also commonly thought that the disease itself the drugs are being taken for also influences cognitive functioning. However, separating the effects of disease and drugs is an almost impossible task. In some Scandinavian countries these combined effects are nevertheless taken seriously and, for instance, students suffering from seasonal rhinitis ('hayfever') are allowed extra time to finish school exams, regardless if they are taking any drugs for relief of their symptoms (Storms 1997, Simons 96). This measure however has been taken on the basis of epidemiological data and not on the results of experimental research.

History of drug testing

Until the turn of the century there was virtually no obligation to test substances sold or prescribed for medical purposes with respect to efficacy or safety. In the US the Federal Food and Drug Act of 1906 (Kessler 1990) was amended in 1938 and was primarily aimed at the safety of drugs. Although toxicity studies were required after this amendment, no proof of efficacy of a new drug was needed. Regulations were further tightened in both Europe and the US after the thalidomide induced phocomelia disaster in the 1960's, resulting in an epidemic of birth defects (Fletcher 1980). In the US this resulted in the requirement to perform more adequate pharmacological and toxicological research, the results of which had to be submitted to the Food and Drug Administration (FDA) before any clinical testing on humans could be done. Many European countries followed these FDA guidelines for testing Investigational

New Drugs (IND) and imposed similar legislation for drug development and marketing. The result was a better but much longer and costly procedure to develop and market new drugs.

Only very few (about 1 out of 8000) initially tested drugs now actually enter clinical trial testing and only 20% of those are actually marketed. At this moment, the total time of drug development from first synthesis to marketing approval averages about 8-9 years (Bergen 1997) and involves about $250-300 million. Both the development time and costs are steadily rising. The resulting, so called 'drug-lag' (Rawson 2000) is of growing concern to medical practitioners who are in need for new drugs to fight life threatening diseases like AIDS (Greenberg 2000) where no or insufficient alternative drugs are available. Regulations are now being adapted to provide for faster access to new drugs in the treatment of serious diseases for which no alternative exists. However, no formal behavioral testing of drugs is yet required in any phase of drug registration, although many companies do perform behavioral tests with an increasing number of new compounds. With CNS active drugs behavioral testing is usually done in early in the development of the drug, with non-CNS drugs testing is mostly carried out in later phases only. Regardless of the nature of the investigational drug the development of a well described and standardized method for behavioral drug evaluation remains an important issue.

On the relation between drug effects and behavioral changes

Results of laboratory tests often poorly predict the impairment of real-life behavior that they are used for to quantify. This is true for both automated psychomotor behavior like driving a car (Parrott 1991a, 1991b, Wetherall 1996, Gengo 1990, Gaillard 1988) as well as higher cognitive functions (Riedel 1996, Roth 1992). Nevertheless an increasing number of often intricate computer based testing devices are being used in studies evaluating the (side) effects of drugs. The outcome of performance on these tests play an important role in specifying the safety profile the drug under investigation although often the theoretical framework that underlies these tests is lacking. Besides the poor relationship between testing methodology and real life behavior another major problem facing pharmacopsychological research is the variability of drug effects. Not only between subjects (inter-subject variability) but also within subject (intra-subject) variability can be very large and often unexplained.

Statistical and theoretical procedures in drug trials often manage to correct for these phenomena in revealing 'mean' drug effects but at the same time leave important questions unanswered: Why do subjects sometimes react so differently to the same drug and why do they react differently under changing circumstances. This variability is important as drugs are prescribed on an individual basis and subjects taking them should be informed as how to interpret the 'mean'

unwanted effects of a drug in relation to their personal circumstances. In other words, what is their personal risk of experiencing the possible side effects mentioned on the product label. Another problem is the extrapolation of experimental results to real life situations. How well can a statistical significant effect of a drug in the laboratory predict actual behavioral changes in real life? In other words: How valid are the warnings for possible side effects mentioned on the product label?

On Behavioral Toxicity

Contrary to pharmacological toxicity, behavioral toxicity is not directly linked to the action of the drug itself, but rather to the behavior that is modified by the drug. It is not an absolute effect but depends on the situation in which the person is exposed to the effects. The most studied topic in the field of this 'second order' effect is that of alcohol-related traffic accidents. Traffic accidents per se are a major cause of death in many countries. In car driving there is a complex interaction between three continuously changing factors: Human behavior, environmental change and vehicle behavior can all contribute to accidents. In a study by Treat et al (1977) it was shown that human error was the sole cause for the accident in 57% of the cases and made a significant contribution in no less than 92%. Therefore, modifying the behavioral capabilities of drivers will very likely lead to an increased risk of becoming involved in an accident.

Moskowitz and Fiorentina (2000) recently reviewed the vast body of both epidemiological and experimental research documenting the relationship between alcohol and accident risks (Vermeeren 1998, De Waard 1991). With respect to other drugs, empirical pharmacopsychological studies have revealed the adverse effects of many drugs on driving and driving-related performance variables (Christofferson 1997, Volz 1995). Among the psychotropic drugs shown to be capable of producing psychomotor impairment are: stimulants (Logan 1998), antidepressants (Sherwood 1998), narcotics (Iversen 1983), antihistamines (Kay 2001), cannaboids (Levy 2000), cardiovascular, hallucinogens, hypnotics (Friedel 1992), anesthetics and neuroleptics. Often in the case of traffic safety research the outcome of experimental tests with these drugs are compared to the effect of some dose-equivalent of alcohol. Given the well documented relationship between blood alcohol levels and traffic casualties (Kerr 1998, Skog 2001, Sivak 1997, Mounce 1992, Borkenstein 1964), this is an attractive way to transfer laboratory findings to safety relevant behavior. However, by only comparing the 'final common outcome' i.e. reduced performance on some behavioral measure nothing is said about causality or mechanism of action of the drug under investigation and hence the findings have only limited value. Embedding the results in a behavioral model would greatly add to the knowledge of how drugs modify behavior and would provide more specific hypothesis in this type of study.

1.3 Psychological models pertinent to pharmacopsychology

Models of behavior

Many models of human behavior exist in Psychology. The view of humans as information processing systems in the study of behavior emerged in the 1960's and marked the shift away from behaviorism of Thorndike (1914, 1926) and Skinner (1938) that had dominated the mainstream of research the previous decades. Behaviorism, with its roots in neurophysiology, could no longer contribute to the debate on the nature of performance limits in man machine interaction. The shift towards more cognitive models of behavior relied at first on principles from engineering and the then emerging field of digital computer sciences. The information processing approach was partly based on a computer analogy; humans were thought to resemble computers that take in information, process it and produce a response (Broadbent 1971, Baddeley, 1992)

Two main lines of research have been developed within this cognitive approach of human behavior, each with distinct assumptions about the nature of 'the information flow' in human information processing: *Structural models*, emphasizing the flow of information through a number of discrete or continuous 'stages' of processing, and *resource models*, in which different tasks and task aspects compete for a limited amount of processing capacity. The information processing approach in drug research has been adopted since a first study by Tharp et al. (1974) and has been applied to drugs which improve as well those which impair performance (Frowein 1981, Wesnes 1990, Warburton 1995, Sanders 1988).

Structural Models of Information processing

Within the structural approach, two conceptions exist to characterize the structure and timing of information processing. The serial stage conception (Donders 1868, Sternberg 1969, Sanders 1980,1990) postulates a series of independent processing stages, each consisting of a set of independent processes. Stages are strictly serial, although later modifications of the model allow parallel operations within a stage. The investigational tool based upon this model is the Additive Factor Method (AFM, Sternberg 1969). It envisions a reaction process as a chain of *discrete stages* linking a signal input with a response. The signal is transmitted through this chain in a sequential and unidimensional way and processing in a stage cannot start before the processing in a previous stage has been completed. The AFM can only be used in the reaction-time (RT) paradigm. The reaction time, considered to be the sum of processing durations of all stages involved, will vary with task manipulations and can be decomposed in processing times per stage.

The alternative approach within the structural models of human information processing is the continuous flow model, in which no serial stages are postulated. In this model it is assumed that stimuli activate two groups of processes simultaneously: perceptual and motor. Evidence based on perceptual processes is gradually build up and transmitted to the motor level where it activates associated responses units. As soon as a certain pre-set criterion of activation is reached, a response is initiated. In the basic form of the model, the build-up of information is thought to be a bottom-up or data driven process and the setting of a reaction criterion a top-down or executive function. Experimental variables can affect either the rate of activation or the response criterion. A number of continuous flow models have been developed (McClelland 1979, Eriksen and Schultz 1979, Rumelhart 1986, McLelland, 1988, Coles 1985).

Most of the work published over the last few years seem to favor the continuous flow model in describing human information processing. The main reason for the debate about *discrete* versus *continuous* processing is the question of whether stage N of a process can start its output before it has finished its transformation(s), and if stage N+1 can start using this information before N has finished. Whether stage N contains an output buffer that holds the information until a 'processing finished' signal is generated, or stage N+1 has an input buffer awaiting a similar signal, is not important. The key feature is that the 'end of processing' of stage N has to be actively signaled in order to start processing of stage N+1. The discussion about the question whether human information processing is best described by a serial or a continuous processing model has been clarified by Miller (1988). He argued that the dichotomy between discreetness versus continuity of a process is not a real dichotomy, but more a matter or degree. The question whether a process is discrete or continuous should be rephrased to the degree to which that process is discrete/continuous. Experimental data reviewed by Miller (1988) and Sanders (1990) can be shown to support both continuous and discrete views of information processing on the level of representation and transformation. However, they argue that transmission between stages is always discrete.

The development of neuroimaging techniques such as positron emission tomography (PET), Event Related Potentials (ERP's) and functional magnetic resonance imaging (fMRI) has added new insights to the stage debate. They offer spatially precise 3-dimensional in vivo mapping of cognitive and psychomotor processes in the healthy brain. Their experimental paradigms always draw upon some variant of the cognitive subtraction theory, comparing brain activity during a specific task with activity during rest or a control task (Petersen 1989, Friston 1994). In many studies employing these techniques attempts were made to 'map' behavior on anatomical structures. Studies on visual information processing (Livingstone 1988) gave evidence that the brain can process information different pathways. Later studies have used the techniques to successfully demonstrate involvement of specific brain areas in higher cognitive functions such as the role

of the left inferior prefrontal cortex in verbal memory encoding (Wagner 1998, Rugg 2000). These studies have steered away from the discrete vs. continuous debate and use the concept of hierarchically structured neuronal networks (Rummelhart 1986) as a model to explain behavior. However, this neuroimaging endeavor is reliant upon sound cognitive psychology since patterns of brain activity are only explicable with regard to the cognitive processes that they represent. If processes or subprocess (stages) are not adequately specified the interpretation of the derived brain activity cannot be interpreted in a valid way (Fletcher 2001).

Resource models of information processing

The resource models are based upon the notion that there is a limited availability of processing resources that can be allocated to information processing tasks or subtasks (Wickens 1991 Gopher 1984). These models have been predominantly studied in a dual task situation, with a focus on performance interference and performance trade-off as a of human information processing limits. In the single resource capacity model originally proposed by Kahnemann (1973) a single a specific pool of resources was proposed which could be labeled as ‘effort’, ‘attention’ or ‘processing capacity’. He proposed that capacity was a variable, the actual amount depending on the level of arousal and the demands of the task. The total amount of supplied resources varies with physiological arousal and is controlled by the demands of the task. The amount of effort invested is not under voluntary control of the subject. The level of arousal is indicated by physiological parameters as skin conductance level, blood pressure and heart rate. According to Kahnemanns view, behavioral measures were unreliable in the study of human performance limits, as the capacity which was needed to express performance varied. The single capacity model was not powerful enough to explain results from a growing number of studies with dual-task methodology. More specific, the model could not explain why no interference was found in a number of dual-task situations that were competing for the same (limited) resource.

Wickens (1980,1991) proposed a ‘Multiple Resource Model’ that incorporated the three basic characteristics of Kahnemann's capacity model: The first is the *scarcity* of resources. If two tasks are performed simultaneously capacity must be shared, which can be empirically determined as the deterioration of performance of one or both tasks. The second is the *plasticity* of resource allocation. Processing capacity can be allocated in different amounts to both tasks, depending on external factors and task requirements. Instructing the subject can cause a performance enhancement (more capacity allocation) on one task, which will be accompanied by a performance deterioration on a concurrent task (less capacity allocation). The third characteristic is the role of *task difficulty*. Wickens (1991) described the role of task difficulty in his ‘Performance-Demand-

Resource' function: **P=R/D** To achieve a certain performance (P), more resources (R) must be invested as the task difficulty (D) increases. Based on empirical data in dual-task research, he proposed a three dimensional structure of dichotomous dimensions in human information processing. Figure 1 shows the graphical representation of his three dimensional model:

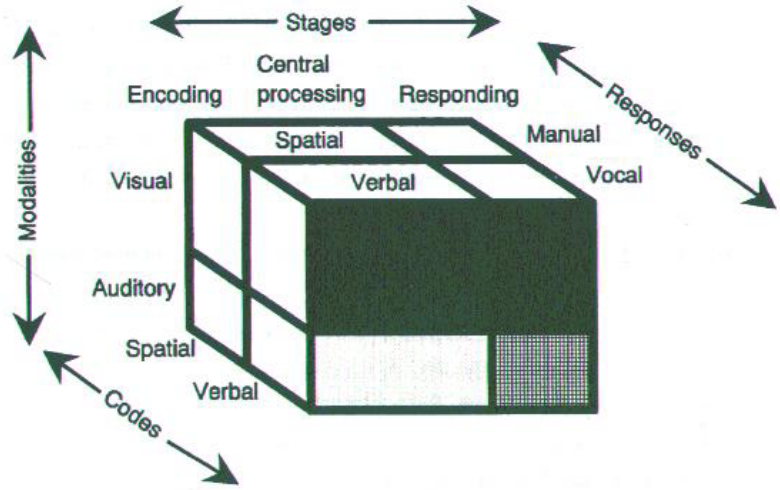

Figure 1. Schematic diagram of Wickens' Multiple Resource Model

- *Stages of processing:* the resources needed for perceptual and central processes are considered to be functionally different from those involved in response selection and execution. This view is supported by the observation that response complexity does not interfere with performance of a perceptually oriented secondary task. This distinction in stages resembles the neuro-physiological model of Pribram and McGuiness (1975) who postulate an arousal mechanism for the sensory input side and an activational mechanism for the motor output side.
- *Sensory modalities:* When two tasks involving different sensory modalities share capacity, the better performance is achieved when the modalities are different (auditory vs. visual) than when they are the same as show by Triesman and Davies (1973)
- *Processing codes:* Verbal and spatial codes are represented in a different way in memory. In particular, the processing of spatial codes seems primarily in the right cerebral hemisphere, whereas the left hemisphere seems to be the main resource for processing verbal information (Posner 1967, Peterson 1988). A similar distinction in processing is proposed by Baddeley (1986,1998) in his model of attention in which he distinguishes separate systems for processing verbal information (phonological loop) and visual information (visuo-spatial sketch

pad). Baddeley however assigns both processes to different neurological structures in the brain.

The Cognitive-Energetic Stage Model

In the cognitive-energetic model proposed by Sanders (1983) the energetic concepts of Kahnemann (1973) and Pribram and McGuiness (1975) are combined with Sternberg's (1969) discrete stage model, integrating structural and resource concepts of information processing. This model (Figure 2) considers resources as structure-specific energizing units for computational processes which themselves are considered to be serially organized. The basic view of the model is that the duration of a specific processing stage is affected by both the computational demands of the task and the state of the subject. The efficiency of the computational stages is influenced by the amount of 'energy' provided to each stage. Three basis energetic processes are distinguished: the first, arousal, regulates the input and the second, activation, controls the preparation for action. According to Pribram and McGuiness arousal is a 'stop' mechanism, interrupting ongoing behavior and providing the conditions for the processing of incoming information. Activation puts the organism in a preparatory state, selecting possible responses on the basis of incoming information. These two are basal mechanisms which are modulated and coordinated by an executive system, effort, which is called into action whenever performance requires controlled processing or changes in the two basal energetical mechanisms.

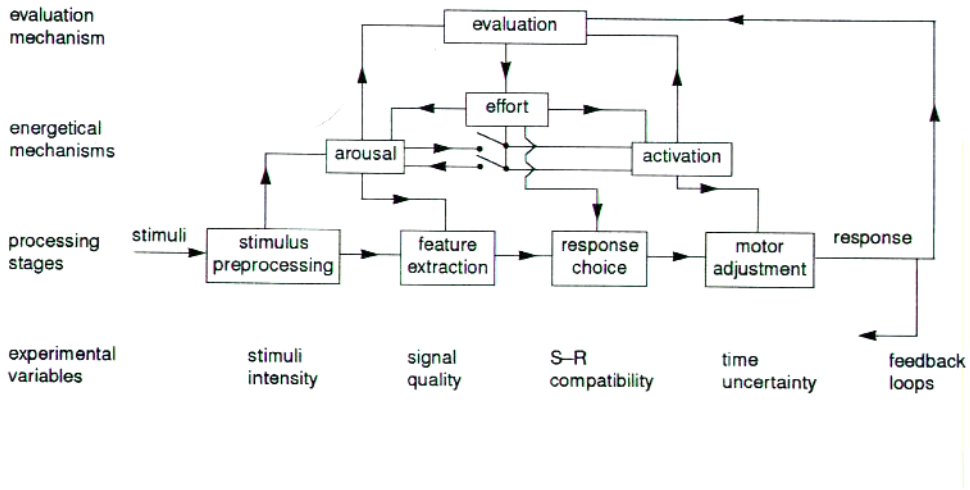

Figure 2. The cognitive-energetic stage model (Sanders 1983)

Mulder (1995) distinguishes two aspects of the effort mechanism: The allocation of effort can be increased when environmental conditions deteriorate (i.e. sleep loss, drugs) by exerting compensatory control over the physiological state. The allocation of effort can also be increased when processing complexity of the task increases. At the top level of the model an evaluation mechanism is proposed as a comparator between actual performance and required performance. If actual performance is less than a required by a pre-set criterion, an increase in effort can correct the situation. Hockey (1993,1996) presented a detailed model of executive control over changes in desired and actual state of information processing. In theory the model allows to identify different mechanisms of drug effects: those on computational processes, activation, arousal or effort.

Although most contemporary models of human information processing have their roots in the 1960's they have since been constantly developed further. Long before Sternberg's Additive Factor Method, F.C. Donders had introduced the subtraction method, which assumes strong additivity. The reaction time (RT) in simple versions of a task is subtracted from RT's of a more complex version of that task. The difference in RT is assumed to be the duration of the additional stages engaged in the more difficult version. However, as Roberts and Sternberg (1994) have since argued this simple notion of such a functional architecture is no longer plausible as nothing in the physiology or anatomy of the brain would point to such simplicity. Using functional imaging methods like fMRI, PET and ERP this has stimulated the development of computational *models* of cognition and motor behavior linking observed behavior with observed brain activity in well described anatomical structures. Some of the prominent ones, including SOAR (Newell 1990), ACT-R (Anderson 1993), EPIC (Meyer 1997), and 3CAPS (Just 1992), account for the error patterns and processing times in problem solving, reasoning, decision making, memory and learning, language comprehension, and visual thinking. 3CAPS models, the predecessor of 4CAPS, account for errors and response times in analogical problem solving (Carpenter 1996, 1990), and normal and aphasic sentence comprehension (Haarmann 1997). Computational models of human information processing are not yet employed in pharmacopsychological research, as this requires much more knowledge of the role of the different neurotransmitter systems in the various functional systems that are proposed.

1.4 The use of stage models in pharmacopsychology

Introduction

The intention of pharmacopsychological research is not limited to measuring the extent of drug-induced changes in human performance but also to determine the psychological mechanisms which have been affected. Both approaches rely on the interpretation of experimental results within the framework of a behavioral model.

Both stage and resource models are being used in research, each with distinct (dis)advantages. Single pool (Kahneman, 1973) or multiple pool (Wickens 1981, 1991) resource models are particularly suitable for the estimation of general 'workload' of tasks, but lack precision in the description of the locus of effect in the information processing system. As a consequence, the way in which manipulation of a task parameter affects or does not affect the resource is less clear cut. The main limitation of the cognitive energetic stage model (Sanders 1990) is its reliance on the single task reaction time paradigm and without question most human behavior outside the laboratory involves much longer sequences of covert events than a typical choice RT task. Furthermore, performance *efficiency* is derived from processing *speed* measures and no inferences can be made as to the relative ease of processing or availability of spare capacities within the this model. On the other hand, the cognitive energetic stage approach does have advantages over both the resources approach and the pure stage approach.

The most important advantage for pharmacopsychological research is that it should be possible to differentiate between the effects of a drug on direct computational and energetical mechanisms in human information processing. If a drug has mainly computational effects, these should be detectable by tests employing the Additive Factor Method (AFM). On the other hand, if no effects on computational stages can be found but there is a performance decrement, the drug will probably exert its effect through energetical mechanisms. In practice, very few studies are conducted explicitly employing the AFM. The main reason, besides the confinement to choice RT tasks, is that the AFM requires a factorial design in which one task is presented at two or more levels and several task variables are measured. This approach can be very costly and time consuming, especially if more doses are to be tested in the study. Therefore, most researchers use a task-battery consisting of different tasks that cover a broad range of behavior and the supposed underlying mental functions. Often the pattern of effects within such a task battery is interpreted using the same logic underlying the AFM. This can be very misleading unless the tests used are individually well documented with respect to their effects in a factorial design (Gaillard, 1988). Effects on information processing through energetical mechanisms has also been observed. These type of effects are usually detected in designs where they interact with 'organismic' variables that are known to influence a subject's energetic mechanisms, such as sleep deprivation, vigilance, task duration and time of day (Frowein 1981).

Models of driving behavior

Models of driving behavior have a different (task oriented) approach compared to pure theoretical human performance models although they share many concepts and include general information processing, zero-risk, threat avoidance and trait models (Rothengatter 1997). Most of these task oriented models are based on the

original classification of Jansen (1979). This classification is based on an AFM model with three distinct levels of processing information:

1. A basic *operational* level, consisting of highly automated behavior and involved in road tracking and adjustment of speed.

2. A *tactical* level, dealing with actual vehicle manoeuvering like the avoidance of obstacles and respecting traffic lights.

3. A *strategic* level that deals with general trip planning, risk evaluation and navigation. (Figure 3)

In models based upon this classification (Bernotat 1990, Hoyos 1986, King and Lunenfeld 1971), the most important distinction between the strategical, tactical and operational levels is the amount of attention resources needed. An overview of these models is given by Ranney (1994). Strategical planning needs many while automatic patterns at the operational level hardly require any to process environmental input and generate the required output. The amount of processing resources needed for different subtasks to perform the actual driving task are not fixed and depend on many characteristics of the environment and the driver. A novice driver will need more resources for 'roadtracking' behavior compared to experienced drivers. The latter will easily and effortlessly find his way around his home town but will find he needs much more effort to find his way in a very busy town abroad he is visiting for the first time. Shifting of resources to a lower level of control is automatic and occurs if control at that level is unsatisfactory. Car-handling that has become automated after long practice will once again come under conscious control if the nature of the behavior changes, is driving a large Van for the first time. The time course of activities is different at all three levels.

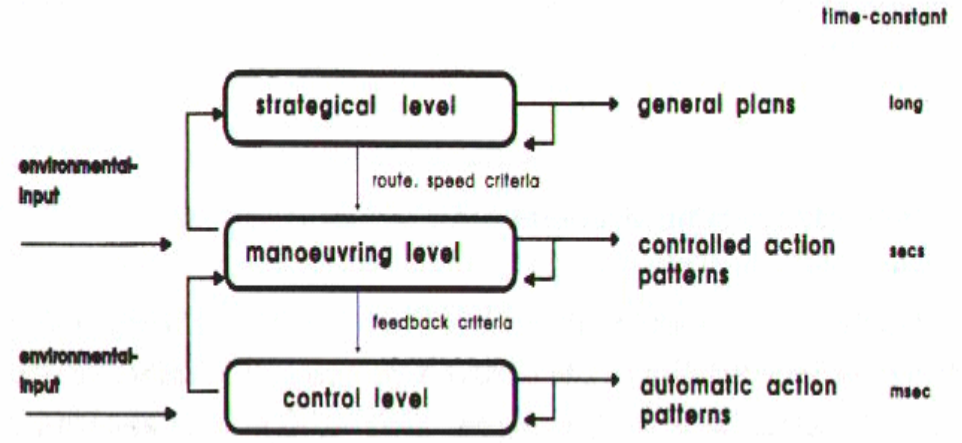

Figure 3 The three-level model of vehicle control (Jansen 1979)

Behavior at the *operational level* will take milliseconds to execute, while *tactical* decisions transpire over many seconds and *strategical* plans make take minutes or more to finalize (Ranney 1994). In explaining drug effects on driving safety most research focuses on effects concerning the *operational* and *strategical* levels. Failure in these domains can easily lead to accidents as the time constant involved is short which leaves little room for correction. Failure cannot only been regarded as the inability to actually perform a certain (sub) task, but also as the failure to recognize this inability by higher levels of control.

Epidemiological studies

These studies retrospectively focus on the analysis of unfavorable consequences of behavior in large cohorts of subjects. An example is looking into traffic accidents and comparing blood samples of drivers responsible for an accident with those of drivers not at fault with respect to drug-levels. The rationale being that this method can identify the influence of a drug as a contributing factor if found more often among drivers responsible for accidents than others. Two fundamental problems arise in this epidemiological approach of drug effect evaluation.

First, the data are more often than not presented without reference to a comparison group. Therefore the prevalence of the drug in other subjects of the population is not known (Mason 1984) Due to ethical and legal restraints it is extremely difficult to randomly collect blood samples from the general population for this purpose. As Klebelsberg (1988) points out, the number of drivers involved in car accidents and tested positive for drug use is far larger than the amount of drug users one would identify if a random sample were drawn from the general motorist community. Hildegard and Berghaus (1998) conducted a meta analysis of over two hundred epidemiological studies involving traffic safety and concluded that ‘a valid estimation of the risk for road safety induced by medicines is hardly possible at present’.

A second fundamental problem is that drug effects are only a contributing factor in safety related behavior. Until the mechanism of action of individual drugs on behavior is known, it is difficult to determine the magnitude, and eventually the clinical relevance of the effect compared to other factors. In the Treat et al (1977) study the investigators identified 3 different categories of cause: Driver related (inadequate vision, decision, reaction), vehicle related (malfunction of tires, brakes, etc.) and environmental (whether, road conditions). They concluded that Driver error partially contributed to 92.6 % of all cases. Given these figures it will be hard to separate the ‘natural’ Driver error from the drug-induced driver error. Thus although epidemiological studies show that drug induced behavioral change contributes to an increased risk in safety relevant behavior it adds little to understand the mechanism of action it works by.

Performance testing

Performance testing is by far the most used investigational method in experimental pharmacological research. Basically the approach is to administer the investigational drug in one or more different doses once or repeatedly to a relatively small group of patients or healthy volunteers and evaluate their performance on one or more behavioral tasks. Generally these tests will include measures of decision/reaction time, attention, perception, memory and vigilance. Most of the tests used have been developed in or adopted from neuro-psychological research. Single performance tests are usually inadequate (ecologically invalid) to predict real-life skills or behavior and most researchers therefore use test batteries to cover all possible aspects of the behavior under investigation. More often than not selection of the individual tests that comprise such a battery is not done following any model-driven rational or as Parrot (1991a) describes it 'comprise an ad-hoc collection of non-standard and poorly documented tests that cover wide areas of human psychopharmacology'. O'Hanlon (1988) found standard laboratory tests 'woefully inadequate' in predicting real-life drug effects.

The lack of a well–conceptualized theory and model of behavior like car driving hampers the translation from laboratory to real-life and limits the implications of the results (Hindmarch 1988). A way to circumvent this problem is to closely mimic real-life under laboratory conditions and 'simulate' the actual real-life task. This has been done very successfully in some areas like piloting an aircraft. Jet-simulators are refined to such an extent that it is possible to actually train novice pilots on a simulator after which the acquired skills are sufficient to fly an actual aircraft. Although driving skills seem to be easier to master the use of driving simulators is more problematic. Many different varieties of driving simulators exist (Irving 1988), varying from simple personal-computer based tracking tests to moving base simulators with 360^{o} vision using 'real' cars.

Nevertheless even the use of sophisticated techniques cannot completely overcome the problem of integrating some basic domains of the real-life task such as visual and visual integration (Moskovitch 1985). This can cause serious side effects by itself like motion-sickness (Kennedy 1992), or exacerbate the effects of drugs or other manipulated variables (Volkerts 1992), and often leads to dropouts. Another, more fundamental problem is that there is no real risk involved in operating a driving simulator. It is perfectly possible to crash a simulator without serious consequences. Hence, any drug that has an effect on risk perception or risk taking cannot be studied in a valid way (Parrot 1991b).

This also puts into perspective the often argued advantage of simulators in creating 'dangerous situations' in an ethical way (Nordmark 1994). Nevertheless there is an increase in the successful use of simulation techniques in traffic

research, although it is unlikely that it will gain the same sophistication as aircraft simulators.

Actual driving

In a landmark study O'Hanlon et al (1982) showed that vehicle control in actual car driving was impaired after administration of Diazepam. This was notably for 'lane keeping' or tracking behavior of the driver. Since this initial studies over 70 studies in three different Laboratories have been performed employing the original *Highway Driving* paradigm (Riedel 1998). Subjects engage in a 100 km long drive while accompanied by a licensed driving instructor. They are instructed to drive normally and maintain a specified and constant speed of 90 km/h, overtaking other vehicles if necessary. The lateral position of the car is measured relative to both lane delineations with a sample rate of 4 Hz. Deviations from the mean lateral position are expressed as the Standard Deviation of Lateral Position (SDLP) and are calculated over segments of consecutive road segments of 5 km that are averaged to yield the primary outcome variable SDLP. With an increasing SDLP the time spent 'out of lane' can be estimated, either on the adjacent lane for other traffic or the shoulder of the road. (Figure 4)

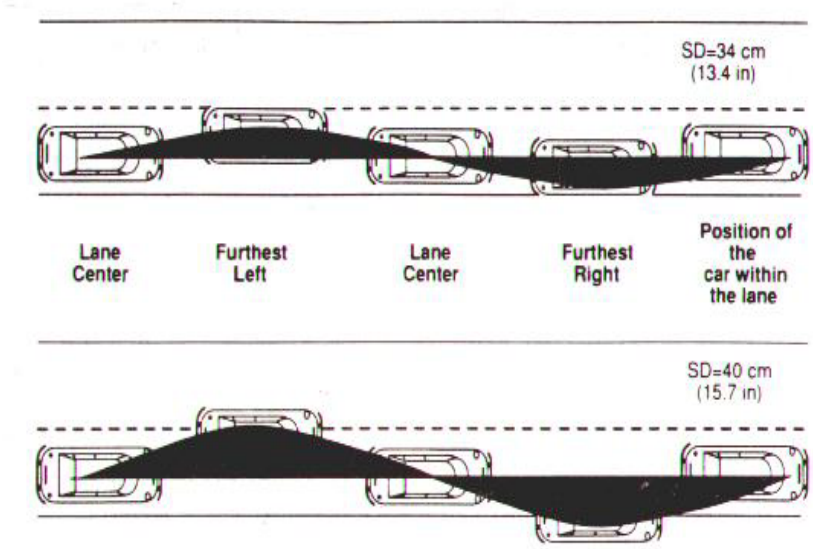

Figure 4. Standard Deviation of lateral Position (SDLP) or 'weaving'

Louwerens et al (1986) conducted a calibration study with different doses of alcohol up to 1.22 mg/ml. They found an almost linear relationship between the Blood Alcohol Concentration (BAC) and the SDLP (Figure 5).

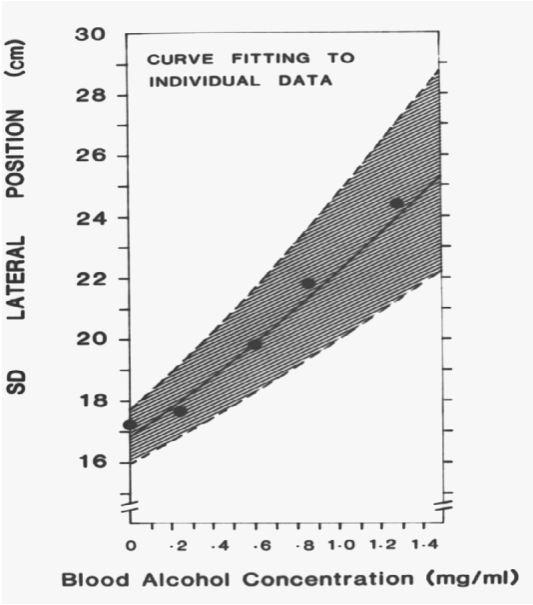

Figure 5: The relationship between Standard Deviation of Lateral Position (SDLP) and Blood Alcohol Concentration)

Alcohol is involved in over 22% of fatal traffic accidents in the European Union (ref-) and is detected in as many as 70% of single vehicle crashes. On the basis of the vast amount of epidemiological data available most researchers agree that BAC's exceeding 0.50 mg/ml will impair driving behavior. Combining these data with the calibration study of Louwerns leads one to the conclusion that any drug causing an increase of SDLP equal or above that of 0.50 mg/ml alcohol will compromise safe driving.

Besides the original driving test a second over the road test was developed later: *Car Following*. Besides monitoring operational control of the vehicle through SDLP in this task interaction with other traffic is systematically measured. Subjects engage in a 30 minute drive following a specially prepared experimental vehicle that systematically follows a number of computer controlled accelerations/decelerations and breaking procedures. The subject's task is to maintain a constant distance to the preceding vehicle and react promptly to breaking signals by removing their foot from the accelerator. Primary outcome variable is the Standard Deviation of Headway (SDH) and mean Brake Reaction Time (BRT).

A final driving test comprises *City Driving.* Subjects follow the standardized directions of the driving instructor leading them through an unfamiliar route in an urban environment. This route has been carefully selected and all major information along this route has been documented (traffic signs, intersections etc). As the test progresses the driving instructor marks the behavior of the

subject on a checklist, indicating possible errors in their driving behavior or omissions in information processing.

The combined driving tests have covered over 800.000 km since the first study was conducted in 1984 and not a single accident has occurred involving subjects either under placebo or drug conditions.

Drug effects on Learning

In western countries formal education is by far the most important activity that children between 6-18 years of age engage in. A child typically spends up to 30 hours a week and 40 week per annum in school. Although many different school and teaching systems exist the basic outcome of the different educational methods are comparable among most countries (v.d. Waard 1999). There is very little known about the effect of medicinal drugs on scholastic achievement (Kay 2001) although systematic disruption of the learning process by drugs or other sources could have serious consequences for the individual. There is no valid instrument to evaluate drug effects on the process of formal learning in an experimental way.

In an attempt to operationalize this 'learning behavior' we introduced a novel method. It consisted of a computer-assisted instruction in the form of a 'didactic simulation', combined with relevant questionnaires, adapted from a program used in German secondary schools to teach interrelated concepts of geography, meteorology, ecology and economics (Leutner and Schrettenbrunner 1989). It was validated as an instrument for evaluating scholastic learning (Leutner 1989) and is now employed for the first time in the context of a drug trial. The simulation was translated into the Dutch language for this study. To begin the simulation, which resembles a computer 'game', the child takes the role of a 'farmer' in an arid region of North Africa and is symbolically provided with a family of productive and dependant members, livestock, 10 plots of land on a sloping terrain and a small amount of money. The game is played by the year, requiring decisions about cultivating different crops, buying or selling livestock, controlling family growth, improving the land, mechanization etc. Each decision has both costs and benefits the magnitude of which can change depending on the situation at a given moment. The objective of the game is to survive as many years as possible. Unpredictable and sometimes extreme weather conditions (drought, flash-flooding) pose serious threats. This is an unfamiliar situation to European children and none of the study's participants knew an effective strategy to cope with these threats beforehand. They learned that while controlling up to 19 different and interrelated parameters that determine the outcome on a yearly basis. If the simulation is played without any strategy, survival is limited to about 3 years; i.e. the average interval before the first occurrence of extreme weather. Employing inappropriate strategies causes the game to end with a famine, forcing the 'farmer' to leave his or her property. After a game is terminated the next

begins immediately, with the same initial values for all parameters but different weather randomization over successive years.

Two teaching functions have been implemented in the simulation: online adaptive advice and non-adaptive background information. The latter consists of a list of the immediate costs and benefits for all decisions, and can be consulted at any time during the simulation. The online function consisted of feedback concerning the appropriateness of decisions. Those which are illogical or risky elicit a warning and advice concerning a more rational course of action. The 'farmer' is thus guided to develop a better strategy and a deeper understanding of the topic. Online adaptive advice and background information on benefits of action were disabled in the final phase of the study, turning the simulation into a test of prior learning.

1.5 Aim and outline of this thesis

The main purpose of this thesis is to evaluate some of the methodological and behavioral issues related to the measurement and interpretation of behavioral changes caused by drug treatment. As the focus is on *applied pharmacopsychology* two important dynamic processes are given particular attention in the design of the experiments: Pharmacokinetics (What does the body do with the drug?) and Pharmacodynamics (what does the drug do to the body?) This results in experiments employing multiple-dose comparisons and/or evaluations that are timed to coincide with the time point of maximum impairment. In designing the experiments the accent lies on *behavior*. The principle guiding factor was the modeling of real-life situations into valid experimental study designs. In doing so, two distinct behavioral tasks have been used in the experiments: Learning and Car-driving. The latter is a well defined skill that varies only a little between various cultures and countries. Given the enormous economic burden that traffic accidents impose on western society, it is of great importance to further improve investigative methods and the role of (new) drugs in traffic safety. The outcome of these studies will provide relevant information for the majority of drivers worldwide. This is less clear for the role of drugs on 'learning' behavior. The studies presented here use the method described above in a first attempt to systematically measure drug effects on school performance.

Seven experimental studies are presented which focus on safety risks of medicinal drugs, especially for car driving and learning behavior. Three studies will be presented in which actual over-the-road car driving is used as an investigational method to determine side effects of drugs. Thereafter a method will be introduced to investigate effects of drugs on learning, using a simulated 'learning environment' closely resembling the primary school classroom. The results of three studies will be presented using this method to determine the effects of seasonal allergic rhinitis and antihistamine treatment on scholastic achievement in young children. Finally, a

study is presented employing a traditional approach to evaluate the side effects of a novel drug on cognition. The manuscript will conclude with a general discussion.

1.6 Overview of the studies in this thesis

Chapter 2 describes a study in which the effects of a new 'third' generation antihistamine (desloratadine) on driving behavior are evaluated and compared to and old antihistamine (diphenhydramine) in a 3-way cross-over design. Two versions of the driving test are used together with a battery of laboratory tests.

Chapter 3 investigates both the acute and subchronic effects on driving behavior of the well known antimalarial drug mefloquine (Lariam®). This study was instigated after reported subjective reports of car driving impairment experienced by military servicemen who were sent to Cambodia.

Chapter 4 is a further analysis of the mefloquine driving study that focuses on the interaction effect of mefloquine and a moderate dose of alcohol on driving.
Chapter 5 describes the effects of 4 different doses of a non-sedating antihistamine drug on driving and psychomotor behavior.

In Chapter 6 an investigational drug (saripidem) with anxiolytic properties was tested in an acute, multiple dose, 5-way cross over design. A battery of psychomotor and memory tests was repeatedly administered over a period up to 4.5 hours post dosing.

Chapter 7 describes a study with 52 children suffering from Seasonal Allergic Rhinitis (SAR, Hayfever) and 21 matched controls. They all received a full day of computer guided tutoring in a classroom setting while the patients were being treated for their symptoms with either an old or a new antihistamine or placebo.

Chapter 8 describes a study with 67 SAR patients and 28 control subjects. All participated in a 4-day course employing the previously developed computer guided learning. The patients received subchronic treatment (14 days) starting on the first day of the course. Treatment consisted of either placebo, a sedating antihistamine (diphenhydramine) or a combination of a non-sedating antihistamine (acrivastine) with pseudoephedrine.

Chapter 9 describes a two-phase study investigating the effects of SAR and antihistamine treatment on learning. In phase one, 72 young patients received treatment with cetirizine or placebo and their scores were compared to 36 matched non-treated controls.

Chapter 10 presents concluding remarks and a summary.

Chapter 2

Effects of Desloratadine, Diphenhydramine, and Placebo on Driving Performance and Psychometric Measurements[1]

ABSTRACT

Introduction: First generation antihistamines taken for relief of allergic rhinitis are sedating and pose serious health risks when driving cars or operating machinery. Desloratadine is a potent, selective, histamine H_1-receptor that does not easily cross the blood–brain barrier. It is believed to be nonsedating at therapeutic doses and consequently should not affect driving or psychomotor performance.
Objective: This study compared the acute effects of desloratadine, relative to placebo and diphenhydramine (as an active control), on healthy subjects' performance using standard over-the-road driving tests (primary objective). The subjects' performance using conventional psychometric tests was also evaluated (secondary objective).
Methods: Eighteen men and women received a single dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo in each period of this randomized, double-blind, 3-way crossover study. Two hours post dosing, subjects operated a specially instrumented vehicle in tests lasting 90 minutes designed to measure their ability to maintain constant speed and lateral position, follow another vehicle at constant distance, and respond to brake signals. Afterward, a full battery of psychometric tests was administered.
Results: There were no significant differences between desloratadine and placebo in standard deviation of lateral position (SDLP); however, diphenhydramine treatment significantly increased SDLP ($p < 0.001$ for both comparisons). Brake reaction time was significantly faster after desloratadine than diphenhydramine (473.72 vs 541.22 milliseconds; $p < 0.001$) or placebo (512.06 milliseconds; $p = 0.033$). There were no differences among treatments in deviation of speed or distance to the leading car. The majority of psychometric tests showed no significant differences among treatments.
Conclusion: Desloratadine in a therapeutical dose does not impair driving performance.

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[1] E.F.P.M. Vuurman, G.H. Rikken, N. D. Muntjewerff, F. de Halleux, J.G. Ramaekers. Effects of Desloratadine, Diphenhydramine, and Placebo on Driving Performance and Psychometric Measurements. *European Journal of Clinical Pharmacology* (in press)

INTRODUCTION

Older, first generation antihistamines, such as promethazine, clemastine and diphenhydramine are lipophilic and easily penetrate the blood–brain barrier. and are often associated with sedation. Although the sedation produced by these traditional treatments for seasonal allergic rhinitis (SAR) is not usually a serious health concern, it does have significant consequences in situations in which safety depends upon unimpaired psychological functioning, such as driving a car or operating machinery (O'Hanlon, 1988, Ramaekers et al., 1992 Volkerts 1995). In numerous studies the effects of older antihistamines on driving have been shown to exceed those of moderate doses of alcohol (O'Hanlon and Ramaekers 1995). Moreover, recent findings suggest that sedation and impaired cognitive functioning, which may affect driving performance, are sequelae of SAR (Wilken, 2000 Spaeth et al., 1996 Marshall et al. 2000). Taken together, these studies underscore the need for effective antiallergic medications that are nonsedating and do not further impair psychomotor performance. Newer, selective acting 'second generation' antihistamines do not readily pass the blood-brain barrier and consequently are relatively nonsedating (Simons 1999, Kay 2000). Furthermore, these second generation antihistamines have a lower affinity for other receptor sites in the brain which minimizes anticholinergic side effects such as blurred vision and dry mouth as often seen in older drugs.

Desloratadine (5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6, 11-dihydro-11-(4-piperidinylidene), is a potent, selective, histamine H_1-receptor antagonist with demonstrated efficacy for the relief of nasal and nonnasal symptoms of allergic rhinitis (Salmun et al., 2000). Peak plasma values after a 5.0 mg dose are typically 3.03 ng/ml and plasma half-life is about 23.8 hrs. Desloratadine also provides effective relief of nasal congestion and stuffiness (Nayak et al., 2000). Because of its low lipid solubility, desloratadine does not easily cross the blood–brain barrier and is nonsedating at therapeutic doses; furthermore, desloratadine does not potentiate the performance impairment associated with alcohol consumption (Scharf et al. 2000, Rikken et al. 2000) Consequently, it is believed that desloratadine should not affect the performance of tasks for which reduced vigilance is associated with safety risks.

This study compared the acute effects of desloratadine, relative to placebo and diphenhydramine (as an active control), on healthy volunteers' performance using standard over-the-road driving tests. Furthermore, the subjects' performance using conventional psychometric tests was evaluated to determine whether any drug-induced changes in psychometric parameters corresponded with changes in actual driving performance.

METHODS

Study design

This single-center, randomized, double-blind, placebo- and active-controlled 3-way crossover study. Eighteen white subjects (8 men and 10 women) were enrolled and completed all 3 treatment phases of the study. Mean subject age was 27.1 years (range, 21 to 38 years), with a mean weight of 67.2 kg and a mean height of 174.3 cm. Subjects were required to have had a driver's license for at least 3 years prior to the study, with driving experience of at least 7,500 km per year during that period. Patients with a history or symptoms of severe mental or physical disorders or substance abuse were excluded from the study, as were subjects with active allergic rhinitis. Additional exclusion criteria included excessive smoking; excessive consumption of caffeinated beverages; body weight > 10% outside the normal average for age, sex, and height; treatment with central nervous system medications or medications with sedative effects; or known allergic reactions to antihistamines. Pregnant or nursing women were excluded from the study, and women of childbearing potential were required to have a negative serum pregnancy test result at screening and to use an acceptable method of birth control prior to screening and throughout the study. Written informed consent was obtained from all subjects prior to participation in the study.

Subjects were required to adhere to specific procedures prior to testing, including abstinence from alcohol or other recreational drugs the day before testing and retiring for sleep a minimum of 8 hours prior to the expected time of awakening. On testing days, sleep quality was measured at the study center using the Groningen Sleep Quality Scale (Simons and Valk, 1988); subjects continued with the testing procedures only if they had good sleep quality (Groningen score < 10) the previous night. In addition, subjects were limited to 1 cup of tea or coffee with breakfast on testing days, and habitual smokers had to refrain from smoking for the duration of the testing (from 30 minutes prior to testing until all tests were completed). Each subject received a single oral dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo in each treatment period, and each treatment period was separated by a minimum washout period of 5 days. Subjects were monitored for adverse events at each visit. A timeline of test-day procedures is provided in Figure 1.

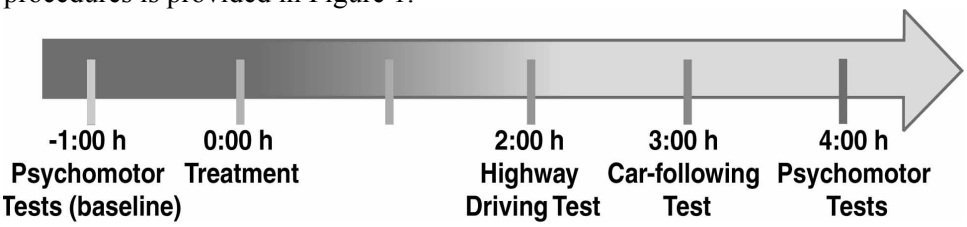

Figure 1. Timeline of test day procedures.

Driving and psychomotor performance testing

Highway Driving Test (60 minutes)

This standardized test consisted of driving a specially instrumented vehicle over a 100-km circuit on a primary highway while maintaining a constant speed (95 km/h) and steady lateral position between the delineated boundaries of the right (slower) traffic lane. During all driving tests, subjects were accompanied by a licensed driving instructor who could intervene if necessary by using duplicate controls at his position in the front passenger seat. During the test the vehicle's speed and lateral position were recorded by computer systems described in detail previously (O'Hanlon 1982). The data were analyzed off-line after removing overtaking maneuvers or disturbances caused by traffic situations. The remainder was used to compute the Standard Deviation of Lateral Position (SDLP, in cm) and Standard deviation of speed (SDS, km/hr). SDLP is the primary outcome variable and an index of road-tracking error or 'weaving'. It has proven to be a reliable characteristic of individual driving performance with an average test-retest reliability coefficient of r=0.85. In over 60 studies it has been proven to be sensitive to many sedating drugs and blood alcohol concentrations as low as 0.035% (Vuurman 1996).

Car-following Test (30 minutes)

This test involved the use of 2 vehicles traveling in tandem. During this test, subjects in a specially instrumented vehicle followed another specially instrumented vehicle driven by an investigator while matching the speed of the preceding vehicle and maintaining a constant 40-m distance between the 2 vehicles (Ramaekers et al., 2001). Subjects were to respond to brake light signals in the leading car (operated by a secondary switch) as quickly as possible by lifting their foot from the accelerator pedal. The primary outcome variables were deviations in distance to the leading car and time between brake light signal and reaction (brake reaction time).

Psychomotor Performance Testing

The standard test battery of our institute was used to asses possible impairment on psychomotor behavior or cognition. Performance assessment was done at baseline (1 hour before dosing) and beginning 4 hours after dosing The analysis for all performance measures was carried out on difference scores between these two points. Using difference scores compensated for day to day differences in individuals' performance. Test used were the following

The Stanford Sleepiness Scale (SSS, Hoddes et al., 1973) was used to measure subjects' feelings of mental alertness. Scores range from 1 (feeling active, vital,

alert, wide awake) to 7 (almost in a reverie, sleep onset soon, lost struggle to stay awake).

The Postural Instability Test (PIT, Kapetyn et al., 1983) involves the use of a balance platform to measure body sway in both the sagittal and lateral dimensions. In this 2-part test, subjects first stood for 30 seconds on the platform with feet together while looking at a wall-mounted target 2 m away, then remained in the same position with eyes closed for an additional 30 seconds.

The Word Learning Test (WLT**,** Rey 1964) was used to measure the immediate and delayed recall of verbal information. In this test, subjects were presented with a list of 30 monosyllabic nouns at a rate of 1 every 2 seconds and were asked to recall as many as possible after the presentation. This procedure was repeated twice, after which the subject engaged in other activities for 20 minutes. The primary outcome variable was the total number of correct, immediately recalled words. After the delay subjects were asked again to recall as many words as possible without prompting. The total number correctly remembered is the Delayed Recall score.

The Digit Symbol Substitution Test (DSST, Wechsler, 1981) was a computerized version of the same test from the Wechsler Adult Intelligence Scale. The subject was briefly shown an encoding scheme consisting of a row of squares at the top of the screen in which 9 digits were randomly associated with nonletter symbols. The task was to match each digit with a symbol from the encoding list and click the corresponding response buttons. Performance was measured by the number of digits correctly encoded within a 3-minute period.

Critical Flicker/Fusion Frequency (CFF, Vuurman et al., 1994) is a traditional method used to measure the sedative effects of drugs. The subject was required to make a series of button-pressing responses indicating perceptual discrimination of a discontinuous light source appearing at optical infinity in a visual tunnel, thus allowing the measurement of a lower boundary (flicker) and an upper boundary (constant) for the perceptual threshold of flicker/fusion.

Critical Instability Tracking (CIT, Jex 1966) measures the subject's ability to control an unstable error control a displayed 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 out the error by returning the cursor to the midpoint The frequency of cursor deviations at which the subject loses control is the critical frequency (lambda-c in rad.sec) The final score is determined from the average of all but the lowest and highest scores of five consecutive trials.

The Divided Attention Task (DAT, Moskowitz and Burns, 1977) measures the ability to divide attention between tracking and monitoring tasks performed simultaneously. The primary task was compensatory tracking, similar to that described previously, with the exception that the error deviation frequency remained constant at 50% of the individual's lambda-c. Mean Tracking error (mm), measured as the average absolute distance between the position of the cursor and the center of the display, was the performance measure for this task. The secondary task involved monitoring 24 peripheral LED displays showing the numerals 0 through 9, which changed at 5- to 10-second intervals, and detecting the occurrence of the '2' numeral in particular and responding by removing his foot from a pedal-switch as quickly as possible. The average reaction time was used to measure performance in this subtask.

In the *Syntactic Reasoning Test* (SRT, Baddely, 1968), subjects were presented with a series of 32 sentences, each describing the order of 2 letters, for example, 'B follows A.' Each sentence was followed immediately by the same 2 letters, which were in the same or reverse order as described by the sentence. Sentence difficulty varied within the series, from simple active sentences to more complicated sentences containing passives, negatives, or both. Subjects were required to indicate whether the letter pair was in the same order as in the preceding sentence. Respons time (sec) was the primary outcome variable.

The Semantic Verification Test (SVT, Collins and Quillian, 1969) involved the visual presentation of 30 short sentences. Half of these sentences were factual, whereas the rest were false. Subjects were to indicate whether the sentence was true or false using the appropriate response button. Although responses were usually correct, their latency was dependent on the time to access long-term memory and recover the information needed to verify the sentence.

Statistical methods

Actual driving performance scores and psychomotor test scores were analyzed using an analysis of variance (ANOVA) model for crossover designs with terms for treatment, phase, and subject. Treatment and phase were tested using the within-subject residual as error, whereas subject was tested using the between-subject residual as error. Pairwise comparisons were to be performed using the least square means from the model.

The primary comparison was that of desloratadine with placebo; the diphenhydramine group was included for reference purposes. Because the study was oriented toward safety, a significance level of $\alpha = 0.05$ was used to detect differences among treatment responses in the statistical tests. No adjustments were made for multiple comparisons.

RESULTS

Driving Tests

In the Highway Driving Test, the mean SDLP was comparable after desloratadine and placebo (20.29 vs 20.71 cm, respectively; Figure 2). In contrast, significantly more weaving behavior occurred after diphenhydramine treatment, demonstrated by a mean SDLP of 24.64 cm ($P < 0.001$ for both comparisons). Furthermore, subjects maintained a more constant speed with desloratadine treatment than with diphenhydramine treatment (1.99 vs 2.19 km/h, respectively; $P = 0.045$). There was no significant difference in the standard deviation of speed between desloratadine and placebo.

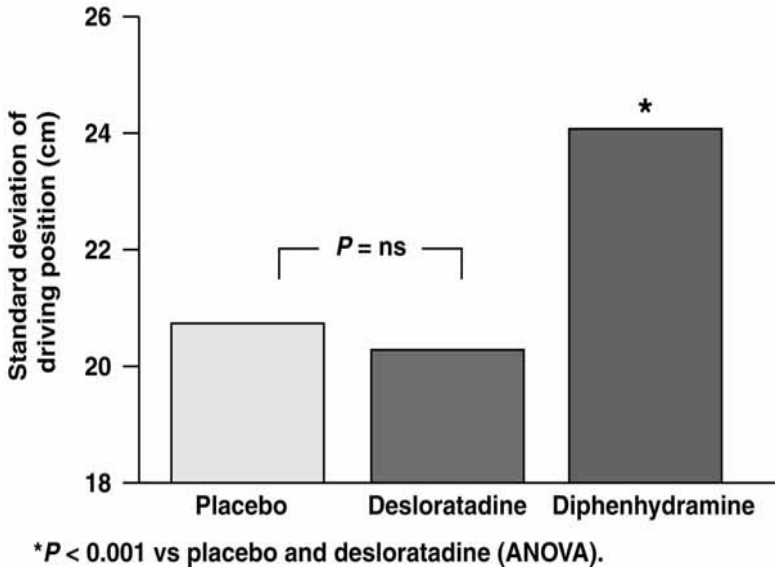

Figure 2. Highway Driving Test results: standard deviation of lateral position (SDLP).

In the Car-following Test, mean brake reaction time was significantly shorter with desloratadine treatment (473.72 milliseconds) than with either placebo (512.06 milliseconds, $P = 0.033$) or diphenhydramine (541.22 milliseconds, $P = 0.001$; Figure 3). This difference of nearly 70 milliseconds translates to a difference in reaction distance of nearly 2 m while driving at a speed of 100 km/hr. No significant difference was observed between the placebo and diphenhydramine treatments. With regard to the distance to the leading car (headway variability), no significant differences were observed among treatments. Mean distance to the leading car was 21.93 m after desloratadine treatment and 22.14 m after both the diphenhydramine and placebo treatments.

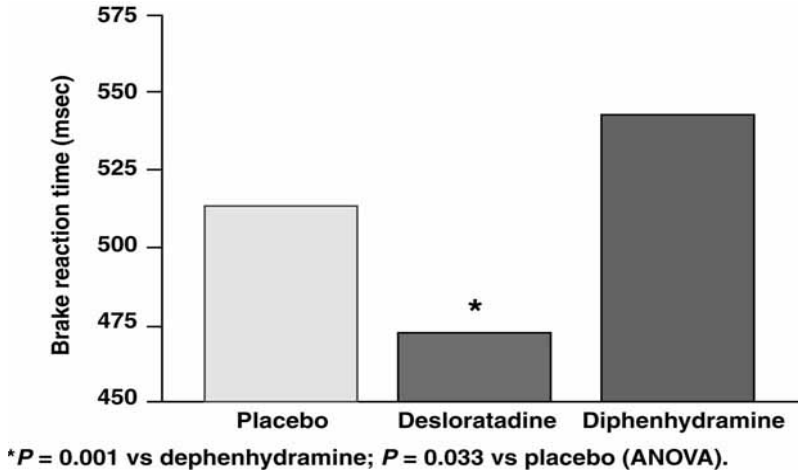

Figure 3. Car-following Test results: mean brake reaction time.

Psychomotor Performance Tests

On the Stanford Sleepiness Scale, subjects treated with diphenhydramine demonstrated a significantly greater increase in sleepiness score from baseline compared with desloratadine (1.56 vs 0.39, respectively; $P < 0.001$) or placebo (1.56 vs 0.17; $P < 0.001$; Figure 4). No difference was observed between the desloratadine and placebo groups.

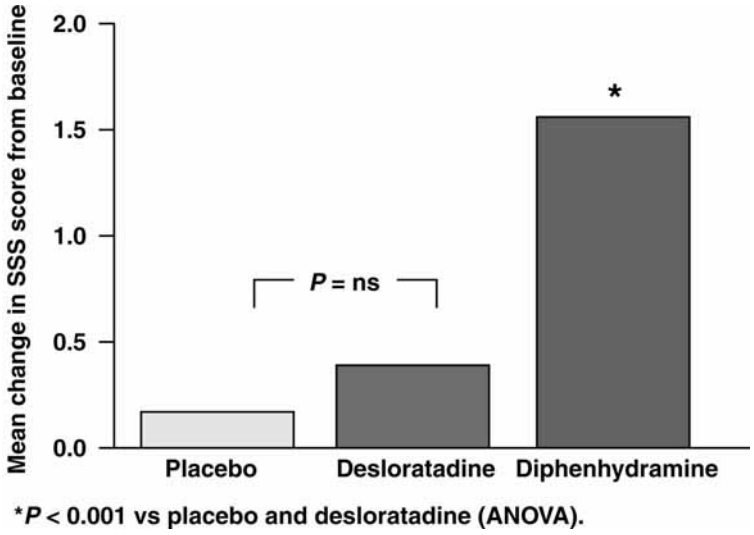

Figure 4. Stanford Sleepiness Scale results.

On the Divided Attention Test, significant differences were noted among treatments in mean tracking error and mean reaction time (Figure 5). Mean tracking error increased by 3.61 mm from baseline after diphenhydramine treatment compared with 1.11 mm after desloratadine (P = 0.002) and 0.94 mm after placebo (P = 0.001). Diphenhydramine treatment also resulted in a significant increase in mean reaction time compared with that of desloratadine (188.56 vs –2.33 milliseconds, respectively; P = 0.014). There were no statistically significant differences between the desloratadine and placebo groups for either of these parameters.

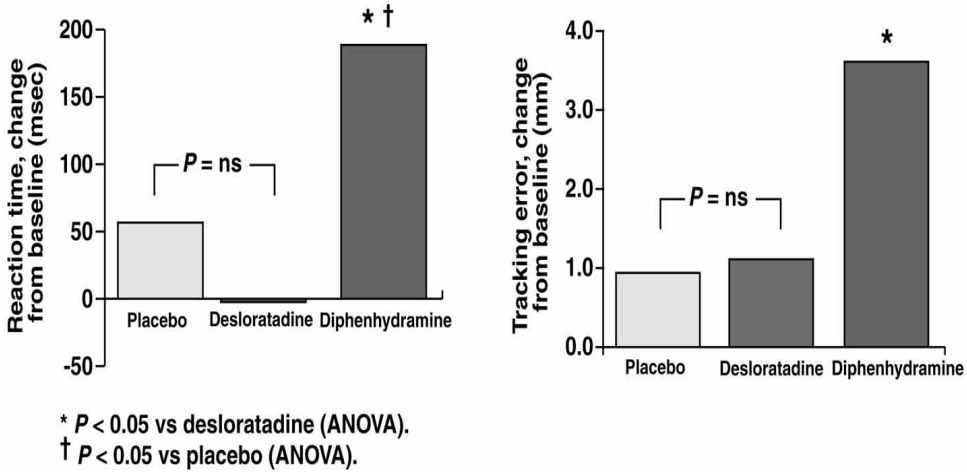

Figure 5. Divided Attention Test results: changes from baseline in (A) mean reaction time and (B) mean tracking error.

With the exception of the Stanford Sleepiness Scale and the Divided Attention Test, drug-induced changes in psychometric parameters were not predictive of changes in actual driving performance. The remainder of the psychometric tests, administered at least 4 hours after dosing, were insensitive to the sedative effects of diphenhydramine (Table 1).

Safety

Overall, treatment with desloratadine was well tolerated. Two subjects treated with desloratadine reported adverse events (earache and rash; neither was considered treatment related) compared with 5 subjects each in the placebo and diphenhydramine groups. All adverse events were mild in intensity, with the exception of 1 in the placebo group that was considered moderate (constipation).

There were no deaths, serious adverse events, or withdrawals from the study because of an adverse event.

	Treatment Group		
Performance Test	**Desloratadine 5 mg (n = 18)**	**Diphenhydramine 50 mg(n = 18)**	**Placebo (n = 18)**
PIT (mm)			
Eyes opened	0.39 (0.22)	6.28 (6.15)	0.17 (0.17)
Eyes closed	–6.44 (6.51)	–1.06 (4.58)	–3.61 (3.37)
WLT (n)			
Immediate recall	–2.67 (1.35)	–2.56 (2.03)	–1.61 (2.39)
Delayed recall	–3.67 (1.03)	–4.06 (1.19)	–3.50 (1.08)
DSST Test* (n)	2.94 (0.98)	2.33 (1.13)	5.00 (1.06)
CFF (Hz)	–0.611 (0.493)	–1.611 (0.100)	–0.500 (0.544)
CIT (rad/sec)	0.013 (0.089)	–0.220 (0.100)	0.005 (0.110)
SRT			
Correct responses (n)	–0.61 (0.41)	–0.56 (0.49)	–0.06 (0.27)
Reaction Time (msec)	–28.22 (19.99)	–18.50 (24.85)	–46.50 (19.68)
SVT			
Reaction Time (msec)	–134.89 (66.16)	11.44 (77.99)	–56.61 (54.28)

*Placebo: n = 16.

Table 1. Psychomotor Performance Test Results: Changes From Baseline (± SE)

DISCUSSION

The efficacy of desloratadine for the relief of both the nasal (ie, rhinorrhea, itching, stuffiness, and sneezing) and nonnasal (itching, tearing, or redness of eyes; itching of ears or palate) symptoms of SAR has been documented in double-blind, placebo-controlled clinical trials (Salmun, Lorber, Danzig, and Staudinger, 2000).

The current study was designed to evaluate possible cognitive or psychomotor side effects after treatment with desloratadine. The results support the notion of the absence of drug-induced impairment in association with desloratadine treatment: performance on most aspects of the Standard Highway Driving Test and the Car-following Test were comparable for both the desloratadine and placebo treatments. By comparison, treatment with diphenhydramine, an anti-histamine noted for its sedative and cognitive effects, resulted in significantly more weaving behavior and less consistent driving speed during the Standard Highway Driving Test, as well as significantly prolonged reaction time during the Car-following Test. The observed change of 3.93 cm SDLP was well above the acceptable safety margin of 2.4 cm which corresponds to the change induced

by a Blood Alcohol Concentration of 0.05 %, the legal limit for driving in the Netherlands.

The results of a full battery of psychometric performance tests also indicate a lack of impairment with desloratadine treatment. On all psychometric parameters measured, subjects performed similarly after both desloratadine and placebo treatment. However, following diphenhydramine treatment, numerical decreases were observed in most of the psychometric parameters measured.

The effects of loratadine, cetirizine, and ebastine on driving performance have also been investigated in studies that utilized similar driving and psychomotor performance test methodology (Ramaekers, Uiterwijk, and O'Hanlon 1992, O'Hanlon and Ramaekers, 1995 Brookhuis et al. 1993) Overall, the results of these studies demonstrated that driving and psychomotor performance impairment varies between first- and second-generation antihistamines and possibly among such second-generation agents as loratadine and cetirizine as well. A review of the literature shows that treatment with the recommended therapeutic dose of ebastine, loratadine, or fexofenadine results in mean SDLP values comparable with placebo. Driving studies with the recommended therapeutic dose of cetirizine are less straightforward and show either moderate impairment (Ramaekers, Uiterwijk, and O'Hanlon, 1992) or lack of impairment (Volkerts et al. 1992). However, all antihistamines affect driving performance when given at twice the recommended therapeutic dose.

The effect on driving seems to be beneficial with fexofenadine (Vermeeren and O'Hanlon 1998) although the mechanism by which this occurs still needs to be explained. In contrast, cetirizine and loratadine cause a less favorable sedative effect. The differential effects on driving performance suggest the second-generation antihistamines may have different mechanisms of action. This theory of dose-dependent differences in the safety profiles of each of these drugs requires future studies with standardized protocols. More extensive investigation into the effects of high dose desloratadine on SDLP is needed. Mean brake reaction time was significantly faster with desloratadine compared with placebo, indicative of a possible alerting action of desloratadine. The exact mechanism underlying such activity is unclear, but does suggests that desloratadine is able to cross the blood-brain barrier. Laboratory tests confirm the findings of the driving tests. Desloratadine has no effect on driving performance scales compared with the sedating effect of diphenhydramine on both the Stanford Sleepiness Scale and the Divided Attention Test. The latter is the most sensitive of the psychomotor performance tests and the failure of other tests to detect the sedating potential of diphenhydramine may be due to the relatively long interval between dosing and testing. The setup of this study with both the driving tests taking over 90 minutes to complete caused psychomotor tests with diphenhydramine to be conducted approximately 1 hour after T_{max} was achieved, when some of the sedating effects may have waned. The lack of any effects on some of the lab tests was expected as not all were known to be sensitive to effects of older antihistamines but were

included as exploratory tests to find unexpected, but nevertheless possible effects of desloratadine.
In conclusion, Desloratadine, given at 5 mg, does not impair actual driving performance, is safe and well tolerated.

ACKKNOWLEDGEMENT

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Chapter 3

Effects of mefloquine, alone and with alcohol, on psychomotor and driving performance[2]

ABSTRACT

Objective. This was to determine whether mefloquine, a quinoline antimalarial drug, affects psychomotor and actual driving performance when given in a prophylactic regimen, alone or in combination with alcohol.

Methods. Forty male and female volunteers were randomly assigned in equal numbers to two groups. They were respectively treated for one month with mefloquine and placebo, double-blind. Drug was taken in 250 mg doses on the evenings of days 1, 2, 3, 8, 15, 22 and 29. Testing occurred on days 4, 23 and 30, the latter after repeated alcohol doses sufficient for sustaining blood concentration at about .35 mg/ml. Two actual driving tests were used for measuring prolonged (1h) road tracking and car following performance, respectively. Critical Flicker/Fusion Frequency (CFF), critical instability tracking and body sway were also measured in laboratory tests.

Results. Mefloquine caused no significant impairment in any test at any time relative to placebo. Instead, the drug significantly improved road tracking performance on day 4 ($p=.005$). A significant ($p=.007$) interaction between prior treatment and alcohol was found in the body sway test; i.e. alcohol-induced changes were less after mefloquine than placebo. Both driving tests and the CFF test demonstrated their sensitivities by showing significant overall alcohol effects but did not discriminate between prior treatments.

Conclusion. Mefloquine did not impair driving performance but rather improved it in the longer test to suggest that the drug possesses psychostimulating properties.

Key words: mefloquine, antimalarial drugs, alcohol interactions, driving performance, SDLP.

INTRODUCTION

Mefloquine,[dl-erythro-α-(-2-piperidyl)-2,8-bis(trifluromethyl)-4-quinoline methanol] is among a number of quinine analogs developed as blood schizonticides. It possesses exceptional efficacy as prophylaxis and curative treatment for malaria caused by multidrug resistant *P. falciparum.* A loading-maintenance prophylactic dosing regimen is 250 mg daily for three days followed by 250 mg on day 8 and at

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[2] Vuurman E, Muntjewerff N, Uiterwijk M, van Veggel L, C. Crevoisier C, Haglund L, Kinzig M and J.F. O'Hanlon J (1999) *Eur Journal Clin Pharmacology* (1996) 50:475-482

weekly intervals thereafter. This regimen is compatible with mefloquine's unusually slow rate of elimination; i.e. $t_{½\beta}$ between 14 and 30 days (Mimica et al., 1983; Pennie et al., 1993).

Mefloquine is not generally considered to be a psychoactive drug but among its most prevalent side effects during treatment and, to a lesser extent, prophylaxis are those of CNS origin. According to the manufacturer's Product Information (F. Hoffmann-La Roche, 1994), these include dizziness, vertigo and headache. As frequent are nausea, vomiting and other gastrointestinal disorders. Rare but more serious CNS side effects have also occurred among patients treated for malaria with higher doses: seizures, depression, acute psychosis and toxic encephalopathy (Bem et al., 1992). These authors were usually able to identify pre-existing risk factors for seizures, such as epilepsy, but less commonly for other reactions. They were unable to identify the mechanism responsible for mefloquine's neuro-psychiatric side effects but hastened to add that the same are seen at similarly low incidences in patients treated with all quinoline antimalarials.

The rare severe reactions might be attributable to high-dose exacerbation of extant or prodromal brain disorders. But that still leaves the question of how important mefloquine's common CNS side effects are for persons who engage in skilled and potentially dangerous tasks during prophylactic therapy. The U.S. military was naturally concerned with the question and instigated a large scale study to provide an answer (Boudreau et al., 1993). Groups of marines were treated for 12 weeks with mefloquine according to prophylactic dosing regimens that did and did not include the loading dose. Though the soldiers experienced certain side effects, similarly during both regimens, they said they were always able to perform their military duties with normal proficiency. One purpose of the present study was to confirm these subjective evaluations by objectively measuring mefloquine's effects, relative to placebo's, on parallel volunteer groups' performances in actual driving tests. The other was to compare the groups' driving performances after challenging them with a low alcohol dose.

METHOD

Subjects

Volunteers were recruited via newspaper advertisements specifying the inclusion criteria: age 20-60y, possession of a driver's licence, driving experience of at least 3000 km/y over two previous years and willingness to provide Informed Consent. They were medically screened by routine blood chemistry and hematology tests, a physical examination including 12-lead ECG recording and urine tests for pregnancy and drugs of abuse. Exclusion criteria were clinically relevant abnormalities in any blood test; far-field, binocular visual acuity that deviated by more than 0.65 diopters from normal, corrected or uncorrected; known hypersen-sitivity to any drug; history of any serious gastrointestinal, hepatic, renal neurologic or psychiatric disorder; evidence of drug or alcohol abuse, excessive alcohol or

nicotine use; blood donation or participation in a drug trial within the prior 2 months; and for premenopausal females, pregnancy, lactation or failure to exercise reliable birth control. Subjects completing the study included 20 males and 20 females, aged 21-59 y (M ± SD; 33.3 ± 11.4 y), and within 15% of their ideal weight for the gender, height and stature (Metropolitan Life Insurance Company, 1983). All were ethnic Caucasians. Subjects were treated in accordance with the Declaration of Helsinki and all its modifications through Hong Kong (1989). The protocol was approved by the Medical Ethics Committee of the University of Limburg.

Design and Treatments

The study followed a randomized, 2-arm, double-blind, parallel group design. Twenty subjects, comprised equally of men and women, were assigned to each group. They respectively received mefloquine 250 mg and placebo in identically appearing tablets according to a prophylactic regimen; i.e. daily for days 1-3 and then weekly on days 8, 15, 22 and 29. Subjects were instructed to take tablets 30 min before the evening meal between 18:00 and 20:00 h. Subjects confirmed tablet ingestion by telephone calls to an investigator. The latter's failure to receive the scheduled calls caused him to telephone the subjects who indicated compliance in every case.

Subjects in both groups were treated with an alcohol challenge on day 30. Ethanol (70%) was given in seven 3.9 g doses at 15 min intervals followed by three adjustable doses at approximately 30 min intervals. All doses were mixed to a volume of 30 ml in orange juice. This alcohol dosing regimen was developed in a pilot study to achieve and sustain a blood concentration (BAC) of about 0.35 mg/ml; i.e. sufficient for affecting test performance but not enough to bring any subject's BAC above 0.50 mg/ml, the local legal limit for drivers. BAC was estimated from expired breath using a Lion SD-400 Alcoholmeter before every dose and following the conclusion of testing. Adjustable doses were contingent upon estimated BAC. Doses of 5.1 and 3.4 g were respectively given when BAC was < 0.30 and 0.30 - 0.50 mg/ml.

Psychometric Procedures

Subjects were tested on days 4, 23 and 30. They had been trained to perform all tests in two sessions during the week prior to treatment. Training continued on tests that involve learning until the subjects' scores during the last three trials were within ± 5% of their average. Training on the other tests consisted of one complete rehearsal. Subjects were prohibited from taking OTC or prescription drugs, except oral contraceptives, for 14 days prior to treatment until its conclusion. They had to obtain at least seven hours of night sleep and avoid strenuous physical activities. Alcohol consumption was limited to two glasses of beer or wine per day except before test days when none was allowed. Subjects had to fast for at least three hours before arrival and abstain from drinking beverages containing caffeine on

test days. Up to four subjects were tested per day with arrivals at 08:00, 10:00, 12:00 and 14:00 h (constant for a given subject). The respective arrivals occurred approximately 11.8-15.0, 13.7-17.0, 16.0-19.0 and 19.1-21.3 h after ingestion of the preceding mefloquine dose (mean ± SD : 16.51 ± 2.37 h). Subjects yielded blood samples within 15 min after arrival and again either 3.0 h (days 4 and 23) or 5.25 h (day 30) later. Plasma samples were later assayed for mefloquine and its carboxylic acid metabolite as described below. Subjects' activity schedule depended where they were in the treatments series. On days 4 and 23, they undertook laboratory and driving performance tests 15-30 and 60-165 min after arrival. The same tests were delayed on day 30 to permit repeated alcohol dosing; i.e. at 105-120 and 165-270 min after arrival. The relationship between alcohol dosing and testing is shown in Figure 3.

A battery of three widely used tests were administered under controlled laboratory conditions. Critical flicker/fusion frequency (CFF, Hz) was measured in the test described by Vuurman et al. (1994). The Critical Instability Tracking Test (Jex et al. 1966) was used for measuring the subject's ability to control a displayed error signal using a joystick in a 1st-order, compensatory tracking task. The signal's velocity increased as the test continued forcing the subject to respond more frequently. Control was lost as the subject's response lagged the error signal by 180°. The frequency at which control loss occurred was recorded as the 'critical frequency' (λ_c, Rad/s). This test is also more fully described in the above publication. The standardized stabilometry method of the International Society of Posturography (Kapteyn et al. 1983) was used for measuring body sway. Subjects stood for 60 sec with their feet open at an angle of 30° on a force platform, first with eyes open and fixated on a target 2m away, then with eyes closed. The analog outputs of transducers within the platform were digitized, sampled and analyzed by a microcomputer. The system (Electropostugraph®, ELP, Brussels) calculated the momentary vector of force extending downward from the body's center of gravity and its movement around the vertical axis over time. The area (mm^2) circumscribed by the vector during recording periods was the basic parameter measuring body sway. As expected, the distribution of this parameter was positively skewed, particularly in tests taken with eyes closed. Data were therefore transformed into $\log_{10}$ values before entering statistical analyses.

Driving performance was assessed in two tests. The standardized Highway Driving Test was developed by O'Hanlon (1984) and has been applied without major revision in more than 50 studies. It was followed in this study by a modified version of the Car Following Test described by Ramaekers et al. (1994). Both tests originated from a staging area adjacent to an entrance/exit on a primary highway (4 lanes, divided). Subjects drove a specially instrumented Volvo station wagon accompanied by a licenced driving instructor having access to redundant controls. They began the Highway Driving Test upon entering the highway. Their task was to maintain a constant speed (95 km/h) and steady lateral position between delineated boundaries of the right (slower) traffic lane. The vehicle's speed and its

distance from the left lane line were continuously recorded. Subjects left the highway after driving 50 km at an exit in the vicinity of the second staging area. On days 4 and 23, they re-entered the highway and resumed driving in the opposite direction. On day 30, they stopped 5 min at the staging area for alcohol breath analysis and dosing. Then they continued as before until returning to the origin of the 100 km circuit. If necessary for alcohol breath analysis and dosing, subjects paused at the first staging area for 5 min. Otherwise they began the Car Following Test without delay. This time they entered the highway following a vehicle driven by an investigator. The vehicles accelerated in tandem to a constant speed of 90 km/h. The subjects' task was to maintain a 40 m following distance, or 'headway', while the preceding vehicle executed a series of speed changes interpolated between 1-5 min periods of constant driving. Speed changes in both directions were controlled by computer manipulation of a conventional cruise-control system. The vehicle's speed rose or fell by 10 km/h to describe a quarter sine function over 25 sec. Between 6 and 8 speed changes occurred as the two vehicles drove 20 km. They then exited and re-entered the highway to perform another 6-8 maneuvers before returning to the origin of this 40 km circuit. The following data were recorded: speeds of both vehicles, the onset of each maneuver, the subject's accelerator pedal movements and headway. The latter was accomplished using a laser distance sensor (Sick DME 2000). It projected 45 ms pulses at 40 Hz from the following vehicle to a reflecting shield on the preceding vehicle. The system measured the phase shift between projected and reflected laser light and converted it to an analog voltage proportional to the distance.

Lateral position data from the Highway Driving Test were reduced to yield the standard deviation of lateral position (SDLP, cm) for each successive 10 km segment, and as the square-root of pooled variance over all segments, for the test as a whole. SDLP is a measure of road tracking error or allowed 'weaving'. Headway data from the Car Following Test were reduced to yield standard deviations within each speed change maneuver. Their average (SDHW, m) was taken as a measure of car following precision. In addition, the average interval between the onsets of speed changes and the subject's corresponding accelerator pedal responses was taken as a measure of reaction time (RT, sec).

After the driving tests, subjects used 10 cm visual-analog scales for describing their mood in three dimensions - 'Alertness', 'Contentedness', 'Calmness'; (Bond and Lader, 1974); the presence and severity of side-effects - drowsiness, weakness, headache, fatigue, nervousness, nausea, dizziness and memory disturbance; and, their perceived driving quality and effort during driving.

Drug Assay

Blood samples (10 ml) were drawn into lithium heparin containing tubes. They were centrifuged within 30 min of collection. Plasma fractions were stored frozen (- 40°C). These were assayed for mefloquine and its carboxylic acid metabolite (Ro 21-5104) using a new LC-MS/MS procedure with Selected Reaction Monitoring

(SRM, Kinzig and Sörgel, 1995). The instrument used was the PE SCIEX API III Plus (Perkin Elmer, Toronto). Plasma was first deproteinized with acetonitrile containing chloroquine and furosemide as internal standards for the parent and metabolite, respectively. Supernatants were injected on to a reversed-phase column (5 μm Spherisorb ODS II) and eluted with an isocratic solvent system of ammonium acetate buffer and acetonitrile. The effluent was monitored in the above system and the resulting chromatogram was analyzed by Mac Quan software (version 1.3, Perkin Elmer, Toronto). Quantification limits were 1.148 and 2.34 ng/ml for mefloquine and its metabolite. Linearity extended to 926.4 and 982.7 ng/ml, respectively. Inter- and intraday errors of estimate were 3.6-4.6% and 2.4-4.0% for mefloquine, 4.3-8.8% and 1.1-2.9% for the metabolite. Respective absolute recoveries were 96.7 ± 4.5% and 95.1 ± 2.9%.

Statistical Analysis

Each parameter was analyzed using the BMDP (Dixon et al., 1988) repeated-measures analysis of variance (ANOVA). Treatments was specified as the grouping factor and Days as the within-subjects factor. This analysis was repeated for days 4-23 and days 23-30 to separately measure the Treatment and Day effects and their interaction without and with the alcohol challenge. Mean differences between the groups' scores on each day were evaluated by separate t-tests (independent means, 2-tailed). Effects associated with $p < .05$ were defined as significant.

RESULTS

Dropouts and Missing Data

Two female subjects dropped out of the mefloquine group after taking tablets on days 1-3 and were replaced. One experienced nausea and vomiting accompanied by dizziness on day 4. Her complaints were deemed to be drug related. The other experienced malaise, fever, headache and cough and was diagnosed as suffering from a flu. Original or replacement subjects provided complete data on every test but one. Due to a recurrent mechanical failure, several car following tests had to be cancelled. The data loss was approximately the same for both groups but distributed unevenly over days. Numbers of subjects whose data were lost on days 4, 23 and 30 were as follows: mefloquine 7, 3 and 2; placebo 6, 3 and 3. Analyses of car following performance were conducted using data from only those subjects who managed to complete both trials in each comparison.

Mefloquine versus Placebo without Alcohol

ANOVA’s of data collected in the laboratory performance tests and the Car Following Test on days 4 and 23 failed to show any significant Treatment or Day effects or any significant interactions. Mean-pair comparisons between the groups'

performances for each day separately likewise failed to show any significant effect. Descriptive statistics for performance measured on all days are given in Table 1.
There were no significant Treatment, Day or Interaction effects on any subjective parameter recorded on days 4 and 23. In general, both groups similarly rated their mood as excellent, side-effects as minimal and driving quality and effort as moderate.

GROUP	**Mefloquine**			**Placebo**		
DAY	**4**	**23**	**30**	**4**	**23**	**30**
Measure						
CFF (Hz)	42.8 (0.9)	42.8 (0.7)	41.6 (0.8)	42.9 (0.9)	43.6 (1.2)	41.21 (1.0)
λ_c (Rad/sec)	4.07 (0.13)	3.91 (0.15)	3.88 (0.17)	3.95 (0.18)	3.99 (0.18)	3.87 (0.19)
SDLP (cm)	19.51 (0.69)	21.69 (0.80)	23.73 (0.84)	22.91 (0.96)	23.24 (0.99)	26.11 (1.41)
SDHW (m)	3.43[a] (0.46)	2.96[b] (0.26)	3.62[c] (0.36)	3.20[d] (0.32)	3.05[e] (0.31)	3.71[f] (0.35)
RT (sec)	9.73[a] (0.44)	10.31[b] (0.35)	10.72[c] (0.45)	9.52[d] (0.48)	9.98[e] (0.35)	10.91[f] (0.47)

Reduced Ns : a=13, b=17, c=18, d=14, e=17, f=17.

Table 1.Mean (SE) for performance measures by groups for days 4, 23 and 30. Statistics for Car Following Test parameters are based upon reduced Ns due to recording failures, otherwise N=20/group.

In sharp contrast, there was a large difference between the groups' performances in the Highway Driving Test. Figure 1a-c shows their mean (±SE) SDLP scores as a function of distance driven on each test day. On day 4, the groups' SDLP scores diverged after they had driven about 20 km. After 50 km, the mefloquine group's performance was substantially better. The groups' divergence in SDLP scores over distance driven was less on day 23, mainly due to a change in the mefloquine rather than the placebo group's performance.

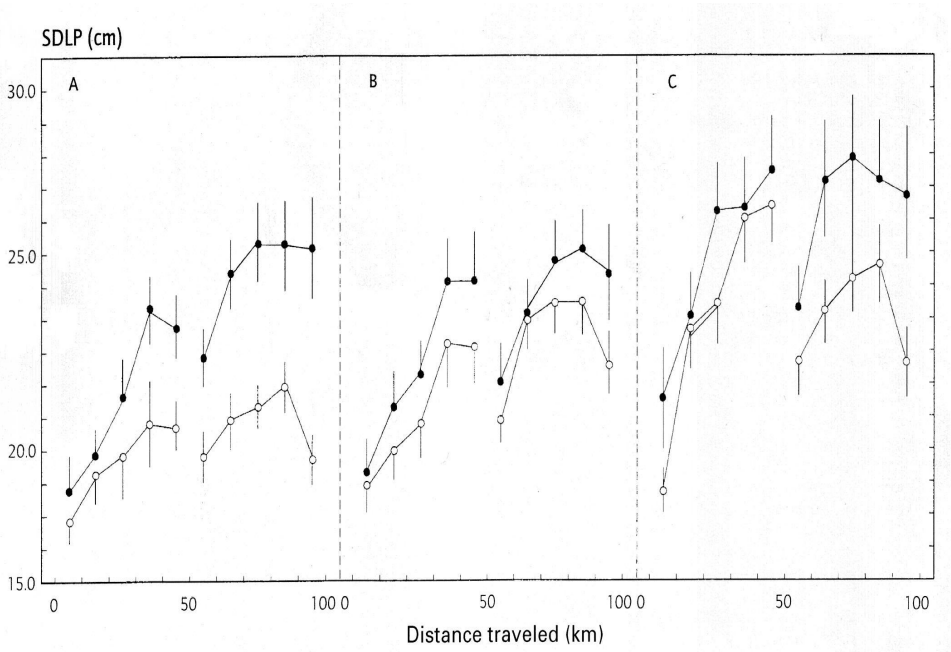

Figure 1. Mean (±SE) SDLP for mefloquine (O) and placebo (●) groups as functions of distance traveled on days 4 (A), 23 (B) and 30 (C) - the latter during an ethanol challenge. Breaks in lines indicate mid-test turning maneuvers.

Analysis of the total SDLP scores confirmed the impression of a group difference. Data combined over days 4 and 23 showed both significant Treatment and Day effects ($F_{1,38}$ = 4.96 & 7.55; p = .03 & .009, respectively). The interaction was also significant ($F_{1,38}$ = 4.13; p = .049). The mean difference in SDLP between groups was significant on day 4 (t_{38} = 2.95; p= .005) but not on day 23.

Mefloquine versus Placebo with Alcohol

The influence of the alcohol challenge on performance parameters was shown by ANOVA tests for the Day effect. Parameters showing a significant Day effect were as follows: CFF ($F_{1,38}$ = 22.83; p = .0000), SDLP ($F_{1,38}$ = 19.57; p = .0001), SDHW ($F_{1,29}$ = 10.21; p = .003) and RT ($F_{1,29}$; p = .04). Yet none of the same ANOVAs showed a significant Treatment effect and separate t-tests for group differences in performance on day 30 likewise failed to provide significant results. With one exception, the Treatment x Day interactions failed to show any evidence that mefloquine and placebo differentially affected the groups' sensitivity to the alcohol challenge. That exception occurred in the body sway test (Figure 2a-c). Body sway with eyes open varied little over days, even after the alcohol challenge. Body sway with eyes closed was generally greater, particularly for the placebo group after alcohol. However, the mefloquine group's body sway was not affected by alcohol to the same extent.

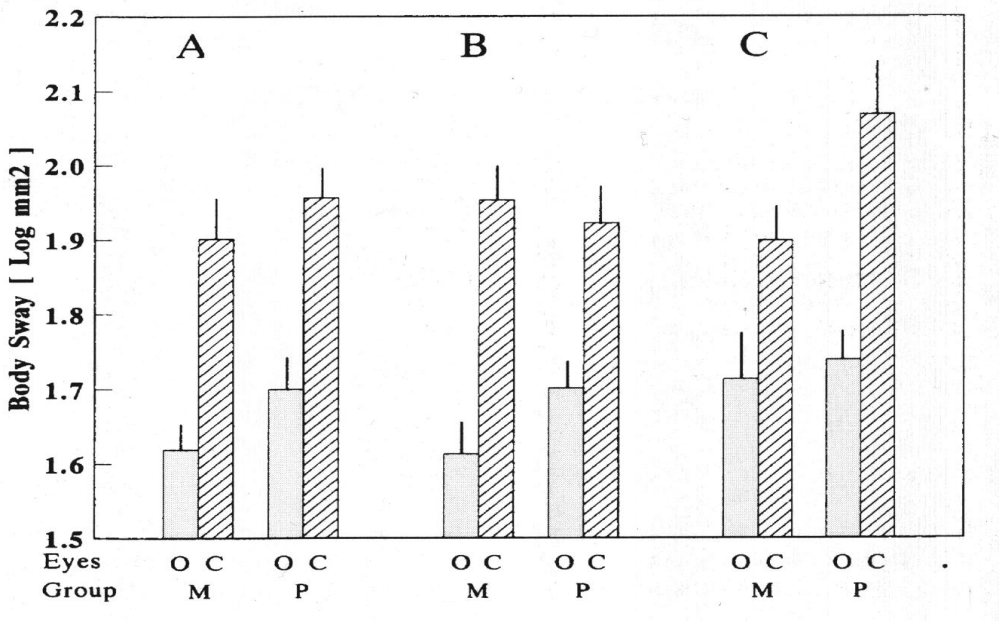

Figure 2. Mean (+SE) Body Sway (posturographic surface area in log_{10} units) with eyes open (O) and eyes closed (C) for mefloquine (M) and placebo (P) groups on days 4 (A), 23 (B) and 30 (C) - the latter during an ethanol challenge.

The ANOVA Treatment x Day interaction showed that the groups' differential reaction to the alcohol challenge was significant ($F_{1,38}$ = 8.01; p = .007). Separate t-tests showed no significant difference between the groups' eyes-closed body sway on day 23 but a nearly significant difference on day 30 (t_{38} = 1.99; p = .054).

There were no significant Treatment or Treatment x Day interactions involving the subjective parameters. However, 'Alertness' ratings for both groups combined fell significantly from day 23 to day 30 to show a modest effect of the alcohol challenge ($F_{1,38}$=4.78; p=.03). For the placebo group the mean (±SD) change was from 89.8 ± 1.5 to 85.6 ± 2.2%, and for the mefloquine group, from 88.7 ± 1.9 to 87.0 ± 2.2%, full scale.

Pharmacokinetics

Mean (±SD) plasma concentrations of mefloquine, and its metabolite, are given in Table 3. Also given are coefficients of correlation calculated separately for mefloquine and metabolite between samples taken successively on each test day.

These correlations indicate the degree to which individual concentrations remained stable as subjects engaged in various activities over days. The mean (±SD, range) cumulative alcohol doses administered over 3¼h to mefloquine and placebo groups were 0.56 ± 0.06, 0.42-0.72 and 0.55±.05, 0.48-0.60 g/Kg, respectively. Mean BACs measured repeatedly in both groups are shown in Figure 3. It should be

apparent that both groups' mean BAC's were stable at about 3.5 mg/ml throughout all tests.

	Mefloquine	Metabolite
Day 4		
1st	779.7 (238.5), 258.3 - 1288.0	580.9 (243.6), 217.4 - 1180.0
2nd	813.8 (247.0), 211.0 - 1218.0	629.8 (241.9), 223.3 - 1113.0
	r = .91	r = .96
Day 23		
1st	936.5 (319.9), 209.0 - 1569.0	1490.6 (713.6), 230.2 - 2917.0
2nd	968.1 (292.4), 228.5 - 1444.0	1572.2 (666.9), 646.3 - 2918.0
	r = .91	r = .93
Day 30		
1st	960.6 (350.8), 255.3 - 1611.0	1686.6 (563.9), 830.4 - 2914.0
2nd	923.6 (273.0), 261.8 - 1271.0	1695.5 (570.2), 813.4 - 2702.0
	r = .82	r = .96

Table 2. Mean (SD), min-max, plasma concentrations (ng/ml) of mefloquine and its acid metabolite in samples taken before and after testing on days 4, 23 and 30; and, coefficients of correlation (r) between both concentrations of drug and metabolite measured on the same days (N = 20).

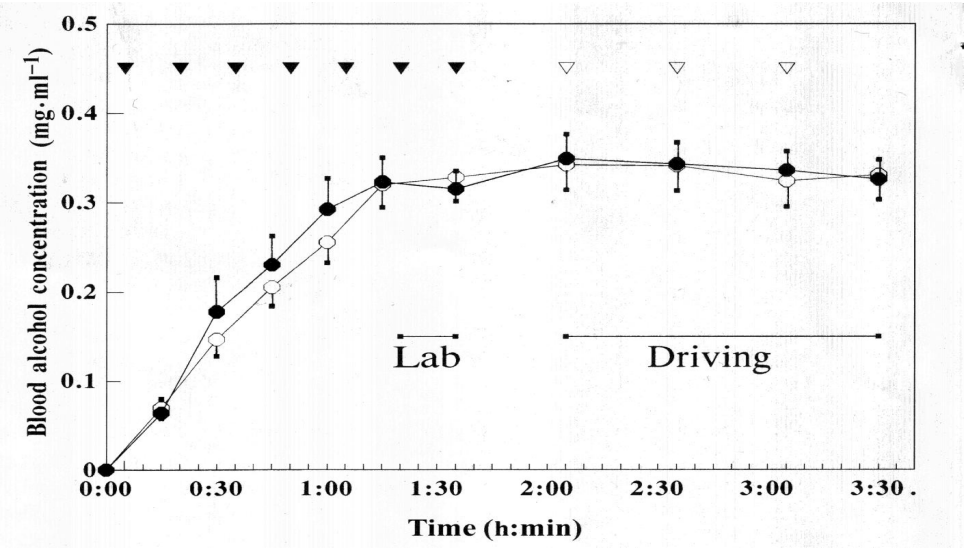

Figure 3. Mean (±SE) Blood Alcohol Concentrations as functions of time from the onset of constant (▼) and adjustable (▽) dosing, and in relation to laboratory and driving tests, for mefloquine (O) and placebo (●) groups on day 30.

Adverse Events

Including the dropouts, 11 (50%) and 9 (45%) subjects in the mefloquine and placebo groups reported at least one adverse event, usually in response to a general question in regularly scheduled interviews on test days. The number of events were

21 and 13, respectively. Events occurring more than once in mefloquine/placebo groups were as follows: nausea (accompanied by vomiting in the dropout) 4/2; dizziness 3/2; fatigue 2/2; headache 4/0; lightheadedness 3/0; and diarrhea 2/1.

DISCUSSION AND CONCLUSIONS

Our subjects and the marines studied by Boudreau et al. (1993) were treated with mefloquine according to the same loading-maintenance dose regimen. However, those investigators fixed the time of dosing and actually observed the marines' tablet ingestion. The question arises whether our decision to permit subjects to ingest tablets at different times of day, and our reliance upon their verbal confirmation of the same, noticeably affected the plasma drug concentrations that were measured in samples obtained on the following days. To answer this question we compared the concentrations measured in the respective groups on day 4 of treatment; i.e. after the third loading dose. Boudreau et al.'s samples were obtained at a single time 24h after drug ingestion. Ours were taken twice, 13-21h and 16-24h after ingestion. The marines' mean ± SD mefloquine concentrations were 665 ± 175 ng/ml. For our subjects, the values measured in successive samples were 780 ± 239 and 814 ± 247 ng/ml. The correlation between individual concentrations on these occasions was r=.91.

Several points may be drawn from this comparison. Our subjects tended to present higher concentrations in both samples, indicating their compliance with the dosing regimen. There was little difference (i.e. 4%) between mean concentrations measured 3h apart in our subjects and the individual levels were exceedingly stable. Thus there is little reason to suppose that mefloquine concentrations would have been much different in our subjects if we had followed the same dosing and sampling procedure as Boudreau et al. The mean differences and correlations between concentrations measured successively on both of the subsequent test days were similar. Thus, one may assume that individual mefloquine concentrations were always stable throughout the periods of testing and also during the ethanol challenge on day 30. The broader implication is that the variable intervals between mefloquine ingestion and activities on test days had little if any effect on the results.

To our surprise, the mefloquine group drove significantly better than the placebo group in the Highway Driving Test on day 4 and maintained their advantage, albeit not significantly, during its subsequent repetitions. It is especially noteworthy that the mefloquine group drove better than the placebo group after the alcohol challenge, particularly during the second half of the Highway Driving Test. These results do not contradict a recent case report of an individual who experienced psychotic episodes after drinking 0.5L of whisky on two occasions during mefloquine prophylaxis (Wittes and Saginur, 1995). The mefloquine group's cumulative alcohol doses were certainly far less. Nonetheless the average dose was equivalent to the quantity a 70 Kg individual would consume while drinking 0.12L

of whisky or 1.0L of beer, respectively containing 40 and 5% alcohol by volume.

Responsible persons would not consume much more shortly before attempting to drive, so the results of this study seem relevant to the driving safety of travelers during mefloquine prophylaxis. So long as their BACs do not exceed 0.5 mg/ml, one should not expect the drug to potentiate alcohol's adverse effects on their driving performance. The question of what might happen should they consume intoxicating quantities of alcohol was not addressed by this study. However, the present results indicate that mefloquine in prophylactic, steady-state concentrations would be unlikely to alter alcohol's pharmacokinetic profile after higher doses. The mean doses taken and the mean BACs achieved were virtually the same in the mefloquine and placebo groups. Yet there was a suggestion that these agents interact pharmacodynamically. Separately they affected driving performance in ways indicating at least partially opposing neurophysiological activities. Their combined effects might be described as weakly antagonistic. In this case, the implied interaction was benign but it might not always be so when alcohol is present in intoxicating concentrations. Further research is clearly needed to determine the nature of the interaction across a wide range of alcohol doses.

A further indication that mefloquine antagonizes alcohol's effects was seen in the eyes-closed body sway test. Mefloquine and placebo groups showed about the same normal postural instability when tested on day 23 without alcohol. The formers body sway was subsequently unaffected by the alcohol challenge on day 30 whereas the latter's increased. The Treatment x Day interaction was highly significant. Separate comparisons showed no significant difference between the groups' postural instabilities on day 23 but a difference just less than significant ($p=.054$) on day 30.

Despite the differences in driving performance and body sway, the mefloquine group's mood, feelings associated with treatments, perceptions of their own driving quality and of effort involved in driving did not differ significantly from the placebo group's. Except for one subject who dropped out because of drug-related dizziness, nausea and vomiting, side effects among the mefloquine group were infrequent, mild and little different from those spontaneously reported by the placebo group.

The duration of the Highway Driving Test was probably the factor responsible for its sensitivity to the beneficial mefloquine effect. Subjects normally show a modest increase in SDLP during the test (O'Hanlon and Volkerts, 1988). In this respect, the driving test resembles the classic ‘vigilance test’ wherein signal detection performance progressively declines as a function of time on watch. Such tests possess bidirectional sensitivity to psycho activating and sedating drug effects. All shorter psychomotor tests, wherein subjects are expected to show their maximum ability at the moment, are much more sensitive to sedating than psycho activating effects. It is therefore not surprising that the shorter tests in this study failed to show any mefloquine effects. Even the Highway Driving Test failed to discriminate between the drug and placebo effects until the groups had driven for

about 20 min. Mefloquine apparently possesses psycho activating or provigilance properties rather than any that enhance maximum psychomotor ability. Psycho activating effects of older quinoline antimalarials have also been seen in healthy volunteers (Engel et al., 1947) and in patients treated with these drugs for rheumatic diseases (Wallace, 1994).

Finally, it should be noted that the method which achieved and sustained a more or less steady state blood alcohol concentration for more than two hours is worthy of emulation. Tests that would not be expected to show any adverse effect of a mean BAC of 3.5 mg/ml after a bolus oral dose, showed highly significant effects of the same concentration achieved by multiple dosing. Only the Critical Instability Tracking Test failed to show impairment due to alcohol. The results obtained in both driving tests were of greater practical relevance. Apparently driving performance impairment is not simply related to the momentary blood alcohol concentration. It also depends upon the time-integral of concentrations that exist beforehand. The implications of this unexpected result will receive the attention they deserve in another article.

ACKNOWLEDGEMENTS
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Chapter 4

Further effects of mefloquine and placebo in combination with alcohol on the actual driving performance of healthy volunteers[3]

ABSTRACT

This article describes the results of a reanalysis of data from a previously published study comparing the effects of mefloquine and placebo on actual driving performance in a standardized test. It was conducted according to a double-blind, 2 parallel group design with 20 male and female volunteers participating in each group. Single 250 mg doses were administered in the evenings of days 1-3 and on days 8, 15, 22 and 29. Driving tests were administered on days 4, 23 and 30, the latter after an alcohol challenge sufficient for achieving and maintaining blood concentration of about 3.5 mg/mI. The previous analysis showed that mefloquine produced significantly superior total-test driving performance on day 4 but on neither of the subsequent test-days. The present analysis revealed that mefloquine also significantly altered driving performance while the test was in progress on day 30. Specially, performance progressively deteriorated after the combination of placebo and alcohol but began the same way and then recovered after mefloquine and alcohol. The persistence of mefloquine's provigilance effect over a month of treatment was thereby demonstrated.

INTRODUCTION

Mefloquine[dl-erythro-α-(-2-piperidyl)-2,8-bis(trifluromethyl)-4-uinoline methanol] is among a number of quinine analogs developed as blood schizonticides. It possesses exceptional efficacy as prophylaxis and curative treatment for malaria caused by multidrug resistant *P. falciparum*. A loading maintenance prophylactic dosing regimen is 250 mg daily for three days followed by 250 mg on day 8 and at weekly intervals thereafter. This regimen is compatible with mefloquine' s unusually slow rate of elimination; i.e. $t^{1/2}\beta$ between 14 and 30 days (Mimica et al, 1983; Pennie et aI., 1993).

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[3] Vuurman E, Muntjewerff N, Uiterwijk M, van Veggel L, C. Crevoisier C, Haglund L, Kinzig M and J.F. O'Hanlon J *Tropical Medicine and International Health (1997) s(1) 10-16*

That mefloquine possesses some sort of activity within the CNS seems beyond doubt. When questioned upon their return from areas where malaria is endemic, the majority of travelers were unable to recall any untoward feelings or behavioral reactions associated with the prophylactic use of mefloquine. Yet a substantial minority, varying between 2 and 22 % in different groups, reported having experienced usually mild and transient side effects of CNS origin; i.e. disturbances in the level of consciousness, dizziness, vertigo, ataxia, headache, insomnia, unusual dreams and sensory anomalies such as diplopia and tinnitus (Palmer et al, 1993) Neuropsychiatric disturbances of a more serious nature have also been reported by physicians attending patients who were temporarily incapacitated while taking either prophylactic or higher therapeutic doses. These reactions, occurring with an incidence of about one case per 10,000-20,000 individuals treated, have included seizures, depression, acute psychosis, and toxic encephalopathy (Bern et aI, 1992).

The rare neuropsychiatric reactions to mefloquine may be attributable to exacerbation of extant or prodromal brain disorders and would be thought of as ‘idiosyncratic’ if that were always the case. On the other hand, they might represent extreme extensions of the same pharmacological activity that produces the drug's more common side effects. Even these may be well up on a dose-effect continuum that begins with mildly altered CNS functions which are subjectively imperceptible. The earliest CNS effects would be of little consequence unless they were to impair mefloquine users' abilities to perform skilled and potentially dangerous tasks.

The U.S. military was naturally concerned with the question of whether or not mefloquine interferes with performance proficiency and undertook a large-scale study to provide an answer (Boudreu et al 1993). Groups of marines were treated for 12 weeks with mefloquine according to prophylactic dosing regimens that did and did not include the loading dose. Though they experienced the common side effects with a similarly low frequency during both regimens, they said they were always able to perform military duties with normal proficiency. One purpose of the present study was to confirm these self-evaluations by objectively measuring mefloquine's effects, relative to placebo's, on parallel volunteer groups' performances in an actual driving test. The other was to compare the groups' driving performances after challenging both with a low alcohol dose. Major aspects of this study have been published previously (Vuurman et al, 1996). Since then, further data analysis has yielded additional results that strengthen the original conclusions regarding mefloquine's stimulating properties that affect driving. The latest results are described in this paper and those published earlier are only mentioned as relevant.

METHOD

Subjects

Volunteers were recruited via newspaper advertisements specifying the inclusion criteria: age 20-60y, possession of a driver's license, driving experience of at least 3000 km/y over two previous years and willingness to provide Informed Consent. They were medically screened by routine blood chemistry and hematology tests, a physical examination including 12-lead ECG recording and urine tests for pregnancy and drugs of abuse. Exclusion criteria were clinically relevant abnormalities in any blood test, binocular visual acuity that deviated by more than 0.65 diopters from normal, corrected or uncorrected; known hyper-sensitivity to any drug; history of any serious gastrointestinal, hepatic, renal, neurological or psychiatric disorder; evidence of drug or alcohol abuse, excessive alcohol or nicotine use; blood donation or participation in a drug trial within the prior 2 months; and for pre-menopausal females, pregnancy, lactation or failure to exercise reliable birth control. Subjects completing the study included 20 males and 20 females, aged 21-59 y (M±SD ; 33.3 ±11.4 y), and within 15 % of their ideal weight for the gender, height and stature (Metropolitan Life Insurance Company, 1983). All were ethnic Caucasians. Subjects were treated in accordance with the Declaration of Helsinki and all its modifications through Hong Kong (1989). The protocol was approved by the Medical Ethics Committee of the Maastricht University.

Design and Treatments

The study followed a randomized, 2-arm, double-blind, parallel group design. Twenty subjects, comprised equally of men and women, were assigned to each group. They respectively received mefloquine 250 mg and placebo in identically appearing tablets according to a prophylactic regimen; i.e. daily for days 1-3 and then weekly on days 8, 15, 22 and 29. Subjects were instructed to take tablets 30 min before the evening meal between 18:00 and 20:00 h. Subjects confirmed tablet ingestion by telephone calls to an investigator. The latter's failure to receive the scheduled calls caused him to telephone the subjects who indicated compliance in every case. Subjects in both groups were treated with an alcohol challenge on day 30. Ethanol (70%) was given in seven 3.9 g doses at 15 min intervals followed by three adjustable doses at approximately 30 min intervals. All doses were mixed to a volume of 30 ml in orange juice. The alcohol dosage regimen was developed in a pilot study for achieving and sustaining a blood alcohol concentration (BAC) between 3.0 and 5.0 mg/ml, the latter being legal limit for drivers. BAC was estimated from expired breath using a Lion SD-400 Alcoholmeter before every dose and following the conclusion of testing.

Adjustable doses were contingent upon estimated BAC. Doses of 4.5 and 3.4 g were respectively given when BAC was < 0.30 and 0.30 -0.50 mg/ml.

Procedures

Subjects driving performance was tested on days 4, 23 and 30. Subjects were prohibited from taking OTC or prescription drugs, except oral contraceptives, for 14 days prior to treatment until its conclusion. They had to obtain at least seven hours of night sleep and avoid strenuous physical activities. Alcohol consumption was limited to two glasses of beer or wine per day except before test days when none was allowed. Subjects had to fast for at least three hours before arrival and abstain from drinking beverages containing caffeine on test days. Up to four subjects were tested per day with arrivals at 08:00, 10:00, 12:00 and 14:00 h (constant for a given subject). The respective arrivals occurred approximately 11.8-15.0, 13.7-17.0, 16.0-19.0 and 19.1-21.3 h after ingestion of the preceding mefloquine dose (mean ± SD : 16.51 ± 2.37 h). Subjects yielded blood samples within 15 min after arrival and again either 3.0 h (days 4 and 23) or 5.25 h (day 30) later. Plasma samples were later assayed for mefloquine and its carboxylic acid metabolite as described by Vuurman et al (1996).

Subjects' activity schedule depended where they were in the treatments series. On days 4 and 23, they undertook the driving test 60-120 min after arrival. The same test was delayed on day 30 to permit repeated alcohol dosing; i.e. at 165-225 min after arrival. The standardized Highway Driving Test was developed by O'Hanlon (1984) and has been applied without major revision in more than 50 studies. It originated from a staging area adjacent to an entrance/exit on a primary highway. Subjects drove a specially instrumented Volvo station wagon accompanied by a licensed driving instructor having access to redundant controls. They began the Test upon entering the highway. Their task was to maintain a constant speed (95 km/h) and steady lateral position between delineated boundaries of the right (slower) traffic lane. The vehicle's speed and its distance from the left lane line were continuously recorded. Subjects left the highway after driving 50 km at an exit in the vicinity of the second staging area. On days 4 and 23, they. re-entered the highway and resumed driving in the opposite direction.

On day 30, they stopped 5 min at the staging area for alcohol breath analysis and dosing. Then they continued as before until returning to the origin of the 100 km circuit. Lateral position data were edited off-line for removing parts recorded during overtaking maneuvers and when the lane line was absent. The remaining data were reduced to yield the standard deviation of lateral position (SDLP, cm) for each successive 10 km segment, and as the square-root of pooled variance over all segments, for the test as a whole. SDLP is a measure of road tracking error or allowed ‘weaving’.

Statistical Analysis

Originally, SDLP measured over the entire test was analyzed using the BMDP (Dixon et al., 1988) repeated-measures analysis of variance (ANOVA). Treatments was specified as the grouping factor and Days as the within-subjects factor. This analysis was repeated for days 4-23 and days 23-30 to separately measure the Treatment and Day effects and their interaction without and with the alcohol challenge. Mean differences between the groups' scores on each day were evaluated by separate t-tests (independent means, 2-tailed). Effects associated with $p < .05$ were defined as significant. The results of these analyses have been published. Reanalysis followed the recognition of what appeared to be differential group reactions over time following the alcohol challenge. The new analysis was therefore applied to SDLP scores recorded during both halves of the tests given on day 30. Treatments were again specified as the grouping factor but now Time (i.e. 1st versus 2nd half) was the within-subjects factor in ANOVA. An additional ANOVA was conducted for comparing the groups 2nd-half SDLP scores between days 23 and 30. The purpose of both was to determine the significance of Treatments by Time or Day interactions.

RESULTS

Pharmacokinetics

Mean (±SD) plasma concentrations of mefloquine measured before driving ascended from 780 ± 239 to 937 ± 209 and finally to 961 ± 351 ng/ml on days 4,23 and 30. The corresponding concentrations of the acid metabolite were 581 ± 244, 1491 ± 714 and 1687 ± 830 ng/ml. Concentrations measured after driving were comparable to those measured earlier on the same days. The drug and metabolite were detected in expected concentrations at all times in every subject. Mean (±SD) blood alcohol concentrations before, during and after the driving tests on day 30 were 0.32 ± 0.11, 0.33 ± 0.12, 0.34 ± 0.12, for the mefloquine group and 0.32 ± 0.11, 0,32 ± 0.09, 0.35 ± 0.12 for the placebo group. There was no significant difference between groups at any time of measurement.

Driving Performance

Mean (±SE) SDLP values are shown in the figure by groups, days and for both halves of the driving test separately. As previously reported, the mean difference in SDLP measured over the entire test differed significantly between groups on day 4 ($t_{38} = 2.95$; $p = .005$) but on neither day 23 ($t_{38} = 1.24$) nor day 30 ($t_{38} = 1.49$). The effect of alcohol as measured by the overall change in SDLP from day 23 to day 30 was significant ($F_{1,38} = 19.57$; $p < .0001$), but not the interaction between Treatments and Days ($F_{1,38} = 0.56$). Despite the latter result, it would appear from the figure that there was a differential effect of the treatments on the

groups' reactions to alcohol, but only in the 2nd half of the test. Reanalysis of the data from day 30 confirmed that impression: the interactive effect of Treatments and Time on SDLP was significant ($F_{1,38}$ = 4.25; p = .046). The separate overall effects of Treatments and Time were not significant ($F_{1,38}$ = 3.06 & 1.55) and neither was the difference between the groups' mean SDLP values in the 1st half of the test (t_{38} = .87). The mean difference in the 2nd half was significant, however (t_{38}= 2.36 ; P = .023). Finally, a comparison of only the 2nd half SDLP scores between days 23 and 30 again showed the significant main effect of alcohol ($F_{1,38}$ = 5.94; P = .02). But now a significant interaction was found between Treatments and Days to indicate the differential effects of treatments and alcohol in another way ($F_{1,38}$ = 4.14; p = .049)

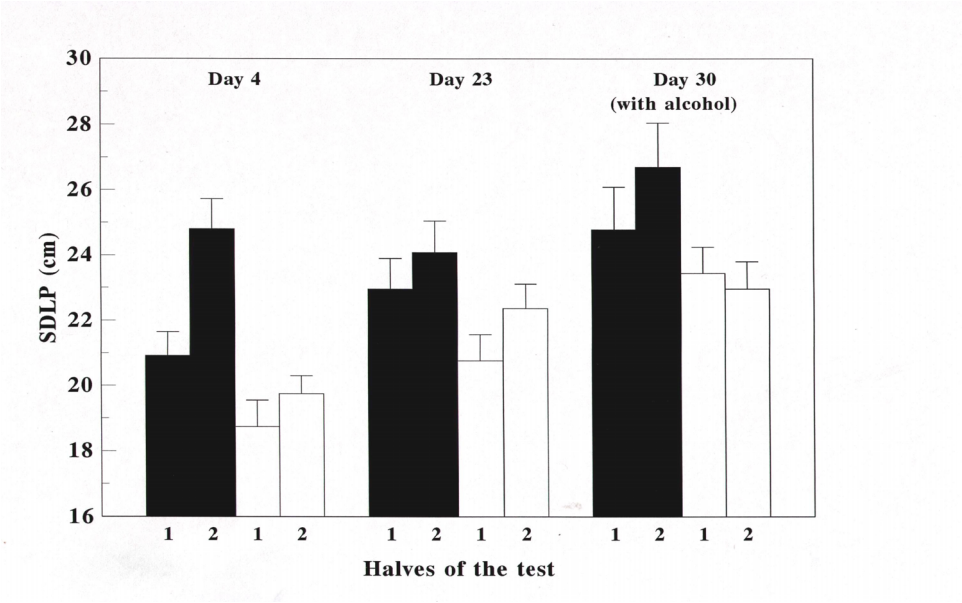

Figure 1. Mean (± SE) SDLP for placebo (shaded bars) and mefloquine (open bars) groups during 1st and 2nd halves of driving tests given on days 4, 23 and 30, the last after an alcohol challenge.

DISCUSSION

The common finding that subjects' road tracking error rises over time while they perform the standard driving test has been attributed to active physiological process of habitation (O'Hanlon and Volkerts, 1988). The process is evoked by repetitive stimulation associated with more or less the same contingent motor responses in all types of monotonous tasks. Its normal function seems to be that of economically reducing brain activity to the lowest level compatible with

achieving the immediate behavioral objective. Habituation in very monotonous ‘vigilance’ tests can be reduced or blocked entirely by the pharmacological activity of all drugs classed as psychostimulants (Koelega, 1993). On the other hand, sedating drugs such as the benzodiazepines (Koelega, 1989) and ethanol (Koelega, 1995) either independently add to or else potentiate habituation by producing an even more rapid performance deterioration in the same tests.

We previously interpreted mefloquine' s effect on driving performance as indicating that the drug possesses mild stimulating properties that partially block the deterioration that normally occurs over time due to habituation. This was mainly evident from the significant difference between placebo and drug effects on day 4; i.e., after three consecutive 250 mg loading doses on as many nights before testing. However, the difference between treatment effects was no longer significant when measured again after dosing had continued for the subsequent three weeks. Did this mean that complete tolerance to mefloquine's stimulating activity had developed in the interim? The results of the present analysis indicate that the drug was still quite active even after another week had passed.

Both groups began driving in the test on day 30 with a higher mean SDLP than they had shown during the 1st half of the test on day 23. The placebo group's performance continued to .deteriorate as after the pause as it had during both of the earlier tests. However, the mefloquine group's performance improved slightly during the 2nd half so that they ended the test with significantly lower SDLP scores than the placebo group. On day 30, the groups' opposing trends in SDLP resulted in a significant Treatments by Time interaction. The groups' differential reactions to the alcohol challenge was also revealed by comparison of their 2nd half performances between days 23 and 30. Whereas the placebo group drove worse after drinking alcohol, the mefloquine group's performance was unchanged. The result in this case was a significant Treatment by Days interaction. These results converge to yield common conclusions. The placebo group's performance showed the impairing effects of alcohol throughout the 60 minute test. The mefloquine group's performance was similarly affected by alcohol but only for 30 minutes. The drug's activity apparently combined with the restorative effect of the pause to enable those subjects to complete the test with no further loss of proficiency.

The latest results confirm mefloquine's stimulating properties and indicate that they persist to some extent for at least one month while the drug is taken continually. However they also show that the degree of stimulation mefloquine produces is very slight. As we reported previously, there was no suggestion from the subjects' routine self-assessments or the adverse events they spontaneously reported I that anyone was aware of changes in subjective feelings that one commonly associates with the use of stimulants. No differential effect of mefloquine and placebo was apparent until after the subjects had engaged in several activities during the 5-minute pause between halves of the test. It would seem that the arousing effect of those activities, in addition to the drug's activity

over the remainder of the test, were both essential for preventing any further deterioration in driving performance under the influence of alcohol. The combined effect seems not unlike that of pausing to drink one or two cups of coffee during the course of a long drive.

One possible mechanism of action to account for mefloquine's stimulating properties has recently come to our attention. Malinski and Fogel (1991) related that quinoline antimalarials are the strongest known inhibitors of histamine-n-methyltransferase. These authors were not specifically referring to mefloquine, whose capacity for inhibiting this enzyme is unknown, but it would not be surprising if it were also found to possess that mechanism of action. That being the case, mefloquine should increase the synaptic concentrations of histamine throughout the CNS. This neurotransmitter has been identified as one of the major mediators of wakeful arousal (Schwartz et aI 1991). Thus, mefloquine's effects in this study as well as many of its common and even rare side effects may be consequences of the drug's facilitation of histamine transmission. The possibility should be investigated.

ACKNOWLEDGEMENTS
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Chapter 5

Effects of mizolastine and clemastine on actual driving and psychomotor performance. [4]

ABSTRACT

The acute effect of doses of mizolastine 5, 10 ,20 and 40 mg, an active control (clemastine 2 mg) and placebo on actual car driving and psychomotor performance have been compared. Twenty four healthy volunteers were treated according to a double blind 6-way cross-over design. In the driving test, lasting about 1 h, lateral position control and speed were continuously measured; the psychomotor test battery, lasting 50 minutes, comprised critical flicker-fusion frequency, critical instability tracking, divided attention, memory search and choice reaction time, and vigilance studies; and mood changes and possible adverse effects were rated on visual analogue scales.

The results showed a dose-response relationship: mizolastine 40 and 20 mg impaired driving and psychomotor performance. The effect of mizolastine 40 mg was strongly correlated with that of clemastine (r=0.78) and was comparable to the effect of a blood ethanol level of 0.8 ml^{-1}.mizolastine 5 mg and 10 mg did not have a significant effect on driving performance and psychomotor tests.

It was concluded that at a 10mg dose of mizolastine, the therapeutic dose, it could be considered a safe antihistamine, although individual adverse reactions cannot be completely ruled out.

INTRODUCTION

Initial claims that second generation antihistamines are fundamentally 'non-sedating', have been questioned in several studies[1]. It now appears that the newer antihistamines also have sedative properties which begin to affect performance after single or multiple doses lying within or just above their therapeutic ranges[2]. Studies aimed at defining performance impairing properties of newer antihistamines should focus on the dose-effect relationship rather than simply measuring the effects of a single dose.

Mizolastine is a new benzimidazole derative possessing the clinical profile of an antihistamine drug (Fig. 1).

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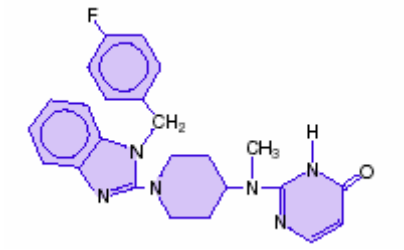
[4] *Vuurman E, Uiterwijk M, Rosenzweig P and O'Hanlon JEuropean Journal of Clinical Pharmacology (1994) 47:253-259*



Figuur 1 Chemical structure of Mizolastine

It is a potent and selective H1-receptor antagonist. It shows rapid absorption, with a t_{max} of about 1 h and a elimination $t_{1/2}$ of about 14 h, independent of the administered dose (Rosenzweig et al 1992). The inhibition of the histamine induced wheal and flare reaction was maximal within 2 h after doses of 10 mg or higher (Rosenzweig et al 1992). Like other second generation antihistamines, mizolastine is highly polar at physiological pH's and slowly penetrates the blood brain barrier as a consequence. It should therefore produce little sedative activity when taken in the expected therapeutic dose of 10 mg, once daily.

In the present study the behavioral effects of four doses of mizolastine were evaluated and compared to those of a reference drug, clemastine 2 mg and placebo, employing a driving test and standard psychometric laboratory tests. The former was developed by O'Hanlon and colleagues[4] and has proven to be a reliable and very sensitive test, showing the mild impairing effects of the usual dose of cetirizine (10 mg o.d) and twice the usual doses of loratadine (20 mg o.d.) and terfenadine (120 mg b.i.d.)[5].

METHODS

Subjects

Twenty four healthy volunteers (12 men and 12 women), aged 21-39 years (mean=26.1;SD=4.4 y), of normal height range (mean 175.9 (SD 10.3) cm) and weight (mean 66.8 (SD 8.7) kg) participated in the study. They were recruited via advertisements in local newspapers and paid for their participation. All held a drivers licence, operating their own vehicles at least 8000 km/year during each of the preceding three years. Subjects underwent a medical screening before entry in the trial including blood chemistry and haematology tests and a 12-lead ECG recording. Approval was obtained from the Medical Ethics Committee of the University of Limburg. All subjects gave written informed consent.

Design

The study was conducted according to a 6-way, double-blind, placebo and active drug controlled cross-over design. Drugs and placebo were administered in single oral doses: mizolastine 5 mg (M05), 10 mg (M10), 20 mg (M20), 40 mg (M40),

clemastine 2 mg (CLM) and placebo (PLA). Treatment order was balanced in a Latin Square design. Subjects were individually trained on the psychometric tests to be used until they reached a stable performance level and undertook a 'dress rehearsal' of the standard driving test prior to the first treatment. Drugs and placebo were taken 8 h after the last meal, and always at the same time for each subject. An interval of at least one week separated successive treatments for each subject. Test sessions began between 08:30 and 10:00 h with the administration of the psychometric test battery including subjective scales and questionnaires to establish baseline values. Subjects then ingested drug or placebo in identical appearing capsules. This was followed by the first repetition of the test battery 2:00 - 3:00 h, the driving test after 3:45 - 4:45 h and the second repetition of the test battery after 5:30 - 6:30 hours post dosing. The scheduling of the driving test was such that it occurred within a period when the effects of mizolastine 40 mg on performance had been maximal in a pilot study. On test days all subjects were served standardized meals and caffeine-free beverages. Smoking was allowed until 30 min before any of the tests.

Driving Test.
The standard driving test has been fully described in numerous publications[6,7]. As usual, the subject's task was to operate a specially instrumented Volvo estate car over a 100 km primary highway circuit at a constant speed (95 $km.h^{-1}$) and keeping a steady lateral position between the delineated boundaries of the right (slower) traffic lane. A licensed driving instructor was seated on the front passenger seat and monitored the subjects' performance. He had access to duplicate vehicle controls to intervene if necessary. Standard deviation of Lateral position (SDLP), an index of 'weaving' amplitude, was the primary measure of driving performance.

Psychometric tests
Subjects performed all psychometric tests at the Institute for Human Psycho-pharmacology in an isolation chamber specially constructed for this purpose. The following tests were administered in the order given:

Critical Fusion Frequency Test (CFF, 6 minutes)
CFF (Vuurman and O'Hanlon 1991) was tested employing a combination of the psychophysical Method of Limits an Successive Approximation in a computer controlled system. The subject was seated looking into a visual tunnel that displayed a bisected, circular, white light source in Maxwellian perspective. The pupillary diameter was not measured or controlled for in this version of the test. To begin, the computer alternatingly increased and decreased the flicker frequency (1:1 light/dark ratio) in the left hemisphere of the source keeping the right hemisphere constant as a standard reference. The subject responded by pressing separate buttons whenever his perception changed from one state to the other. Three complete cycles yielded an approximate value of the subjects CFF according to the Method of Limits. At this

point, the program identified five frequencies one Hz apart: Two below , two above and at suspected threshold frequency. Each stimulus was shown 5 times in separate, randomized presentations lasting 3 sec. apiece. The subject was instructed not to respond during the presentation period and then give one of two responses indicating the perception of flicker or fusion. The proportions of each type of response were used to calculate intersecting linear functions in the frequency domain. The equal probability point where the functions intersect defined the CFF, with an accuracy of 0.2 Hz.

Sustained Attention or Vigilance Test(VIG, 11 min)
The vigilance (Neuchterlein et al. 1982) test involved rapid serial discriminations between visually degraded images of numerical signals (‘0’) and non-signals (‘2’,’3’,’5’,’6’,’8’,‘9’). Stimuli lasting 34 ms were shown at a rate of one every 2 s. A trial contained 160 signals and 488 non-signals in random order. The subjects depressed a button each time they believed the stimulus had been a signal. Correct detections and false detections were transformed into A'_t,a measure of perceptual discriminability, according to the formula by Pollack and Norman[10].

Critical Tracking Test (CTT, 5 min)
This test (Jex et al 1966) measured the subjects' ability to control a displayed error signal using a joystick in a first-order compensatory tracking task. Error was shown as a horizontal deviation of a cursor from the midpoint of a linear scale. As the task progressed, the velocity of the cursor's deviation increased and the subject was required to make compensatory movements with a progressively higher frequency. Eventually the response frequency lagged the error signal by 180^0. At that point the subject's response added to rather than subtracted from the error and control was lost. The frequency at which control loss occurred is defined as the ‘critical frequency’ or λ_c. The subject performed this test in five trials on each occasion and the median λ_c was recorded as the final score.

Divided Attention Test (DAT, 12 min)
This test (Moskowitz 1973) measured the ability of the subject to perform two tasks simultaneously. The first subtask was identical to the CTT except that the error signal velocity was fixed at a constant level, 50% of that which was just controllable by the particular subject. The absolute mean tracking error over the entire test was taken as the first subtask score. The second subtest was that of monitoring 24 LED displays fixed in 2x3 clusters at every corner of the main display. The displays presented the numerals 0-9, which changed asynchronously every 5 sec. The subject reacted with one foot on a pedal switch after detecting the presence of the target numeral ‘2’. Inter-target times varied randomly between 5 and 25 seconds. Mean reaction time was recorded as the second subtask score.

Choice Reaction Time (CRT, 12 min)
This test was based on Sternberg's[11] memory search paradigm. Each trial was divided in three blocks. The subject was shown sets of 1, 2 or 4 letters at the beginning of each block and told to memorize them. After the presentation of each set he was shown a series 90 letters presented at intervals of 2 seconds. The subject responded as quickly as possible with using a push-button if the letter presented belonged to the memorized set. The presented letters comprised equal numbers of members and non-members of the memory set, in random order. Average reaction time for correct responses was recorded as the performance measure.

Subjective assessments

Mood (5 min).
Mood was assessed using Bond & Laders[12] series of visual analogue scales. The authors recommended procedure was followed for deriving three independent mood scores: Alertness, Contentedness and Calmness.

Subjective Feelings (VAS, 5 min)
Feelings related to possible drug side-effects were measured on 10 cm visual analogue scales indicating the presence and severity of: drowsiness, weakness, headache, fatigue, nervousness, nausea, dizziness and memory disturbances. These were bounded by the descriptive terms ‘absent’ and ‘intolerable’.

Statistical analysis

Analysis of each dependant variable was done in the same way. First the effects of placebo and the active control, clemastine 2 mg, were compared to establish the sensitivity of the particular test for impairment caused by antihistamine drugs. This was done by repeated-measure analysis of variance (ANOVA). Secondly, a multivariate analysis of variance (MANOVA) was applied to determine whether any overall significant ($p<0.05$) difference existed among the effects of all mizolastine doses and placebo. A final step involved separate mizolastine dose-placebo comparisons. These were made by successive applications of repeated-measure ANOVA using a pooled error variance term as common denominator for all F-tests in the series. The criterion p-value for achieving statistical significance was adjusted for multiple comparisons according to the sequential Bonferoni (i.e. Bonferoni-Hölm) adjustment[15]. Adverse effects were analyzed using non-parametric procedures as the data were skewed. All initial tests involved gender as a between group factor. If this factor was not significant subsequent analyses treated the subjects as a homogenous group. All analysis were conducted employing the SPSS/PC+ statistical program series[16].

RESULTS

Driving performance

Mean SDLP for both males and females and the group as a whole varied between conditions as shown in Figure 2. The average SDLP of the group was highest after clemastine 2 mg and lowest after placebo, indicating that their worst an best driving performance occurred in the appropriate circumstances. Average SDLP varied between these extremes as a monotonic function of mizolastine dose. The major findings were a significant difference in SDLP between CLM and PLA ($F_{1,22}$= 19.2; p<0.001) and a significant overall difference between mizolastine's effects on SDLP in the four dose conditions and PLA ($F_{4,19}$=7.80; P=0.001). Separate mizolastine dose-placebo comparisons revealed that the latter was due to the 40 mg and 20 mg doses ($F_{1,88}$= 16.71 & 9.65; p<0.000 & p=0.003 respectively). The lower mizolastine doses, 10 mg and 5 mg, had no significant effects on SDLP relative to placebo when judged in relation to the adjusted p_α criteria ($F_{1,88}$= 4.43; p=0.038; p_α=0.025 and $F_{1,88}$=2.63; p=0.108; p_α=0.05 respectively). Gender was significant in the CLM-PLA comparison ($F_{1,22}$= 5.00; p=0.036) and almost significant in the overall mizolastine - placebo comparison ($F_{1,22}$=4.07; p=0.056). However, no significant interactions of Gender by Clemastine ($F_{1,22}$=3.07; p=0.094) or Gender by Mizolastine ($F_{4,19}$= 0.63; p=0.648) were found.

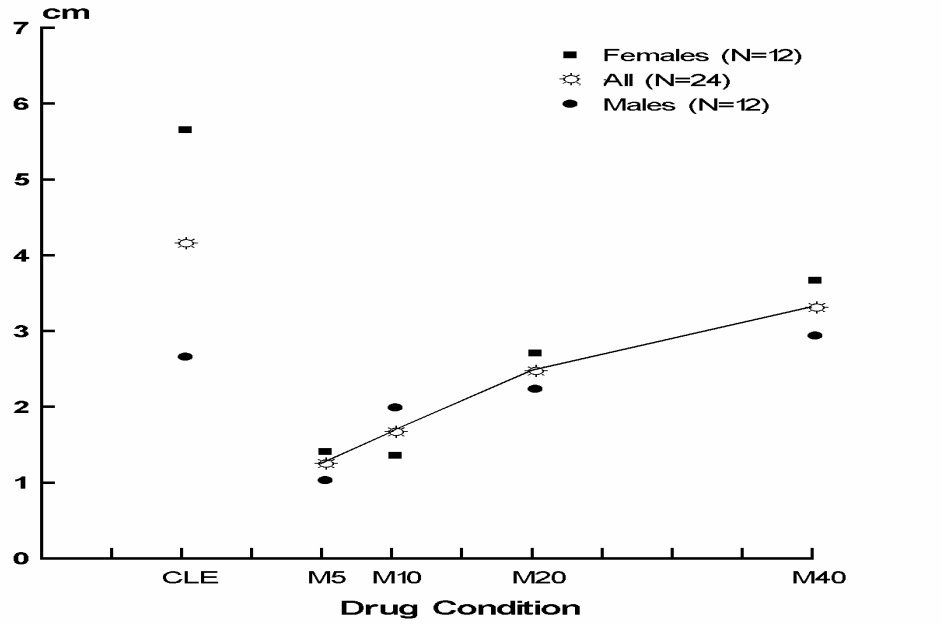


Figure 2. Mean change in SDLP from placebo for females (N=12) males (N=12) and both groups together as a function of drug treatment.

Psychometric tests

There was no significant mean differences between performances of men and women on any psychometric test. All data were analysed as changes from pre-drug baseline score. The baseline scores were equal for all conditions in each of the tests employed.

CFF

Mean CFF changes in all conditions is shown in Fig 3. A significant effect of clemastine was found in the 1st test ($F_{1,23}$=4.67; p=0.041) and separate dose-placebo comparisons showed that both mizolastine 40 mg and 20 mg caused a drop in CFF relative to placebo ($F_{1,92}$=8.43; p=0.005 and $F_{1,92}$=6.53; p=0.012).

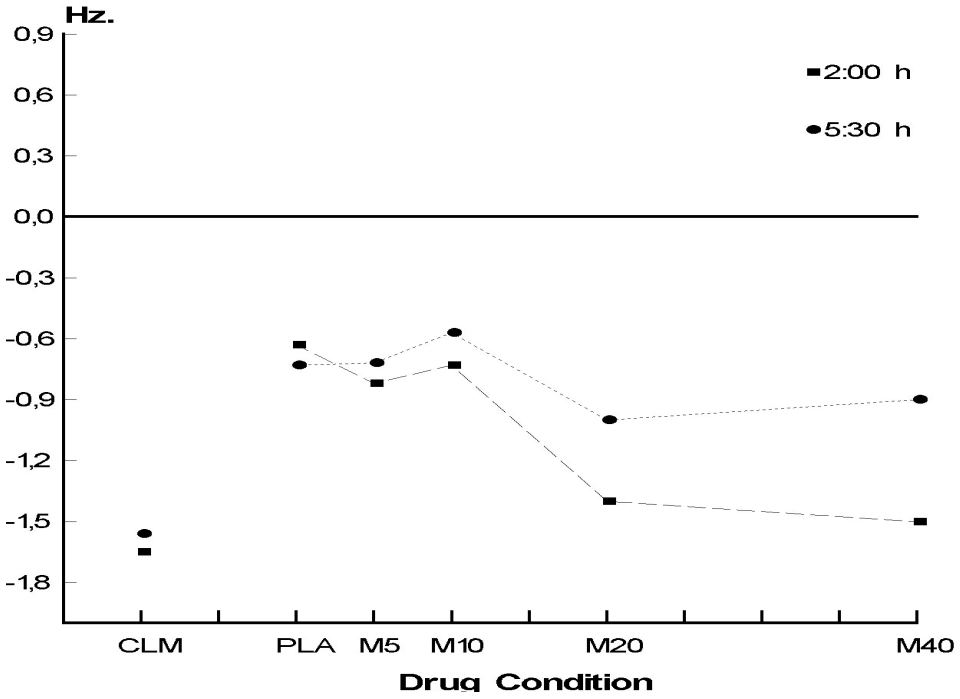


Figure 3. Average change in CFF threshold, relative to morning baseline and as a fuction of drug treatment for the 1st and 2nd test.

CTT

Changes in mean CTT performance are summarized in Fig 4. Changes in λ_c were significant in both the first and second test, after clemastine ($F_{1,23}$=17.21 & 6.99;

p<0.000 & p=0.014 respectively). Separate dose-placebo comparisons showed that M40 had a significant effect relative to PLA in the first test ($F_{1,92}$=35.05; p<001).

DAT

The performance measures from the two subtasks were analyzed separately. Fig.5a shows mean changes in tracking error. Clemastine impaired tracking performance in both the 1st and 2nd test ($F_{1,23}$=9.35 & 4.37 ; p=0.006 & p=0.047 respectively), and Separatedose-placebo comparisons showed a highly significant effect of mizolastine 40 mg in both tests ($F_{1,92}$=22.79 & 8.60; p<0.000 & p=0.004 respectively) as well as of mizolastine 20 mg ($F_{1,92}$=13.46 & 10.10; p<0.001 & p=0.002).

Mean changes in reaction time are shown in Fig. 5b. Clemastine significantly lengthened reaction times in the first and second test ($F_{1,23}$=7.17 & 7.19; p=0.013 & p=0.013). Effects of mizolastine were found in the first test after 40 and 20 mg ($F_{1,92}$=7.20 & 6.05; p=0.009 & p=0.016).

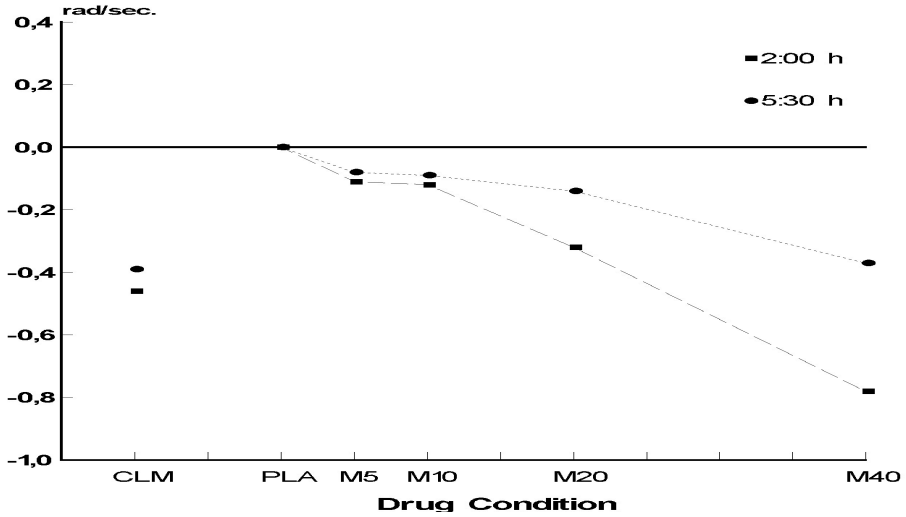


Figure 4. Average change in λ-c, relative to morning baseline and as a function of drug treatment for the 1st and 2nd test.

VIG

No significant mizolastine dose-placebo or clemastine-placebo differences were found.

CRT

The change in mean choice reaction time (RT) over all three memory sets are shown in Fig. 6. Clemastine significantly lengthened mean RT in the first ($F_{1,23}$=5.58; p=0.027) but not in the second test. A significant effect of mizolastine versus

placebo on mean RT was found after 40 and 20 mg in the first test ($F_{1,92}$=10.93 & 6.58; p=0.001 & p=0.011), and none in the second test.

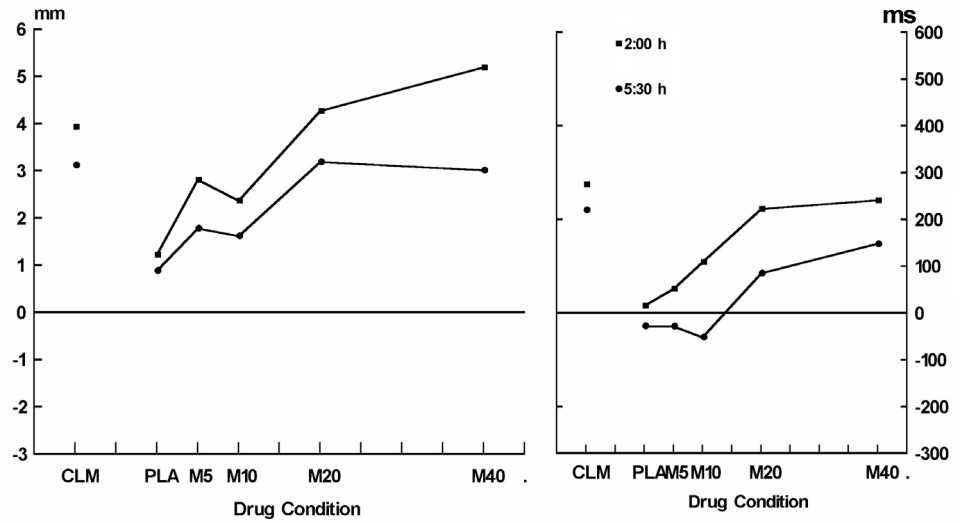


Figure 5a+b. Average change in DAT tracking error (left panel) and DAT reaction time (right panel), relative to morning baseline and as a function of drug treatment for the 1st and 2nd test.

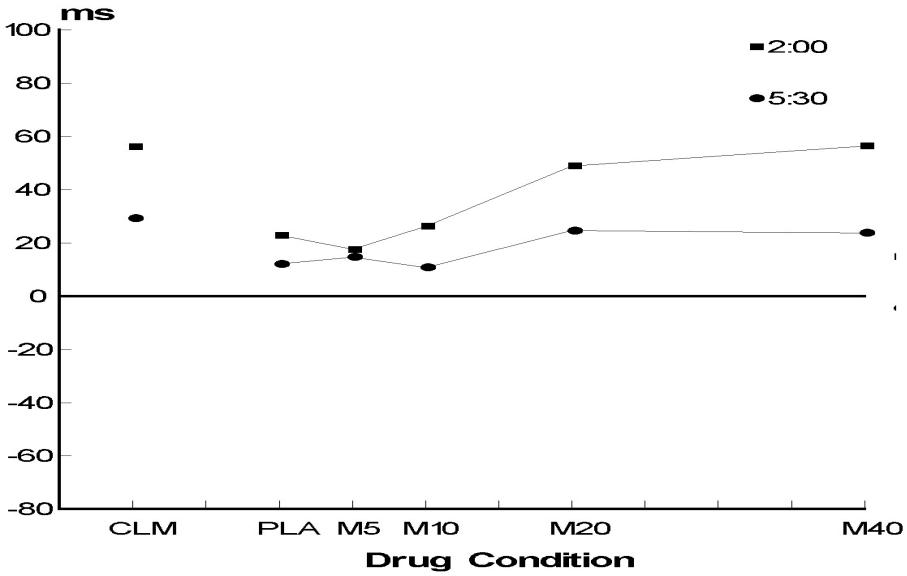


Figure 6. Average change in choice reaction time, relative to morning baseline and as a function of drug treatment. The data are combined for all memory sets and shown for the 1st and 2nd test.

Mood

Clemastine significantly depressed the mean Alertness score ($F_{1,23}$=5.09; p=0.034). There were significant overall mizolastine effects on mean Contentedness and Calmness scores ($F_{4,20}$=4.95 & 2.96; p=0.006 & p=0.045), indicating adverse effects on mood. Separate dose-placebo comparisons showed only a significant effect of the highest dose on contentedness ($F_{1,92}$=9.88; p=0.002).

Subjective Feelings

Among the eight side effects rated by the subjects, two showed significant treatment effects. Clemastine significantly increased ratings of 'drowsiness' and 'lack of concentration' (Wilcoxon, Z= -3.78 & -3.25 ; P<0.001 and 0.001). 'Drowsiness' was significantly increased as an overall effect of mizolastine (Friedman, X^2= 14.87; p<0.05) and dose-placebo comparisons showed significant effects of the 40 and 20 mg doses (Wilcoxon, Z= -3.00 & -2.84; p< 0.001 & 0.01).

Five rides were stopped prematurely by the driving instructor when he judged that the subjects were becoming too drowsy to continue safely. This occurred twice after mizolastine 10 mg, twice after mizolastine 20 mg and once after clemastine 2mg. In all cases, this happened after the ride was more than 75% complete.

DISCUSSION

The results of this study show that mizolastine, like any other H_1 antagonist, becomes sedating and impairing when present above some threshold concentration in the brain. A single 40 mg dose of mizolastine (four times the therapeutic dose) clearly produced sufficient sedation to cause general behavioral impairment. The mean effects of the 5 and 10 mg doses were not significant, while that of mizolastine 20 mg was intermediate. These findings confirm the results of previous studies (Patat et al. 1993, Shaffler et al. 1990, Danjou et al 1990). Although the mean effect on most performance variables varied as a monotonic function of mizolastine doses this was not always true in individual cases.

Clemastine 2 mg had a large effect on SDLP. Clemastine's influence on SDLP was comparable to the effect of ethanol at blood levels of 0.8 mg/ml [20]. The effect of mizolastine 40 mg closely resembled that of clemastine, both with respect to mean change and individual reactions. The high and significant correlation between SDLP changes from placebo levels (r=0.87; p<0.000) in these conditions suggests there is a common mechanism underlying harmful effects of the two drugs. The mean effects of the 5,10 and 20 mg doses were low to moderate (1.20, 1.56 cm and 2.30

cm respectively) and were more difficult to interpret. Judged by the statistical tests, only mizolastine 20 mg caused significant impairment. However, after both the 10 and 20 mg conditions two subjects were unable to complete the driving test for safety reasons. After the 10 mg this occurred after achieving moderate and high SDLP scores, and after 20 mg there was a high score in both tests. Yet, the same two subjects whose driving was stopped after treatment with mizolastine 10 mg showed very little impairment after receiving mizolastine 40 mg. The correlations between effects on SDLP of the 40 mg dose and each of the three lower doses were low ($r<0.30$), supporting the idea of a sedative 'threshold', that varies both between and within subjects. Mizolastine seems to merely increase sedative activity towards this threshold in a dose dependant manner. Whether the drug's activity actually crosses the threshold might depend on the additional effects of other factors such as sleep loss, fatigue or emotional stress. Restrictions imposed on the subjects' activities in the present study should have reduced the possible influence of extraneous factors but it is doubtful whether they were eliminated entirely.

The difference in mean driving performance between males and females was an interesting finding. The females reacted more adversely to clemastine 2 mg than males. Although no significant sex by drug interactions were found, the results indicate that females reached the sedative threshold after lower doses of mizolastine. This also appears to be the case with at least two other second generation antihistamines: acrivastine and cetirizine. Robbe and O'Hanlon[18] found no mean effects on SDLP after acute or subchronic treatment with acrivastine 8 mg in a group of 15 male subjects. Employing the same test, Ramaekers et al[19] did find a significant mean increase in SDLP after a single dose of acrivastine 8 mg in a group of 18 female subjects. Volkerts et al[20] employed male subjects and found no significant effects of cetirizine 10 mg on SDLP, but Ramaekers et al[3] measured a significant rise in SDLP in a mixed-gender group. Regardless of the underlying cause of these differences, the suggestion is strong that females generally have a smaller safety margin while taking antihistamine drugs.

The results of the psychomotor test battery generally supported the findings in the driving test, although no mean differences in test performance were again seen between males and females. The strongest effects of both mizolastine and clemastine were found in the 1st repetition of each test. The impairing effects of clemastine usually outlasted those of mizolastine, which conforms with the observation that clemastine's sedative activity persists for at least 6.5 hours after a single dose[21].

The primary practical goal of this investigation was to determine whether the expected therapeutic dose of mizolastine, 10 mg, is free of sedative effects that could pose a safety problem for patients. A decision based solely upon the results of statistical tests would conclude that this dose is nonsedating. But to do so would ignore certain disconcerting indications that sedation occurred in some individuals, especially during the driving test. Similar effects have been found in studies conducted with other 'nonsedative' antihistamines, Previous studies of terfenadine and loratadine given in twice their normal doses[5] and of acrivastine and cetirizine

given in normal doses[3] all recorded instances of subjects who were unable to complete the driving test for safety reasons. Moreover the adverse effect of mizolastine 10 mg on mean SDLP in the present study was comparable to those of terfenadine 120 mg, loratadine 20 mg and cetirizine 10 mg measured previously. The latter were all statistically significant as would have been the case in the present study for mizolastine 10 mg without the adjustment of the p_α for multiple testing.
We conclude that it is unlikely but not impossible that patients treated for the first time with mizolastine 10 mg will experience sedation causing practically relevant performance impairment. Yet the likelihood that the drug given in this dose would cause important impairment in any individual is very low, probably comparable to that after cetirizine 10 mg or terfenadine 120 mg. Relative to its alternatives, mizolastine 10 mg should be considered as a very safe antihistamine.

ACKNOWLEDGEMENTS
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Chapter 6

Effects of saripidem on psychomotor performance and memory in comparison with diazepam and placebo in healthy volunteers[5]

SUMMARY

Saripidem, an imidazopyridine with selective affinity for central benzodiazepine receptors (BZR) acts as a partial BZR agonist in animals. The pharmacodynamic effects of single oral doses of saripidem (10,20 and 30 mg) on psychomotor performance and memory in 20 healthy volunteers were compared to those of placebo and diazepam 10 mg. Psychomotor functions and sedation were assessed using both objective tests and visual analogue scales, before and up [6]to 4.5 hours post dosing. Short term and long term memory of a word list was evaluated. Saripidem 10 mg was devoid of any impairing effect. Saripidem 20 and 30 mg impaired psychomotor performance to the same extent from 0.5 - 1.5 hours and disturbed memory 1 hour post dosing but less pronounced than diazepam 10 mg. The results of the study suggest partial BZR agonistic properties of saripidem in man.

INTRODUCTION

Saripidem is a new imidazopyridine which binds at BZω receptor sub-populations. In vitro radioligand displacement studies showed that saripidem possessed very high affinities for the 'central' subpopulations, ω_1 and ω_2 (IC_{50} = 2.7 and 4.6 nM/l, respectively), but none for the 'peripheral' subpopulation, ω_3 (Benades et al 1990). Reference benzodiazepines, flunitrazepam and diazepam, had lower affinities for ω_1 and ω_2 subpopulations; i.e. former, IC_{50} - 5 and 6 nM/l, and latter, IC_{50} = 25 and 18 nM/l. Various rodent models indicated saripidem's anxiolytic efficacy after relatively low i.p. and oral doses and its failure to produce overt sedation until doses that were about 10x higher (Zivkovic et al 1990). This anxiolytic-sedative dose separation was greater than those of conventional benzodiazepines. Even more interesting were data obtained in two models for gauging BZR-ligands' intrinsic pharmacological activities. The first compared saripidem's and zolpidem's dose-related tendencies to increase isoniazid-induced convulsion in mouse. Both drugs were separately given in i.p. doses between 1 and 30 mg/kg. All BZR agonists increase convulsion latency as

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[5]E.F.P.M. Vuurman, A. Patat, L.M.A. van Veggel, C. Lavanant, N.D. Muntjewerff and J.F. O'Hanlon *Clinical Pharmacology* (1995)48: 105-111

a sigmoidal function of the dose and saripidem was no exception. However, zolpidem's effect was much greater: After the highest doses, zolpidem increased mean latency by 300%, whereas saripidem did so by only 150% (Zivkovic et al 1990, Perrault et al 1990). Further evidence came when the zolpidem dosing series was given again in combination with a fixed saripidem dose (10 mg/kg i.p.). The latter significantly antagonized the former's effect on convulsion latency. The second model compared saripidem's, zolpidem's and diazepam's effects on evoked dorsal root potential amplitude in decerebrate cat. Both zolpidem and diazepam caused the expected rise in potential amplitudes but while saripidem's effect began at a lower dose it reached a much lower relative maximum and then declined as the dose continued to rise. The effects in both models can best be explained by postulating that saripidem is a partial BZR agonist. The most telling argument was its ability to antagonize the BZR-mediated effect of a full agonist, zolpidem, in the ionized induced convulsion model.

Safety was found to be satisfactory up to single oral doses of 48 mg and multiple doses of 30 mg t.i.d. Preliminary pharmacodynamic studies employing critical flicker fusion (CFF) and choice reaction time (CRT) tests showed impairing effects after 30 mg and higher, with a peak effect one hour post dosing and a duration of less than three hours. Sedative adverse events were reported following doses of 16 mg and higher. The drug is rapidly absorbed (T_{max} about 1 hour) and has a short elimination half life ranging from 0.6 - 5.5 hours.
This study's objective was to define saripidem's pharmacodynamic properties as these influence performance and subjective feelings after single 10, 20 and 30 mg doses, relative to those of placebo and diazepam 10 mg.

METHODS

Subjects

Twenty healthy male volunteers, aged 18 - 35 years (mean=23.0; SD 3.2) with normal ratios of weight (mean=75.3 kg; SD=8.2) relative to height (mean=180.7 cm; SD=5,5) participated in the study. They were recruited via advertisements in local newspapers and paid for their participation. Subjects underwent a medical screening before entry in the trial including blood chemistry and haematology tests and a 12-lead ECG recording. Subjects gave written informed consent and all those who entered completed the study. Approval was obtained from the Medical Ethics Committee of the University of Limburg.

Design

The study was conducted according to a 5-way, double-blind, placebo and active drug controlled, cross-over design. Drugs and placebo were administered in single oral doses to constitute respective treatment conditions: Saripidem 10 mg (SAR 10), 20 mg (SAR 20), 30 mg (SAR 30), diazepam 10 mg (DZP) and

placebo (PLA). Treatment order was balanced in a Latin Square design. Subjects were individually trained on the psychometric tests until they reached a stable performance levels. Subjects fasted at least 8 hours before arrival to begin test sessions. These began between 8:30 am and 9:00 am with the administration of the psychometric test battery and subjective scales/questionnaires to establish baseline values. Subjects then ingested drug or placebo in identical appearing capsules. This was followed by the repetition of the psychomotor test battery at 0:30 h, 1:30 h, 3:30 h 3:30 h and 4:30 h. The memory tests were administered at 1:00 h and 3:00 post dosing. Blood samples were drawn one hour post dosing to determine plasma drug levels. The quantification of saripidem in plasma was done employing the HPCL method using spectrofluometric detection. Plasma concentrations of diazepam were determined by a capillary GC method with electron capture detection. (Weinfeld et al. 1977). Adverse events were recorded throughout each study day. Times of treatment and testing were kept constant for each subject. Standardized meals and caffeine-free beverages were provided during all sessions. An interval of at least one week separated successive treatments for every subject

Psychometric tests

Subjects performed all psychometric tests in an isolation chamber specially constructed for this purpose. The following tests were administered in the order given:

Critical Fusion Frequency Test (CFF, Vuurman and O'Hanlon 1990, 6 min)

CFF was tested employing a combination of the psychophysical Method of Limits and Successive Approximation in a computer controlled system. The subject was seated looking into a visual tunnel that displayed a bisected, circular, white light source in Maxwellian perspective. Pupillary diameter was neither measured or controlled in this version of the test. To begin, the computer alternatingly increased and decreased the flicker frequency (1:1 light/dark ratio) in the left hemisphere of the source keeping the right hemisphere constant as a standard reference. The subject responded by pressing separate buttons whenever his perception changed from one state to the other. Three complete cycles yielded an approximate value of the subjects CFF according to the Method of Limits. At this point, the program identified five frequencies one Hz apart: Two below, two above and one at suspected threshold frequency. Each stimulus was shown 5 times in separate, randomized presentations lasting 3 sec. apiece. The subject was instructed to withhold responding during the presentation period and then give one of two responses indicating the perception of flicker or fusion. The proportions of each type of response were used to calculate intersecting linear functions in the frequency domain. The equal probability point where the functions intersect defined the CFF with an accuracy of 0.2 Hz.

Critical Tracking Test (CTT, Jex and McDonell 1966, 5 min).
This test measured the subjects' ability to control a displayed error signal using a joystick in a first-order compensatory tracking task. Error was shown as a deviation of a cursor from the midpoint of a horizontal scale. As the task progressed, the velocity of the cursor's deviation increased and the subject was required to make compensatory movements at a progressively higher frequency. Eventually his response frequency lagged the error signal by 180^{o}. At that point the subject's response added to rather than subtracting from the error and control was lost. The frequency at which this occurred was defined as the 'critical frequency' or λ_c. The subject performed this test in five trials on each occasion and the median λ_c was recorded as the final score.

Choice Reaction Time (CRT, 5 min)
This was a 2-choice reaction time test with visual distraction. Forty-eight combinations of Warning and Imperative Stimuli were used. Each was drawn by random exhaustive selection from four sets of 12 stimuli. Sets were distinguished by the interval separating Warning and Imperative stimuli, these being 1,2,4 and 8 seconds respectively. Stimuli were presented on a computer display and responses were made by pressing separate buttons with the left and right index finger. Each trial commenced with the 400 ms presentation of the Warning Stimulus (the word, 'attention' , in the centre of the display). A rectangular fixation point was presented in the centre of the display during the interstimulus interval. This was followed by the 100 ms presentation of the Imperative Stimulus. It consisted of the word 'left' or 'right', each for 50% of the trials. The Imperative Stimulus was presented directly to the left or right side of the fixation point, again for 50% of the trials on each side. Subjects were instructed to respond using the left button if the Imperative Stimulus was the word 'left', irrespective of its position on the display. Similarly they responded using the right button if the Imperative Stimulus was 'right', again irrespective its position. Subjects were urged to respond as quickly as possible. Randomization of stimuli was such that 50% of stimuli presented at each location were compatible (e.g. 'left' presented on the left side) and 50% are incompatible (e.g. 'left' presented on the right side). After each response there was a intertrial interval of 2 sec during which the display was blank. Average reaction time was scored over all 48 trials.

Body Sway (2 min)
Postural instability, or body sway, was measured using the stabilometry method according to procedures recommended by the International Society of Posturography (Kapteyn et al. 1983). The test procedure began with the subject standing on the centre of a force platform (ELP-electroposturograph, Brussels, Belgium) with his feet making an angle of 30°. Two, 60-second recording epochs followed, the first with the subject's eyes open, the second, closed. With

eyes open, the subject was required to fixate on a target mounted on the wall at a distance of 2.0 m. The final scores were the length (mm) and the area (mm^2) circumscribed by the path of an estimated vector of force extending vertically downward from the body's centre of gravity.

Memory tests , Subjective Scales and Questionnaires:

Immediate and delayed recall of verbal information (MEM, Deelman et al., 1980, 6 min.)

This clinically validated test for verbal memory began with the sequential presentation of 15 monosyllabic common nouns. Each word was shown on the computer display for 2 seconds and the subject was required to read it aloud. When the series ended, the subject was required to recall as many words as possible. Thereupon the same list was presented in the same manner on four successive occasions. All separate trial scores were summed to yield the total Immediate Recall score. After a 1 hour delay, the subject was asked to name as many of the words he could still recall and the number correct was taken as his Delayed Recall score. Different, equivalent word lists were used on separate occasions for the same subjects and all subjects received these lists in the same order.

Visual recall and recognition (VRR, Danjou et al 1991, 5 min)

VRR was applied in saripidem's tolerability trials to show a transient effect of doses higher than 30 mg on memory. Basically the test measures the ability to acquire, store and later recall non-verbal visual information. The subject's task began with the sequential presentation of 12 images of common items (e.g. a particular flower). Images appeared on the computer display terminal at a rate of once every 10 seconds. The subject was instructed to name each image aloud and covertly compose a story for relating all images as they occurred. After a 1- hour delay, the subject was required to name as many of the images he could recall. The number correct was scored as the measure of his delayed Free Recall. Then the subject was shown a series of 24 images, including the original set plus 12 distracter items, each of which was similar to one of the original set (e.g. another flower). The order of original and distracter images were random and they were presented at a rate of one every 5 seconds. After each image, the subject was required to make a dichotomous decision and indicate whether or not it was one of the original set. The number correct was the measure of correct Visual Recognition.

Bond and Lader Visual Analog Scales (Bond and Lader 1974, 2 min)

Mood states were assessed using 16, bipolar, 100 mm visual analog scales (VAS). Three weighted sums of raw scores obtained on different sets of scales

yielded three factor analytically defined mood scores: Alertness, Contentedness and Calmness.

Spielberger State Anxiety Inventory (STAI-Y1, Spielberger 1983, 2 min)
This test consisted of a 20-item 4-level inventory of feelings related to tension and apprehension. The final score was the intensity-weighted sum of item responses.

Statistical procedures

Parametric statistical tests were used for testing drug effects on all dependant variables; ie all performance scores and those derived from the subjective assessment questionnaires. For psychomotor and subjective data, analyses were done on the changes from baseline at each time point in the assessment series. Absolute memory test data were analyzed. Testing was done employing programs from the SPSS/PC+ statistical software series (Release 4.0, Norusis 1986). Before evaluating treatment effects, the baseline psychomotor and subjective assessment scores were tested for possible effects of treatment period and first-order carry-over effects, employing a three factor analysis of variance (ANOVA, subject(20) x period(5) x 1^{st} order carry-over(5)). Treatment effects were analyzed subsequently for each point in time after treatment: First, the difference scores of placebo and the active control, diazepam 10 mg, were tested by ANOVA to establish the sensitivity of the particular test for impairment caused by anxiolytic drugs. Secondly a multivariate analysis of variance (MANOVA) was employed to differences among the effects of the three doses of saripidem and placebo. Finally two series of comparisons were made to separately compare each saripidem dose effect with, respectively, those of placebo and diazepam. Comparisons were made by successive applications of ANOVA using a pooled error variance term as the common denominator for all F-tests in the series. The criterion p-value (i.e. $p\alpha_c$) for achieving statistical significance was separately defined for each test in the series according to the Bonferroni-Holms or Sequential Bonferroni Adjustment (Overall and Rhoades,1987).

RESULTS

There were no significant first order carry-over effects on any baseline measure of psychomotor or memory performance. A significant period effect was found only for CRT performance ($F_{4,72}$=7.22, $p<0.001$), indicating a small learning effect over the duration of the study. Saripidem 10 mg had no significant effects on any psychomotor or memory test relative to placebo.

CFF (Figure 1). Relative to placebo, diazepam lowered CFF threshold in all tests between 0:30 h and 3:30 h ($F_{1,19}$= 7.72 - 3.54; p= 0.011 - 0.050). Saripidem 20

and 30 mg's effects were significant at 1:30 h ($F_{1,57}$= 17.89 & 16.79 ; p < 0.001 respectively). Relative to the peak diazepam effect, occurring at 1:30 h, those of all saripidem doses were significantly less ($F_{1,57}$= 37.15, 5.13 & 5.76 ; p < 0.001, p= 0.027 & 0.019 respectively)

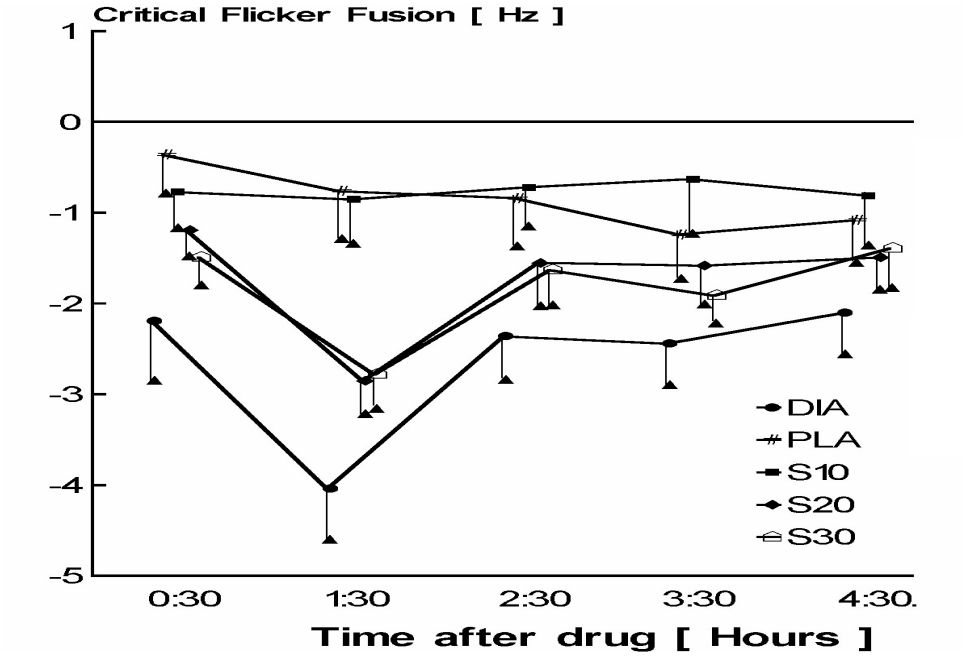

Figure 1. Mean changes (+SEM) of Critical Flicker Fusion threshold as a function of time after treatment.

CTT (Figure 2)

Relative to placebo, diazepam affected performance significantly at 1:30 h, at which time there was also an overall effect of saripidem ($F_{1,19}$=17.47; p<0.001 & $F_{3,17}$=6.09; p<0.05 respectively). At this time, both the higher doses of saripidem affected performance more than placebo ($F_{1,57}$=8.50 & 7.07 ; p=0.006 & p=0.011 respectively). Also, performance after diazepam 10 mg was significantly worse than following saripidem 10 mg ($F_{1,57}$=20.42; p<0.001).

CRT (Figure 3)

Saripidem's but not diazepam's effects occurred earlier in this test than the others. Saripidem's maximum effect was at 0:30 h , diazepam's at 1:30 h. The overall effect of saripidem was only significant at 0:30 h ($F_{3,17}$=5.63; p=0.007) while the effect of diazepam was significant up to 4:30 h. At 0:30 h the effects of both the 20 and 30 mg saripidem differed significantly from placebo ($F_{1,57}$=8.45 & 11.27; p=0.005 & p<0.001 respectively). Relative to saripidem 10 mg, diazepam significantly lengthened reaction times from 0:30 up to 3:30 h ($F_{1,57}$= 10.03,

30.05, 11.16, & 11.28 ; p=0.002, p<0.001, p<0.001 & p<0.001 respectively). At 1:30 h this was also found when compared to the effects after saripidem 20 mg and 30 mg ($F_{1,57}$=15.03 & 21.85 ; p<0.001 & p<0.001 respectively).

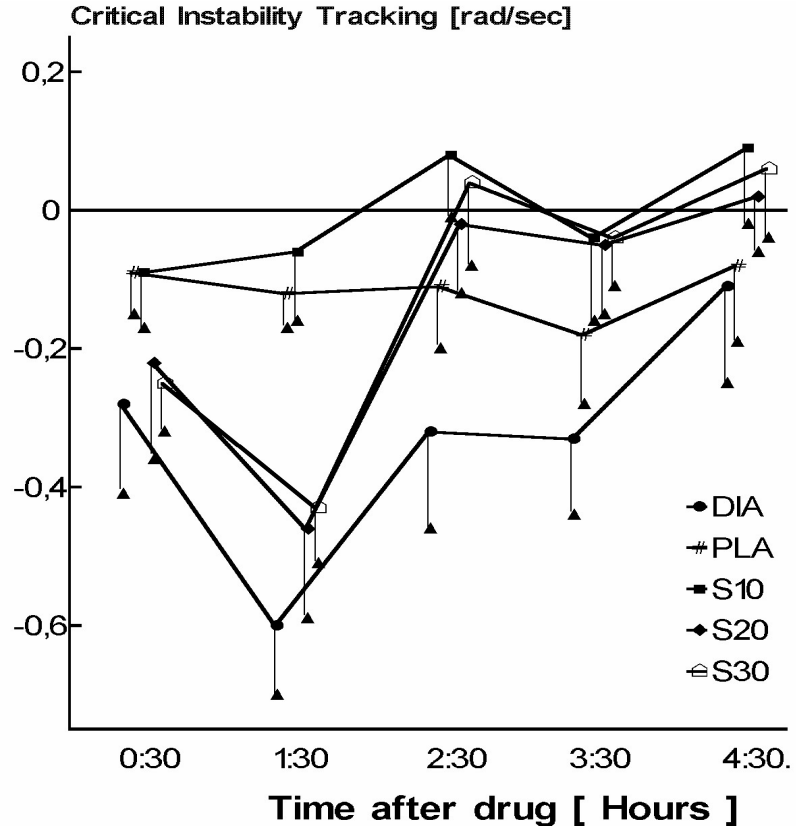

Figure 2. Mean changes (+SEM) of Critical Instability Tracking as a function of time after treatment.

Body Sway (Figure 4)

Curve Area and Curve Length were analyzed for the eyes open and eyes closed conditions. The effects on Curve Area were similar for both conditions, showing a peak effect at 1:30 h and with effects being larger in the eyes-closed condition. At this time the overall effect of saripidem was significant ($F_{3,17}$=3.21 & 4.25; p=0.049 & p=0.020 for eyes-open and eyes-closed conditions respectively) as well as the effect of diazepam ($F_{1,19}$=7.34 & 4.85 ; p=0.014 & p=0.040 for eyes-open and eyes-closed conditions respectively). The results of the curve length closely resembled the results of curve area.

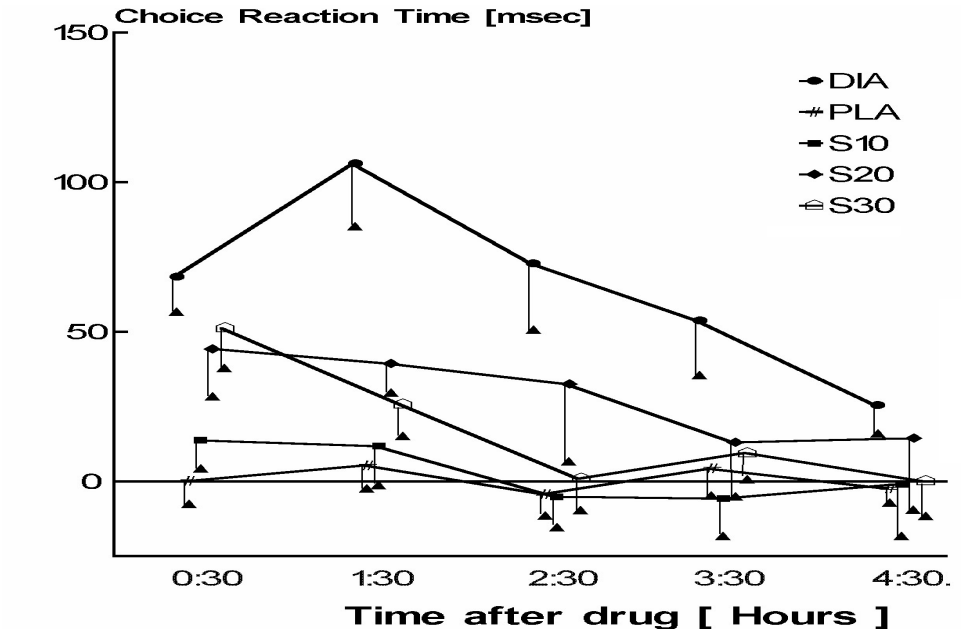

Figure 3. Mean changes (+SEM) of Choice Reaction Time as a function of time after treatment.

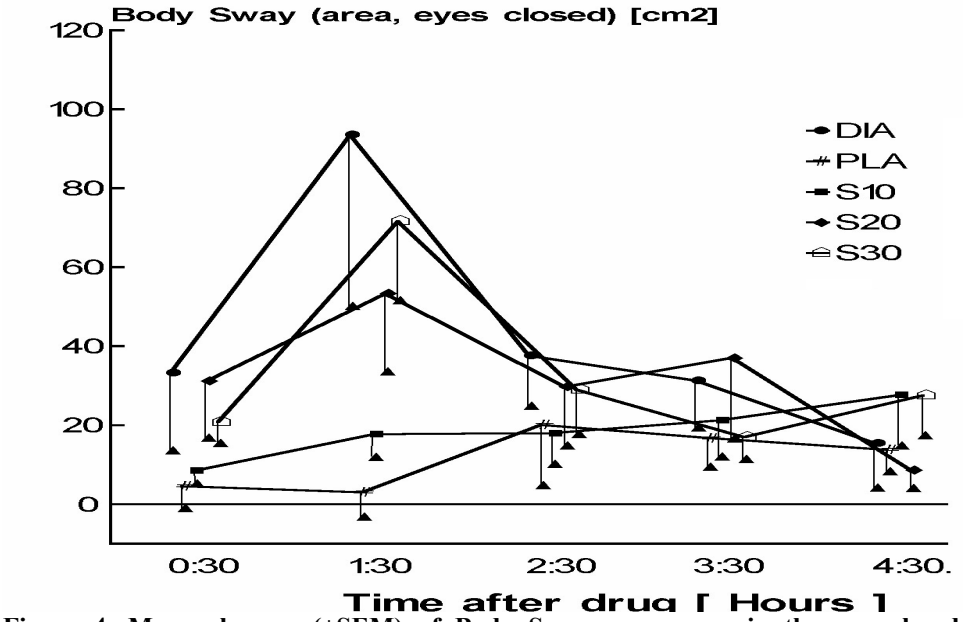

Figure 4. Mean changes (+SEM) of Body Sway curve area in the eyes-closed condition as a function of time after treatment.

Verbal Memory.(Figure 5)

All groups reached about the same performance level at the end of the fifth presentation trial, one hour post dosing. The cumulative, immediate free recall, score over the five trials showed a significant difference between the groups treated with diazepam and placebo ($F_{1,19}$=14.26, p<0.001) but not with any dose of saripidem. The mean performance of Delayed Recall one hour later showed a dose dependent effect of saripidem versus placebo ($F_{1,57}$=25.38 & 19.94; p<0.001 for 20 mg an 30 mg respectively) as well as a significant difference between diazepam and placebo ($F_{1,19}$=15.17, p<0.001). There were no significant differences between diazepam and saripidem. No effects were found on the performance of the second presentation of the memory test at 3:00 h post dosing.

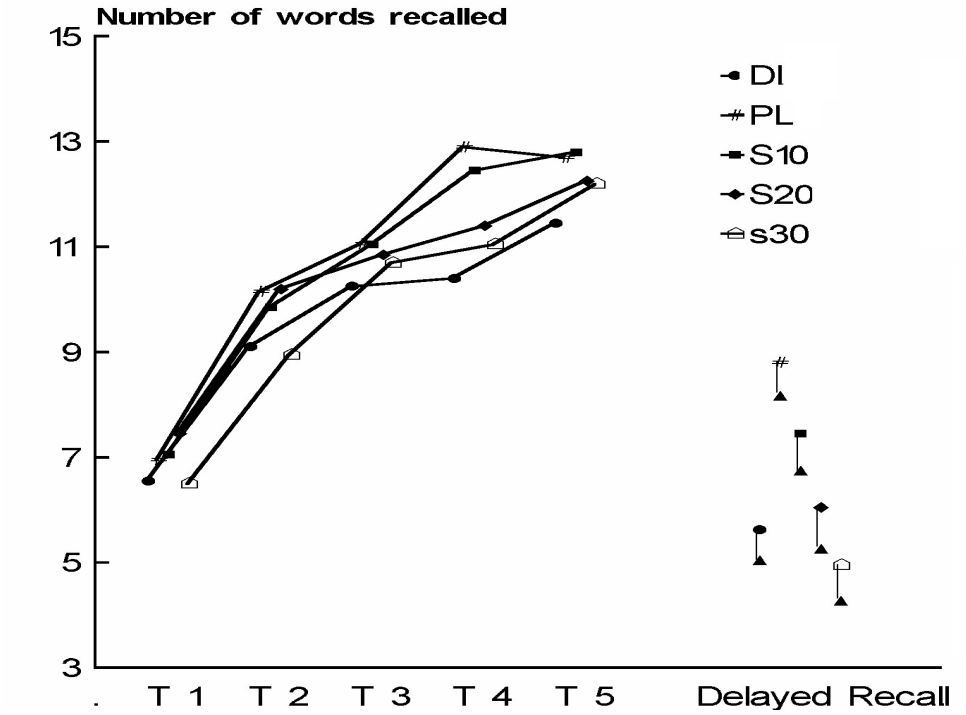

Figure 5. Mean number of words recalled after each of five (T1-T5) presentations of the word list (left panel) at one hour post treatment. Mean (+SEM) number of words recalled one hour after presentation (Delayed Recall score, right panel).

Non-Verbal memory

Mean scores of delayed free recall of non-verbal visual information only showed a significant drop in performance after diazepam compared to placebo for the presentation at 1 hour post dosing ($F(1,19)=4,69$, $p<0.043$).

Mood (Figure 6)

Diazepam significantly lowered Alertness from 0:30 h until 2:30 h ($F_{1,19}$=5.86, 22.15 & 22.63 ; p=0.026, p<0.000 & p<0.000 at 0:30 h, 1:30 h and 2:30 h respectively). Saripidem's overall effect was significant at 1:30 h ($F_{3,17}$=3.32, p=0.045). at which time the two higher doses lowered Alertness significantly compared to placebo ($F_{1,57}$=8.20 & 9.17; p<0.005; & p=0.004 for saripidem 30 and 20 mg respectively). Furthermore, differences between scores after diazepam and saripidem 10 and 20 mg were significantly different ($F_{1,57}$=20.56 & 4.52; p<0.000 & p=0.038 respectively). The difference between diazepam and saripidem 30 mg almost reached significance ($F_{1,57}$=5.22, p=0.026 α_c=0.025). No significant effects were found for the Factors Contentedness or Calmness.

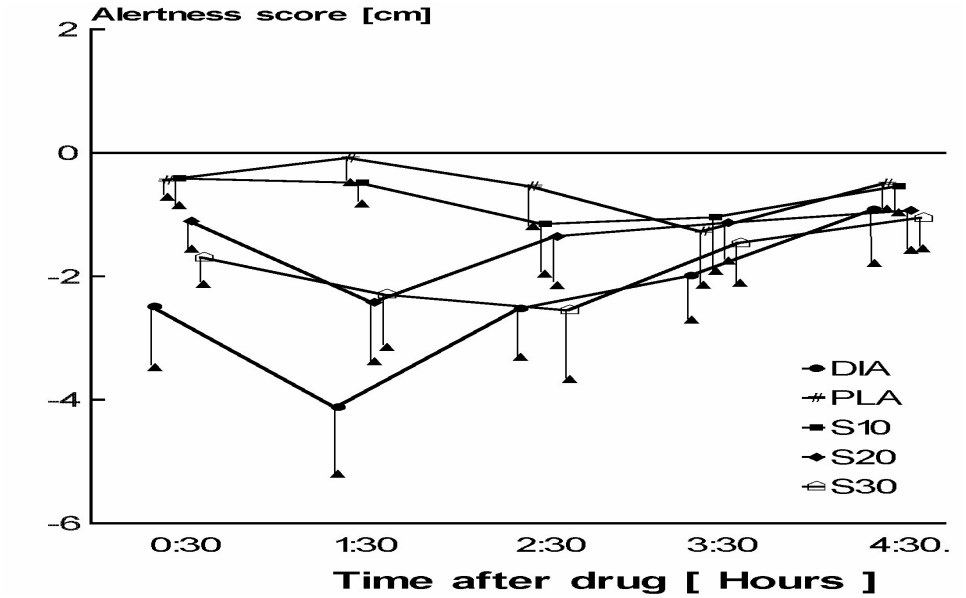

Figure 6. Mean changes (+SEM) in subjective Alertness score as a function of time after treatment.

STAI-Y1

No significant overall effect of saripidem was found but diazepam increased scores relative to placebo at 0:30 h, 1:30 h and 2:30 h ($F_{1,19}$=4.92, 18.23 & 6.15 ; p=0.039, p<0.000 & p=0.023 respectively). At 1:30 h post-dosing saripidem 30 mg increased scores relative to placebo ($F_{1,57}$=6.09; p=0.017). At this time diazepam's effects were larger compared to all saripidem doses ($F_{1,57}$=15.07,

9.96 & 7.22; p<0.000 , p=0.003 & p=0.009 for 10, 20 and 30 mg doses respectively).

Pharmacokinetics and safety
Table 1 shows mean (± SEM) plasma drug concentrations 1 hour post dosing and the frequencies of subjects reporting the most common (> 10, overall) adverse events after each treatment.

	Treatment				
	SAR 10mg	SAR 20mg	SAR 30mg	DIA 10mg	PLA
Plasma concentration (1hr)					
nMol/ml	0,063	0,012	0,183	1,01	-
(sd)	(0,008)	0,016	0,022	0,070	-
Ng/ml	21,7	39,3	62,4	287,4	-
(sd)	(2,7)	(5,6)	(7,6)	(19,8)	-
Adverse Events					
Drowsiness	6	10	10	12	5
Poor concentration	1	2	2	8	0
Abnormal coordination	0	4	8	8	0

Table 1.Mean (SEM) plasma concentrations of saripidem and diazepam at one hour post dosing; and, frequencies of subjects reporting the most common (> 10, overall) adverse events after each treatment.

Saripidem 10 mg failed to cause any significant impairment in psychomotor and memory tests relative to placebo. The effects found after saripidem 20 and 30 mg were usually maximum in tests administered 1:30 h post dosing. All effects diminished to approximate placebo's within the next hour. Diazepam's effects peaked at the same time but persisted longer. For example, the drug's effect on CRT performance remained significantly different from placebo's in all test repetitions including that which began 4:30 h post dosing. These objective impairments as well as subjective feelings of diminished alertness were generally congruent with the respective drugs' pharmacokinetic profiles, although the percipitious decline in saripidem's effects was somewhat faster than its supposed rate of elimination.

It is difficult to compare the magnitudes of separate saripidem peak dose effects with diazepam's in the absence of efficacy data in anxious patients. It is therefor necessary to estimate which saripidem dose came the closest to diazepam 10 mg for achieving the same degree of brain BZR occupancy. Many factor determine maximum receptor occupancy after oral dosing but only two are

definitely known to differ between saripidem and diazepam; i.e., systemic bioavailability and BZR binding affinity. Diazepam's bioavailability in man approaches 100% (Goodman and Gilman, 1990). Saripidem's bioavailability in man is unknown but the animal data indicated it ranges from 33 to 65 % depending on species and sex. Some indication of how much can be gleaned from the drugs' plasma concentrations measured 1 h post dosing in the present study. Following 10, 20 and 30 mg saripidem doses, the mean molar concentrations were 6, 11 and 18% of diazepam's. Yet saripidem's in vitro affinities for ω_1 and ω_2 receptors were found to be approximately 9 and 4 x higher than diazepam's. thus it would seem that diazepam's greater bioavailability is roughly balanced by saripidem's greater receptor affinity in so far as BZR occupancy is concerned. These limited data suggest that either the 10 or 20 mg saripidem dose came closest to matching the maximum receptor occupancy achieved by diazepam 10 mg.

Yet saripidem 10 mg, produced no objective or subjective sign of sedation whereas diazepam 10 mg was highly sedating. Saripidem 20 and even 30 mg affected the subjects' performance significantly less than diazepam did in two tests (i.e. CFF and CRT). It would seem that saripidem possesses less intrinsic activity responsible for sedation than diazepam, thereby fulfilling the basic criterion for a partial BZR agonist (Haefely et al., 1992).

Further evidence for saripidem's partial agonistic properties was obtained in the trio of tests that measured the acquisition and processing of information from an external source (i.e. CFF, CTT and CRT). Performance in each of them markedly deteriorated as the dose rose from 10 to 20 mg but no further as it ascended to 30 mg. A similar relationship was found for the subjects' feelings of alertness. They experienced no sedating effect of the 10 mg dose but about the same marked peak effects of both higher doses. There was, however, a difference between the durations of significant effects after the higher doses. The only time the subjects felt less alert after saripidem 20 mg than placebo was at 1:30 h post dosing. Yet after 30 mg their feelings almost differed significantly when first tested 30 min after drug and placebo ($p = .024$, $p\alpha = .0167$). The difference was thereafter significant at both 1:30 and 2:30 h post dosing. Nonetheless peak feelings of sedation following both higher saripidem doses were significantly less than after diazepam. Both psychometric and subjective data are consistent with the common concept of a partial agonist's pharmacodynamic profile; i.e. with effects rising to a lower asymptotic level than that of a full agonist.

On other functions saripidem's effects seem to suggest that the drug does not act as a partial BZR agonist. The subjects appeared about equally capable of acquiring information in the verbal memory test after all saripidem doses and placebo, as indicated by the similar improvements in learning, suggesting a lack of effect on short term memory. Nonetheless, one hour later (two hours after dosing) their delayed free recall showed a clear dose effect. The number of recalled words diminished as a linear function of the saripidem dose so that both

the effects of 20 and 30 mg differed significantly from placebo's, indicating an effect on long term memory. Diazepam's effect in this test was similar or less than that of saripidem 20 and 30 mg, in contrast to the results obtained in the psychomotor tests.

Saripidem's peak effect on postural stability in the Body Sway test also increased linearly with the dose and again differed significantly from placebo's though not diazepam's after 20 and 30 mg. Superficially it would seem that the two tests showing linear saripidem dose-effect relationships have nothing in common. However, there is apparently something similar between the mechanisms that mediate BZR ligand effects on memory and postural stability. The transfer of information from short- to long-term memory involves the hippocampus (Kandel, 1994). BZRs in that organ are predominantly of the ω_2 subtype (Sieghart, 1988). Static postural stability is largely dependent upon reciprocal facilitation/inhibition of contralateral muscle contraction through segmental spinal reflexes. BZRs in the spinal cord are almost exclusively comprised of the ω_2 subtype (Langer et al., 1988). As mentioned, saripidem possesses only about half of the affinity for ω_2 as it does for ω_1, which predominates in the cortex and is presumably more involved in all conscious processes.

Therefore, a rising saripidem concentration should exert maximum effects on those processes mediated through ω_1 before those affected by ω_2. If the former effects are maximal after 20-30 mg oral doses, the latter should not reach their limits until the dose is approximately twice as high. Thus it might have been possible to show saripidem's partial agonistic effects in all tests if the highest doses were able to saturate both receptor subpopulations. Those who go on to test psychomotor and memory effects of putative partial BZR agonists in the future may profit from these observations.

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Chapter 7

Seasonal Allergic Rhinitis and Antihistamine effects on Children's Learning [7]

ABSTRACT

Children suffering from seasonal allergic rhinitis and matched normals were instructed on the use of a didactic computer simulation in a realistic classroom situation. Groups of atopic children received different treatments before instruction; i.e., sedating (diphenhydramine HCL) or nonsedating (loratadine) antihistamines or placebo. All returned after 2 weeks for an examination measuring factual and conceptual knowledge and the application of a learned strategy. Examination results showed large and consistent impairing effects of the allergic reaction on prior learning. Both the placebo and diphenhydramine groups learned significantly less than normal controls. The loratadine group's learning performance was superior to either of the other atopic groups' but still inferior to the normals'. Our conclusions are that the allergic reaction reduces learning ability in children and that this effect is partially counteracted by treatment with loratadine and aggravated by diphenhydramine.

INTRODUCTION

Seasonal allergic rhinitis afflicts up to 10% of school age children and 21-30% of adolescents (Ricketti 1985). Absences from school and poor performance while attending school are deemed to be among the most serious personal and societal consequences of the disease (Sly 1980). Children attending school whilst symptomatic are often described as apathetic, absent-minded and disinterested in educational or social activities (Avner and Kinsman 1988). Peripheral symptoms are generally identified as a responsible factor as is the medication most commonly taken to reduce those symptoms; i.e. H1-receptor antagonists or 'antihistamines'.

Though nonsedating antihistamines have been available by prescription in most countries since the mid-1980's, none is currently registered for the indication of childhood allergy in the United States. Particularly there but presumably elsewhere, children suffering from seasonal allergic rhinitis while attending school may often be burdened with the additional impairing effects of sedating antihistamines. Evidence from one British survey indicates that scholastic achievement is cumulatively retarded by the disorder and/or its treatments (Guy 1986). The present study was undertaken to provide the first experimental evidence of the adverse

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effect of seasonal allergic rhinitis on learning in children; and also to show how it might be modified by acute treatment with nonsedating and sedating antihistamines; i.e. loratadine and diphenhydramine Hcl, respectively.

METHODS

Subjects

Participants were 52 primary school children with a history of seasonal allergic rhinitis and 21 children with no history of allergy (ie 'normals'). They ranged in age from 10-12 years (mean ± SD = 11.2 ± 0.9). They were recruited through newspaper and radio advertisements addressed to their parents. All 73 were medically screened to satisfy the inclusion criteria: general good health, normal body weight (> 30 kg) and height ; no history of chronic illness; no sensory, motor, neurological or psychiatric disorders; and no history of drug hypersensitivity. The 52 atopic children had to have been treated medically for seasonal allergic rhinitis at least the year previously. Their prescribed medications included a variety of topical prophylactics, nasal decongestants and systemic antihistamines. Only one child had previously taken loratadine in tablet form, and none, diphenhydramine. The former had not yet been registered for the indication of childhood allergy in The Netherlands or Belgium and the latter was only registered there for prescription use as an antitussive. Informed consent was obtained from both the children and their parents and the study was approved by the institute's IRB.

Normal children were recruited and selected after atopic children so that their respective age distributions and sex ratios would be approximately the same. No effort was made to match these groups with respect to intelligence but it seemed important to determine whether they differed greatly in this respect. Children's cognitive abilities were therefore measured from combined scores on nonverbal reasoning and verbal fluency subunits of a standard Dutch-language intelligence test. After division of the atopic children among three treatment groups (see below) their respective age distributions, sex ratios. and cognitive test scores differed little from each other's or from the normals' (Table 1).

Learning Model

The study employed computer-assisted instruction in the form of a 'didactic simulation', combined with relevant questionnaires, presently used in German secondary schools to teach interrelated concepts of geography, meteorology, ecology and economics (Leutner and Schrettenbrunner 1989). It was validated as an instrument for evaluating scholastic learning (Leutner 1989) and is now employed for the first time in the context of a drug trial. The simulation was translated into the Dutch language for this study. To begin the simulation, which resembles a computer ‘game’, the child takes the role of a ‘farmer’ in an arid region of North Africa and is symbolically provided with a family of productive and dependant members,

livestock, 10 plots of land on a sloping terrain and a small amount of money. The game is played by the year, requiring decisions about cultivating different crops, buying or selling livestock, controlling family growth, improving the land, mechanization etc. Each decision has both costs and benefits the magnitude of which can change depending on the situation at a given moment. The objective of the game is to survive as many years as possible. Unpredictable and sometimes extreme weather conditions (drought, flash-flooding) pose serious threats. This is an unfamiliar situation to European children and none of the study's participants knew an effective strategy to cope with these threats beforehand. They learned that while controlling up to 19 different and interrelated parameters that determine the outcome on a yearly basis. If the simulation is played without any strategy, survival is limited to about 3 years; i.e. the average interval before the first occurrence of extreme weather. Employing inappropriate strategies causes the game to end with a famine, forcing the 'farmer' to leave his or her property. After a game is terminated the next begins immediately, with the same initial values for all parameters but different weather randomization over successive years.

Two teaching functions have been implemented in the simulation: online adaptive advice and non-adaptive background information. The latter consists of a list of the immediate costs and benefits for all decisions, and can be consulted at any time during the simulation. The online function consisted of feedback concerning the appropriateness of decisions. Those which are illogical or risky elicit a warning and advice concerning a more rational course of action. The 'farmer' is thus guided to develop a better strategy and a deeper understanding of the topic. Online adaptive advice and background information on benefits of action were disabled in the final phase of the study, turning the simulation into a test of prior learning.

	Male			**Female**		
Group	N	Age	Cognitive test score	N	Age	Cognitive test score
NOR	13	11.4 (1.1)	75 (5.1)	8	11.1(0.9)	74 (6.6)
LOR	11	11.0 (0.9)	74 (6.7)	6	11.4 (0.8)	76 (6.1)
PLA	12	11.1 (1.0)	79 (5.5)	5	11.2 (0.5)	76 (6.9)
DIP	12	11.2 (0.7)	76 (6.1)	6	11.2 (1.2)	78 (7.3)

Table 1. Group characteristics: numbers, age, sex and cognitive test scores (Mean; SD)

Experimental setting.

The experiment was conducted in a 'classroom' situation, designed by a professional teacher and closely resembling a typical primary school classroom for the age group. Each of six pupils' desks was fitted with a stand-alone

microcomputer, keyboard and 14’ color display. The teachers' desk in front of the classroom had six displays in parallel to those at the pupils' desks for monitoring the children's performance.

Design and treatments.
All children progressed through a series of three sessions on separate days. Introduction occurred while children were asymptomatic. Its purpose was merely to provide them and the normal controls with the prerequisites for going further and to confirm their expected minimal knowledge about the topic of the didactic simulation.

Training occurred during the pollen season. Atopic children were included as they became symptomatic. The objectives of this session were to divide the atopic children among three matched groups; treat each group differentially for allergic symptoms; and, provide all children with the same learning experience in the didactic simulation. Group differences in knowledge acquisition were not tested on this occasion since they could be expected to show transient effects whether or not learning ability was actually affected. Atopic children were serially assigned to one of the three groups upon arrival. Assignment proceeded according to observer and subject-blind procedures that continually minimized group differences with respect to age and sex, in that order. Depending on the group, children were treated with 10 ml of syrup containing loratadine, 10 mg, diphenhydramine HCL, 25 mg, or placebo. The diphenhydramine group received the same dose four hours later, and others, placebo. Normals who participated in this session over the same period were untreated.

A 2-week interval intervened between training and examination. During that interval all atopic children's symptoms were controlled by the same, or in one case, different antihistamine medication (see below). When they arrived for the final session all children were unmedicated and essentially asymptomatic.
The objectives of the examination were to provide all children with the same opportunity to express what knowledge they had acquired in the previous session by means of performing several tests that measured different aspects of learning; and, measure group differences in performance for inferring the separate and combined effects of the allergy and treatments on prior learning.

Procedure

Introduction took place in the winter and early spring of 1991. Each child and accompanying parents were individually introduced to the investigators and the methods. Each child was shown how to operate the computer that was to be used in Training, and somewhat to our surprise, all indicated reasonable prior knowledge of keyboard functions. The topic of instruction was described as agriculture in the Sahel dessert of Africa. At this point. At this point, the children were asked to complete a 27-item questionnaire to indicate prior knowledge about the topic,

answering only the questions they could without guessing (the number of correctly answered items did not differ significantly between groups). Their score on this test was later used as a baseline for measuring knowledge acquisition. Children and their parents were then informed of requirements for the future. Parents were to note the emergence of up to 8 allergy symptoms (rhinorrhea, congestion, sneezing, pruritus-nasal, pruritus-eyes, pruritus-palate/ears, lacrimation, conjunctivitis) . The parents were asked to resume contact with the investigators as soon as the child experienced at least two symptoms, moderately or severely. Thereupon the investigators would attempt to schedule the particular child's Training the next day. As it happened, 96% were scheduled within 24 hours and all within 48 hours. Normals were called as needed to ensure that 2-6 children were present on a given day.

On the morning of **Training**, atopic children's symptoms were verified upon their arrival. These children were assigned to three groups, and treated at 09:00 am. Instruction for all children started at 09.15 am. During the lunch break (12:15 pm - 01:00 pm), attended by the teacher, children were allowed to discuss everything except their activities during the morning. Most of the period was spent with each child individually attempting to control the computer simulation. From time to time this was interrupted for group instruction by the teacher. The instruction focused on procedural matters and was always given by the same teacher according to a fixed protocol. Individual questions were only answered if they concerned computer operation. At 3:15 pm the children were taken home and told they would return in 14 days for a 1-hour paper and pencil test concerning the simulation. The atopic children were all provided with a supply of loratadine syrup to use, when needed, for symptomatic relief of during the period up to the Examination. One child reverted to his normal medication (cetirizine) due to perceived lack of efficacy. All the children were instructed to discontinue any medication on the day they returned for examination.

Examination was scheduled from 03.30 pm to 05.00 pm. Upon arrival, all atopic children reported being free from disturbing symptoms, and none showed any. Three aspects of learning were then evaluated in this session. First, recall of game-specific facts (i.e. the cost of drilling a well) was assessed by means of a 31-item multiple-choice questionnaire, indicating how well the subjects memorized and could recall the previous learned facts. The number of items correctly answered was taken as the *factual knowledge score*. Second, increase in the ability to generalize from simulation to real-life was assessed using the same questionnaire the children had completed in the introduction. Items concerned the concepts the concepts the simulation had originally been developed to engender (e.g., how to best prevent soil erosion).The change in items correctly answered was taken as the *concept knowledge score*. Finally all children engaged in the simulation once more until they could no longer survive or 20 minutes of time had passed, whichever came first. Log number of survival years constituted the *knowledge application score*. Children had not been informed of this requirement to avoid possible discussion of strategies if some should happen to meet in the period between training and examination. The

values of the parameters at the beginning of the game were slightly modified to make the game more difficult, forcing the children to adapt their former strategies.

RESULTS

Each of the three aspects of learning were analyzed separately, first by comparing the scores of all atopic groups, combined, with the normal group, employing Analysis of Variance (ANOVA); and subsequently, by comparing each atopic group with normals using t-tests with an adjusted α-criterion (Overall and Rhoades 1987). After this, children's' raw scores on each of the three different post-treatment performance tests were transformed to corresponding sets of T-scores. The three T-scores for each child were combined to yield his/her Composite Learning Score. Figure 1 shows the correlations between the separate scores and their composite. Correlations between the separate scores were low to moderate, showing the tests measured different aspects of the learning process and that their combination produced a more comprehensive measure.

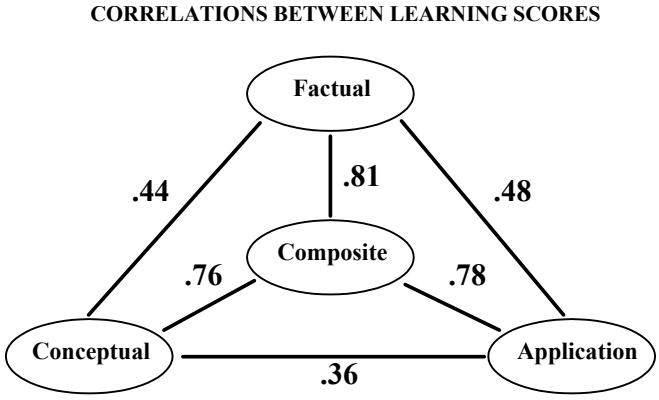

Figure 1. Correlations between the three learning scores and the Composite Learning Score.

Figure 2 shows Mean (±SE) Factual Knowledge Scores for all groups. The atopic children were significantly less knowledgeable than normal controls ($df=1,69$; $F=6.33$; $p<0.01$). Paired comparisons of each atopic group with normals showed a significant effect of diphenhydramine ($df=27$; $t=-2.59$; $p=0.012$; $\alpha_c=0.0167$). Considering only the atopic groups, children treated with loratadine performed

better than those treated with placebo, although the difference was not statistically significant.

Figure 3 shows the mean (±SE) increase in Conceptual Knowledge Scores. Atopic groups were again significantly less knowledgeable than normals (df=1,69; F=5.55; p<0.02). Pairwise comparison of each atopic group with the normals again revealed a significant difference between diphenhydramine and normals(df=36; t=3.56; p=0.001; α_c=0.0167). Moreover the order of groups achievement on the second test was the same as the first; i.e normals> loratadine > placebo > diphenhydramine.

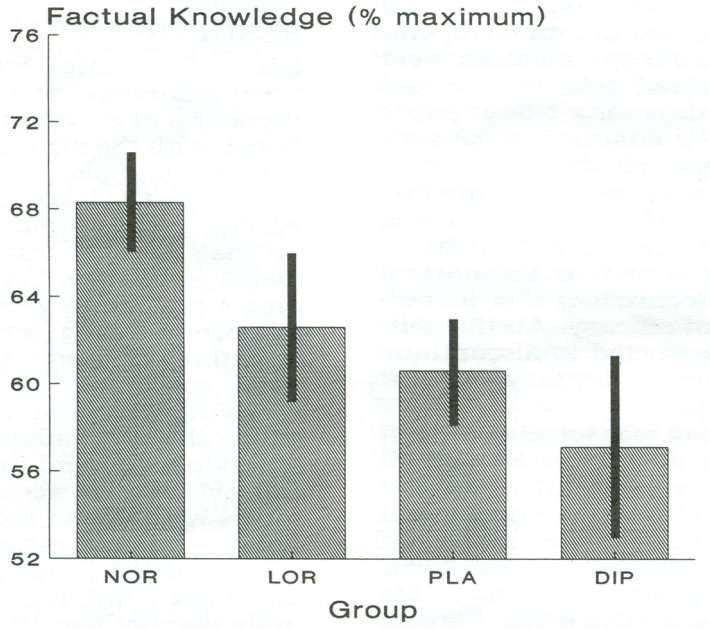

Figure 2. Mean (±SE) Factual Knowledge Score for every group as percent of maximum.

Figure 4 shows the geometric mean (±SE) time of survival for each group, the Application Score. Again, the difference between all atopic groups combined and normals was significant (df=1,69; F=5.48; p<0.02). Strikingly the order of atopic group achievement, although not significantly different, was the same as before, with loratadine superior to placebo and diphenhydramine inferior.

Figure 5 show the mean (±SE) Composite Learning Score for all groups. As expected the difference between normals and all atopic children was highly significant (df=1,69; F=9.93 ; p< 0.003) as were those between normals and the atopic groups receiving either placebo or diphenhydramine (respectively , df=31; t=-2.91; p=0.007; α_c=0.025 and df=35; t=-3.30; p=0.002; α_c= 0.017).

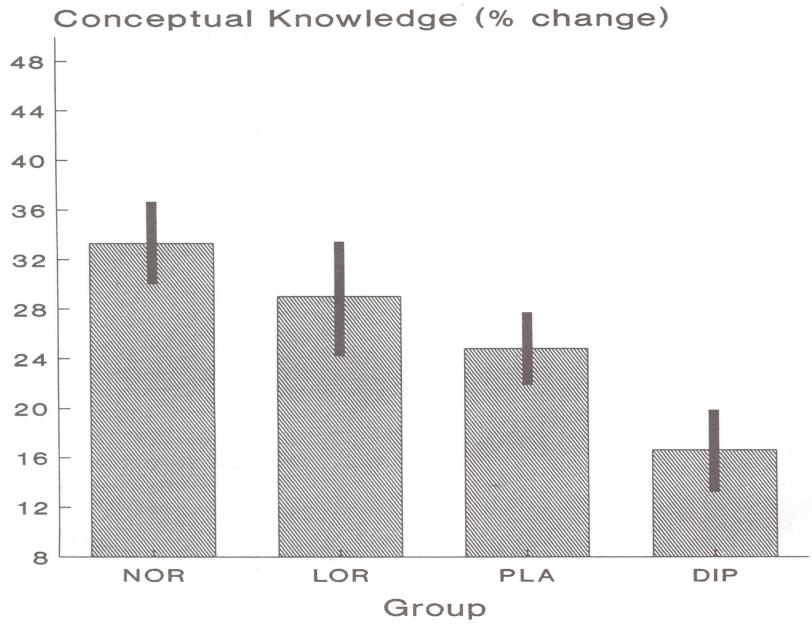

Figure 3. Mean (±SE) Conceptual Knowledge Score for every group as percent change from baseline.

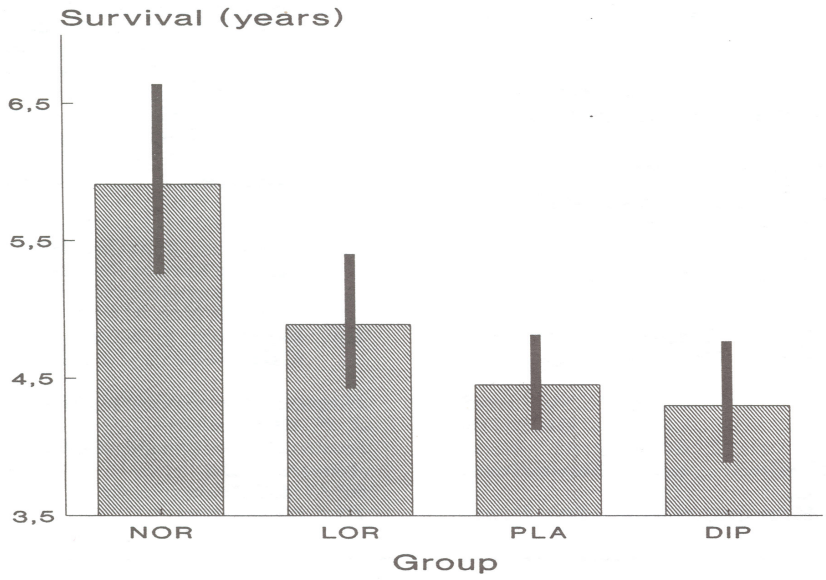

Figure 4. Mean (±SE) survival years (Application Score)

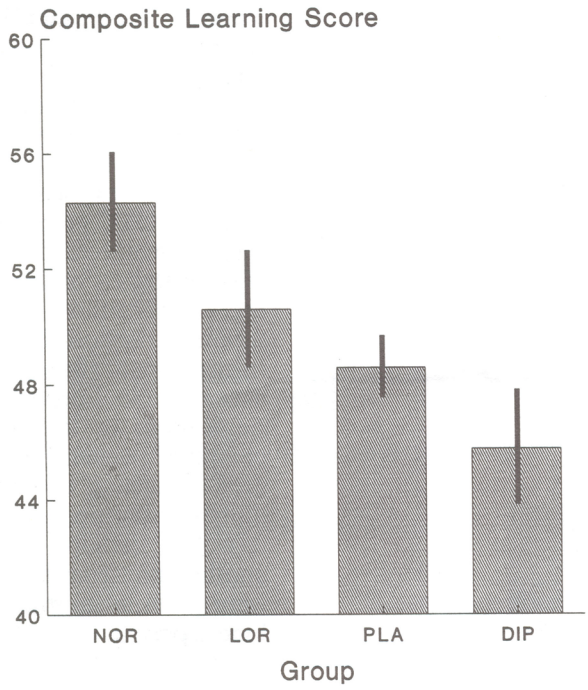

Figure 5. Mean (±SE) Composite Learning Score for every treatment group.

DISCUSSION

The normal children's average learning performance was in every way superior to the allergic children's, no matter how the latter had been treated before training. The greatest group differences in performance scores were between normals and children treated with diphenhydramine but those between normals and the placebo treated group were nearly as large. Though the latter were not significant for any particular test, the difference between these groups' composite scores was highly significant. From these findings we conclude that seasonal allergic rhinitis, by itself, can cause learning impairment. The acute effects of loratadine and diphenhydramine were in the expected opposing directions relative to placebo's. Although loratadine did not completely reverse the learning impairment caused by the allergic reaction, the beneficial effect was consistent in all three aspects of learning.

There are important practical implications of this study. The usual coincidence of the pollen season with preparation for end-term examinations discriminates unfairly against children suffering from the effects of seasonal allergic rhinitis. Unless those children's disorder can be effectively treated allowing them to maintain the same rate of learning as their normal peers it would be fair and wise to postpone crucial tutoring and examinations until the

pollen season has passed. Treatment of school children should probably not involve the administration of sedative antihistamines. Although tolerance may develop to the drug's sedative activity during continual medication, most children are treated intermittently in correspondence with the emergence and disappearance of symptoms dependent upon climatic factors. Traditional prescribing practices, regulatory restrictions as well as wider availability of sedative antihistamines in OTC preparations are factors currently favoring the use of those drugs by children. Nonsedating antihistamines should be prescribed to school children suffering from seasonal allergic rhinitis whenever possible. Loratadine given in a single dose in this study did not completely reverse the atopic children's learning deficit, but unlike diphenhydramine, it did not make it worse. Perhaps if loratadine or another nonsedating antihistamine were given in multiple doses over a longer period, the deficit would disappear.

However, there are theoretical arguments to suppose that peripheral symptoms do not fully account for the learning deficit in children. The immediate hypersensitivity reaction in seasonal allergic rhinitis proceeds, in 30-50% of all cases, to a late-phase reaction as nasal symptoms change from sneezing, rhinorrhea and pruitis to congestion[9]. The transition is thought to proceed with the infiltration of antigen-specific T-lymphocytes and their release of mediators (lymphokines) which initiate the cascade of cellular interactions responsible for inflammation and edema[10]. Many of the same mediators are released during the immune system's response to viral infection and known to pass through the circulation to brain receptors where they generate the syndrome known as ‘sickness behavior’[11]. In animals, this is recognizable by inhibited goal-directed behavior, and in humans from feelings of apathy, fatigue and malaise. These symptoms bear a suspicious resemblance to those experienced commonly in seasonal allergic rhinitis, and by analogy, suggest a common cause.
Lymphokines so far identified as promoting sickness behavior are also pyrogens. Recent evidence however, indicates that lymphokine-mediated sickness behavior can occur in the absence of fever (Kent et al. 1991). It is therefore conceivable that the children's learning deficit was another manifestation of sickness behavior, produced as part of a systemic reaction to the offending allergen.

This concept is encouraged by the discovery that the serum concentration of one lymphokine, ã-interferon, is chronically elevated in euthermic patients suffering from seasonal allergic rhinitis (Beatrice et al 1988). If this is essentially correct, only a drug that prevents progression of seasonal allergic rhinitis from the acute hypersensitivity to the delayed phase would be fully effective.

Whether loratadine or any other H1 antagonist can do this is unknown and further research along this line would be necessary to optimize the treatment of children attending school with seasonal allergic rhinitis.

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Chapter 8

Effects of Semprex-D and diphenhydramine on learning in young adults suffering from seasonal allergic rhinitis.[8]

SUMMARY

Objectives. The purpose of this study was to test the hypothesis that learning ability is impaired in patients with seasonal allergic rhinitis relative to untreated individuals and to evaluate a combination compound (acrivastine 8mg + pseudoephedrine 60 mg) for attenuation of the learning impairment in these patients.
Background. In a previous study employing the same method it was shown that young children (10-12 yrs) suffering from seasonal allergic rhinitis performed significantly worse on tests of learning and using knowledge after acute treatment with a sedating antihistamine (diphenhydramine 50 mg) or placebo. This effect was partially reversed by treatment with loratadine.
Methods. Sixty-seven young adults suffering from seasonal allergic rhinitis and 28 matched controls were trained on didactic simulation for three consecutive days. Atopic subjects were treated differentially during training according to a double-blind, randomized parallel group design with either diphenhydramine hydrochloride 50 mg, a combination compound (acrivastine 8 mg + pseudoephedrine 60 mg, A+P) or placebo, administered qd. After training, all atopic subjects were maintained on A+P treatment for 14 days at which time all groups returned for examination.
Results .Mean performance at the end of training was worse for all atopic subjects combined compared to normals. Subjects treated with diphenhydramine performed significantly worse than either normals ($p<0.001$) or those treated with A+P ($p<0.001$). At the examination, the diphenhydramine group's performance differed significantly from those of the normal ($p<0.001$) and A+P groups ($p<0.001$).
Conclusions. The study supports our previous finding that allergy symptoms reduce learning ability which is further reduced by diphenhydramine. Atopic subjects with allergies treated with acrivastine + pseudoephedrine learned as well as normal subject

INTRODUCTION

Allergies interfere with many daily activities, including learning. Treatment with certain antihistamines which alter cognitive function or cause sedation may make the situation worse. In a previous study we employed a didactic computer simulation, widely used in German secondary school systems, to demonstrate that

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[8]Eric F.P.M. Vuurman, Loe M.A. van Veggel, Ronald L Sanders, Nienke D. Muntjewerff1 and James F. O'Hanlon *Annals of Allergy* 1996 76:247-252

seasonal allergic rhinitis and diphenhydramine impaired childrens' learning and retention[1]. Separate patient groups were treated with diphenhydramine, loratadine or placebo and trained for a single day. The effects on learning retention were measured after two weeks of continuing treatment with loratadine. This study assessed the effects of a new antihistamine decongestant product, acrivastine 8 mg plus pseudoephedrine hydrochloride 60 mg (A+P, SEMPREX-D™ Capsules), on learning in young adults suffering from seasonal allergic rhinitis. As in the previous study,[1] the effects of A+P were compared to those of diphenhydramine and placebo, but using older subjects and with training/treatment periods extending over three days. Learning acquisition during training, as well as retention two weeks later, were measured in the same task

A+P is efficacious for the management of seasonal allergic rhinitis.[2] Its efficacy is predicated upon the complementary pharmacological activities of the antihistamine and decongestant for relieving allergic and nasal symptoms. Ramaekers and O'Hanlon[3] showed modest impairment of actual driving in females after single doses of acrivastine 8 mg, but no effects after A+P. Robbe and O'Hanlon[4] found modest driving performance improvement relative to placebo in males treated for four days with A+P t.i.d., but no effect of acrivastine alone. Together these results suggest physiological antagonism between the respectively mildly sedating and stimulating activities of acrivastine and pseudoephedrine, respectively. Earlier, Gaillard and Verduin[5] had demonstrated the same antagonism between the separate and combined effects of an older, more sedating antihistamine, azatadine, and pseudoephedrine. The former impaired, the latter improved, and the combination failed to affect performance in a choice reaction time test.

The objectives of the present study were to (1) confirm the previous finding regarding impairment of learning by seasonal allergic rhinitis and diphenhydramine and to (2) evaluate the effects of A+P. Additionally, a standard memory test was added to ascertain whether it is necessary to use the much more complex computer learning task in studies of this sort.

METHODS AND MATERIALS

Subjects

A total of 67 allergic subjects completed the study together with 28 control subjects (normals) with no history of allergy. They ranged in age from 16-25 years (mean ± SD =20.0 ± 2.3) and groups were matched for age and intelligence. Inclusion criteria were general good health, normal body weight and height, participation in formal education for at least 16 hours per week. Exclusion criteria, applied following a medical examination, were a history of severe mental or physical disorders, alcohol or drug abuse, requirement for chronic medication and any drug hypersensitivity.

Atopic subjects had documented medical treatment for seasonal allergic rhinitis over the prior two years and were required to have minimum diary symptom scores

≥ 9 prior to drug treatment. The occurrence and severity of six symptoms (rhinorrhea, nasal congestion, sneezing, mouth breathing, itchy nose/throat and tearing or red eyes) were scored in a diary on a 5-point scale ranging from 'absent' to 'very severe, interfering with daily activities'. Atopic subjects were placed on study medication on the evening of the day they first achieved the minimum symptom score. Symptoms were scored daily until the end of the study.
Informed consent was obtained from all subjects and, if under 18 years of age, also from their parents . The study protocol was approved by the Institutional Ethics Committee.

Study Medications
Placebo, diphenhydramine 50 mg (BENADRYL™), and A+P capsules were packaged and supplied by Burroughs Wellcome Co., Research Triangle Park, NC, USA in coded, indistinguishable, opaque bottles. Medication was dispensed to the atopic subjects by a physician who did not participate in any of the learning tests.

Design, treatments and procedures

All subjects participated in the three phases of the study: Introduction, Training and Examination.

During *Introduction*, lasting about two hours, subjects were tested for prior knowledge of the simulation's topic and were briefed regarding further activities. Introduction occurred while all individuals were asymptomatic. Physical exams were administered and study inclusion/exclusion criteria were verified.

Training transpired over three consecutive evenings from 18:00-22:00 hr (Days 1-3). Atopic subjects were serially assigned to one of the three treatment groups according to observer and subject-blind procedures, minimizing the group differences with respect to age and intelligence. Intelligence was determined from combined scores on nonverbal reasoning and verbal fluency subunits of a standard Dutch intelligence test. Depending on the group, subjects were treated with the combination of A+P, diphenhydramine 50 mg or placebo, all q.i.d. Treatment started the evening before the first training session and successive doses were given at 8:00 hr, 13:00 hr, 18:00 hr and at 23:00 hr or just before the subject retired for the night. Untreated normals comprised the fourth group. All subjects were provided with the same learning experience over sessions. All training sessions were conducted as follows: Subjects' verbal memory was tested upon arrival at the laboratory. Then they were given three 30-minute practice sessions to explore different strategies for mastering the computer simulation. After each practice segment they performed a single simulation trial, using the knowledge and experience acquired up to that moment. At the end of Day 3 subjects were dismissed and instructed to return two weeks later for a final session. All atopic groups were given a supply of A+P to control their symptoms according to a q.i.d. dosing schedule during this period.

The objectives of the *Examination* phase were to assess retention of the knowledge acquired previously and to measure group differences in performance attributable to the combined effects of the allergy and treatment during Training. Examination lasted about one hour and consisted of a final simulation performance test and two multiple choice questionnaires, respectively testing game-specific factual knowledge and the ability to generalize simulation knowledge acquired to real-life problems. Table 1 summarizes the treatment, procedures and demographic characteristics for the four groups.

Number and gender	**NOR** 10♂ 18♀	**A+P** 13♂ 9♀	**PLA** 7♂ 15♀	**DIP** 14♂_10♀
Age	20.2(2.6)	20.0(2.7)	19.8 (2.0)	20.1 (1.7)
Phase		**TREATMENT**		
Introduction	NONE	NONE	NONE	NONE
Training	NONE	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d	placebo	diphenhydramine 50 mg q.i.d
Period of 14 days	NONE	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d
Examination	NONE	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d	acrivastine 8 mg + pseudoephedrine 60 mg q.i.d

Table 1. Treatment schedule and group characteristics (Mean age (± SD) and sex ratios) for patient groups receiving diphenhydramine (DIP), acrivastine + pseudoephedrine (A+P), placebo (PLA) and non-treated normal controls (NOR).

Learning model
The study employed a 'didactic simulation', in the form of computer-assisted instruction. This simulation is currently used in German secondary schools to teach interrelated concepts of geography, meteorology, ecology and economics[6]. It is a validated instrument for evaluating scholastic learning and fully described in our previous publication[5]. The simulation resembles a computer 'game'. The subject takes the role of a 'farmer' in an arid region in North Africa. He must learn a strategy to optimally manage limited resources and prepare for unexpected climatic changes by simultaneously controlling up to 19 separate parameters. The goal is to survive as long as possible and the number of survival years is the primary outcome variable.

Verbal Memory test
A clinically validated verbal memory[7] test consisted of sequential presentation of 15 monosyllabic common nouns on a computer display for 2 seconds each. The subject read the word aloud. When the series ended, the subject recalled as many words as possible. The number correct was scored as the first trial score. Thereupon the list was presented in the same manner on four successive occasions. Numbers correct were scored as before. All separate trial scores were summed to yield the Immediate Recall score. After a 1 hour delay, the subject was asked to name as many of the words as he could still recall and the number correct was taken as his Delayed Recall score.

Statistical analysis
Variables from the memory tests and symptom scores were first tested separately using repeated analyses of variance (ANOVA), comparing group changes over time. Thereafter, ANOVA was applied to these variables for each day separately. Finally scores of each atopic subject group and those of normals were compared, pair wise, using t-tests with an adjusted alpha probability-criterion[8]. The distribution of simulation test scores was positively skewed and analysis was performed on the log-transformed data. Separate ANOVA's were applied on the data obtained at the end of Training (Day 3) and Examination contrasting results of atopic subject groups combined with normals, each followed by pair wise comparisons as described above. All analyses were conducted employing modules from the BMDP statistical program series[9].

RESULTS.

Symptom scores
Subject entry occurred from April to August 1993, coinciding with the Dutch pollen season. Weather conditions were very unstable during that period, with the month of June being the wettest of the century. Figure 1 shows the symptom scores for the atopic subject groups over the entire study period. Complete symptom scores data

were obtained from 59 subjects, 8 subjects having returned an incomplete diary. Symptom scores at inclusion were similar for all groups and above the entry criterion (≥9). Scores dropped over training for all three groups, more rapidly during drug treatment than placebo. Analysis of scores showed a significant treatment effect on Day 1 ($F_{2,56}$=3.49; p=0.037). Pair wise comparisons on Day 1 showed significant symptom improvement compared to placebo in both the diphenhydramine and A+P groups (t_{56}=2.32; p=0.024 and t_{56}=-2.24; p=0.029, respectively). There were no significant treatment effects on Days 2 or 3. At Examination, symptom scores were generally low and not significantly different between groups.

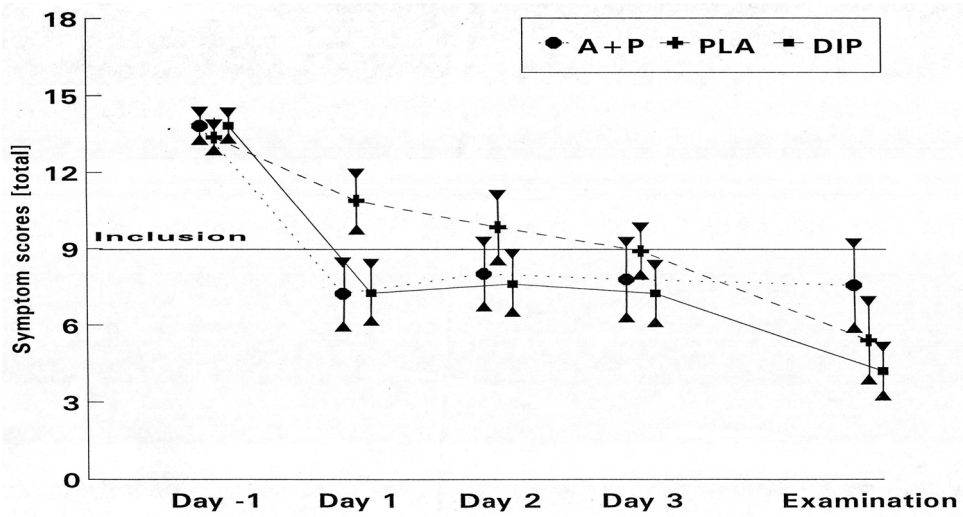

Figure 1.Mean (± SE) sum scores of six allergy symptoms (rhinorrhea, nasal congestion, sneezing, mouth breathing, itchy nose/throat and tearing or red eyes) for each patient group respectively treated with diphenhydramine (DIP), acrivastine + pseudoephedrine (A+P) or placebo (PLA) over the entire study period.

Memory test

Figure 2 presents the mean (±SE) number of words during Immediate Recall for all groups. These data were obtained from 95 subjects. ANOVA showed no overall treatment effects ($F_{3,91}$=0.39; p=0.761) but a significant increase over time in overall performance ($F_{2,182}$=7.41; p<0.001). Analysis of the scores for each day separately showed no significant differences between the groups on any day. The mean Delayed Recall results varied in a similar manner. Again, no overall effect of treatment was found on any day or over all days, but again there was a significant increase over time ($F_{2,182}$=16.68; p<0.001).

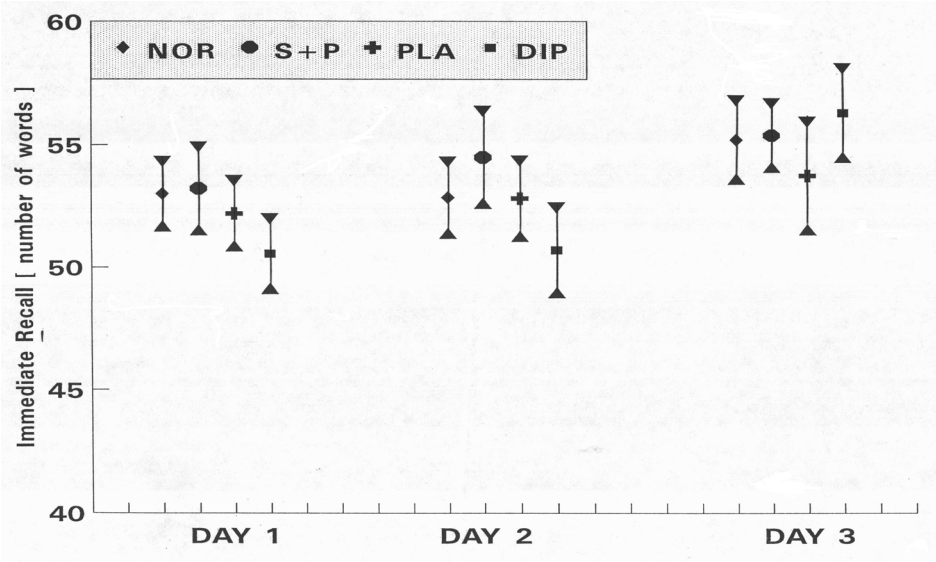

Figure 2. Mean (± SE) scores of Immediate Recall on the memory test for patient groups receiving diphenhydramine (DIP), acrivastine + pseudoephedrine (A+P), placebo (PLA) and non-treated normal controls (NOR) on each training day.

Learning test

Figure 3 shows mean (± SE) years of survival over Training and at Examination. Scores increased over training for all groups, indicating the acquisition of learning, although at a different rate for each treatment. First, performance scores at the end of training (Day 3) were analyzed. All allergic subjects combined had significantly lower scores than normals ($F_{1,91}$=4.21; p=0.043). Paired comparisons between normals and each atopic group showed a significant performance deficiency only after diphenhydramine (t_{91}=3.46; p<0.001). Furthermore, performance after A+P was significantly better than after diphenhydramine (t_{91}=3.37; p=0.001) and the difference between the placebo and diphenhydramine groups was not statistically significant (p=0.067). Performance after A+P was not significantly different from the placebo (p=0.13) and normal groups (p=0.87).

Performance at Examination was analyzed in the same way. Taken together, all atopic subjects again performed significantly worse than normals ($F_{1,91}$=6.59; p=0.012). Pair wise comparisons of normals with each atopic group showed a significant performance deficiency after diphenhydramine (t_{91}=4.04; p<0.001) and an almost significant deficiency after placebo (t_{91}=1.81; p=0.073). The mean performance after A+P was more than twice as good as diphenhydramine's (t_{91}=3.43; p=0.001). There was no significant difference between the normal and A+P groups (p=0.73).

Mean scores on the multiple choice questionnaires were high (77-80 % correct) and no differences were observed between the groups.

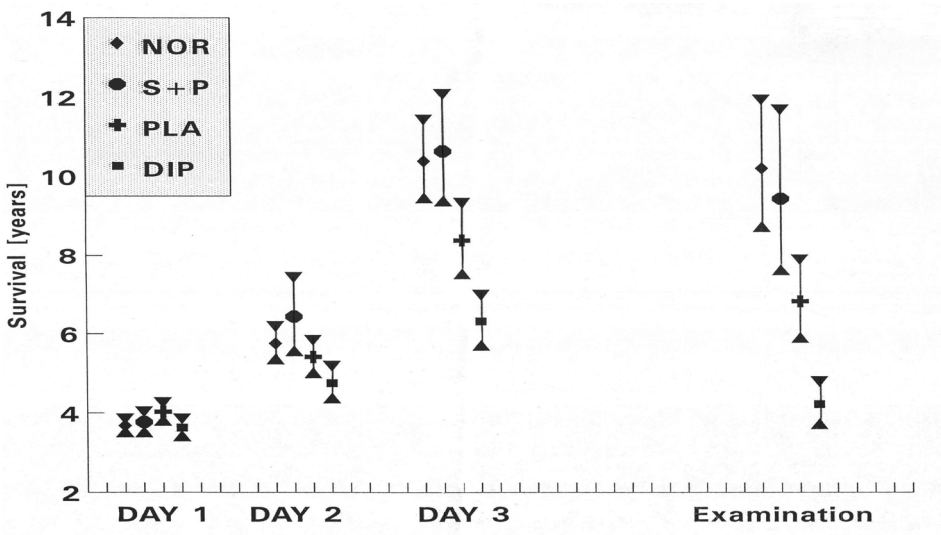

Figure 3. Mean (± SE) years of survival on the simulation for patient groups receiving diphenhydramine (DIP), acrivastine + pseudoephedrine (A+P), placebo (PLA) and non-treated normal controls (NOR), during Training and Examination sessions. There was a 2-week period between Day 3 of the Training and the Examination.

DISCUSSION

We previously reported that children, aged 10-12 years, suffering from seasonal allergic rhinitis had deficient retention of learning that was acquired in the didactic simulation after one training day. The fundamental disease effect was shown by comparison of untreated normals to an atopic group treated with placebo. A deficiency in learning was exaggerated in another group who were treated with pediatric doses of diphenhydramine. The present study, undertaken with atopic young adults who were treated with placebo and adult antihistamine doses during training over three days, confirms these earlier findings.

Not all of the procedures used for measuring learning in children were able to demonstrate an effect of allergy for the older subjects. Specifically, questionnaires measuring factual recall and the ability to generalize conceptual knowledge were apparently too simple for the young adults: all had high scores, regardless of treatment or presence of allergy. A second possible explanation for the failure to show differences between normals and the atopic subject groups may have been the mildness of the allergy season during the study. Yet the application of knowledge in computer-assisted didactic simulation trials readily discriminated the effects of

allergy and diphenhydramine in both studies. Together these results augur well for using the test to measure other drugs' effects on learning in groups varying in age from primary school children to college students.

Mean performance during Training was significantly worse for subjects treated with diphenhydramine compared to normals and subjects treated with acrivastine + pseudoephedrine. The difference between the diphenhydramine group's scores and those of the placebo group was not statistically significant ($p=0.067$). Similar significant differences between the diphenhydramine groups performance and both the normal and A+P groups' performance persisted at Examination; i.e after all atopic groups had been maintained on A+P for two weeks.

The placebo group's performance during Training and Examination did not differ significantly from the normal group's, though on the latter occasion the mean difference was lager than the former ($p=0.073$). Failure to find a consistent difference between normals and allergy patents receiving placebo in this study seems attributable to the weather. Subjects entering Training with high symptom scores often became much less symptomatic with the occurrence of rain and subsequent decline of the airborne pollen concentration. The performance of the A+P group was very similar to that of the normal group. A+P had no adverse effect on learning acquisition or retention and reversed the tendency to perform poorly after treatment with placebo. It is of interest to note that the diphenhydramine group's performance at Examination was not better than at the beginning of Training. In other words, the final test scores revealed that atopic students who were trained under diphenhydramine medication failed to retain whatever they had been able to learn at the time (Figure 3).

The standard memory test showed no differential treatment effect. The failure to measure an effect of diphenhydramine on verbal learning and recall was hardly surprising since none has apparently been reported before. In fact our review revealed only two studies wherein any sedating antihistamine's effects on memory were assessed. Tripolidine 5 mg q.d. increased errors in a digit recall test on the first but not the second day of administration.[10] However chlorpheniramine given to children according to a pediatric dosing regimen had no effect on reading comprehension and memory, in spite of subjective drowsiness, when given for three days[11]. The standard memory test may be too crude a measure of learning to detect the differences noted in this trial.

Didactic simulation confronts the subject with two different learning problems[12]. The first is to understand and memorize all the available options in working towards the goal of survival in the simulation. Subjects in all groups succeeded in memorizing their options as indicated by the results of the Factual Recall questionnaire: No significant difference existed in their abilities to recall specific information regarding the simulation during Examination.

However, knowledge of the rules and parameters alone is insufficient for acquiring the best strategy to operate the simulation. The second problem addresses this more complex issue: Learning can only take place if a subject repeatedly

engages in the process of making decisions, analyzing them and incorporating the results in the next set of decisions aimed at optimizing performance. The subject is never told how or what to learn, but has to 'discover' it by reasoning. This process is fundamental to learning and depends on memory but is not equivalent to it. Related measures of cognitive functioning correlate significantly with those of 'intelligence'[13], 'self-confidence and motivation'[14] and 'anxiety'[15], whereas simple memory test performance do not. Diphenhydramine in the present study apparently interfered with the learning process. How the drug did so is unknown. Whatever the cause, it seems clear that diphenhydramine did not prevent the acquisition of information but rather affected the way it was used. Acrivastine + pseudoephedrine, on their other hand, caused no such impairment. Atopic subjects with allergies treated with acrivastine + pseudoephedrine learned as well as normal subjects.
In summary, allergies interfere with the student's ability to learn. A sedating antihistamine like diphenhydramine causes the learning deficiency to increase while A+P returns learning ability to normal. It would seem that didactic simulation or similarly complex learning paradigms are the preferred methods for showing drug effects in students engaged in educational activities.

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Chapter 9

Effects of Loratidine, Cetirizine and Placebo on learning ability in children suffering from Seasonal Allergic Rhinitis compared to non-treated healthy controls[9]

SUMMARY

The objectives of this study were: (1) to confirm that learning ability is impaired in pediatric patients with seasonal allergic rhinitis (SAR) relative to untreated normal children, and (2) to compare differences in learning ability between groups of patients suffering from SAR and treated with loratadine 10 mg, cetirizine 10 mg and placebo, q.a.m. The study followed an observer-blind, matched parallel-group design with a design-external, untreated, normal control group. A total of 93 atopic children, equally divided between treatment groups, and 30 normal controls, participated in the study. The children were between 10 and 14 years of age. Group matching was with respect to age, intelligence and gender ratio. They continued on medication, as needed, for the subsequent two weeks before returning to participate in a 1-hour Examination Session. Normal children participated in both sessions in a similar manner but without treatments. Learning occurred in the didactic computer simulation 'Hunger in North Africa©'. During Training, subjects performed the simulation during 6 consecutive 45-minute practice/test cycles. Learning acquisition was measured by the increase in simulation performance proficiency over cycles. In addition, separate tests for measuring attention and verbal memory were given between the 3rd and 4th simulation cycles. Examination consisted of a final test for applying learned strategies to control the simulation and of separate written tests for factual and conceptual learning. Atopic children began treatment with their first doses of loratadine 10 mg, cetirizine 10 mg or placebo on the morning after the emergence of SAR symptoms above a severity criterion. They received the second doses the following day as a prelude to participation in a 6-hour Training Session.

The results showed a significant difference between the normal groups simulation performance and that of all the atopic groups combined during Training. Similarly, the normal group's performance in the attention test was significantly better than that of all of the atopic groups combined. However, there were no significant differences between the performances of the three atopic groups on any test. At examination, the normal groups' simulation performance was worse, and those of the three atopic groups, uniformly better, than at the end

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of Training. As a consequence, the groups' final simulation performances did not differ significantly. Though the atopic groups factual and conceptual learning scores were somewhat better than the normal group, the differences were also not significant in either case. The study failed to confirm that learning ability is necessarily impaired in pediatric patients suffering from SAR. It was clear that the simulation performances of all three atopic groups treated respectively with loratadine, cetirizine and placebo were similarly impaired. relative to the normal controls', during Training. Yet all three went on to demonstrate during Examination that learning had nonetheless occurred to the same extent as in the controls. In conclusion, it can still be said that SAR impairs scholastic performance while symptoms are present; and, that whatever the fundamental mental deficit might be, it is neither exacerbated nor ameliorated by either antihistamine. But under the rigorous training procedures applied in this study, it would appear that learning can occur as well in pediatric SAR patients as in healthy children.

INTRODUCTION

We have previously demonstrated that atopic children and young adults, suffering from symptoms of seasonal allergic rhinitis (SAR), are less capable of learning the procedures involved in controlling a didactic computer simulation than age-, gender- and intelligence-matched normal controls. In the first study (Vuurman et al 1993), three groups of symptomatic atopic children (10-12 yrs) were respectively treated with loratadine 10 mg q.a.m., diphenhydramine 25 mg b.i.d. and placebo on the day they received instruction and training to perform the simulation. An untreated normal group were similarly trained. All returned two weeks later for an examination measuring the knowledge acquired earlier. Examination results showed large effect of the allergic reaction on prior learning; i.e., both the placebo and diphenhydramine groups learned significantly less than the normal controls. The loratadine group's average learning scores were superior to the placebo group's and inferior to normal controls', but not significantly in either case. Results from the second study (Vuurman et al, 1996) partially confirmed those from the first, despite differences in the subjects' ages and the amount of training they received prior to the examination.

There were again four groups but now comprised of young adults (16-25 yrs). Three atopic groups, suffering from SAR, were respectively treated with placebo, diphenhydramine and the combination of acrivastine 8 mg + pseudoephedrine 60 mg, all q.i.d.. Treatment continued as these groups, and the normal controls, undertook 4-hour training sessions on each of three consecutive days. They then continued to take these medications until the evening before the examination day, two weeks later. Simulation performance was measured once in each the training session for showing the occurrence of learning acquisition over days and once during the examination for showing retention. All atopic subjects combined had

significantly lower acquisition scores than the normals. The diphenhydramine group had significantly lower acquisition and retention scores than the normals. The placebo group's scores fell between these groups but the differences only approached significance (e.g. placebo-normal, p=.07). The group receiving the combination preparation performed significantly better than the diphenhydramine group though not the placebo group.

The results of both studies clearly indicated that learning ability in children and young adults is adversely affected by SAR and further, that their use of diphenhydramine, a sedating antihistamine, exacerbates that disability. These results reinforce the common belief that older, sedating antihistamines are contra-indicated for children or adolescents who must pursue educational goals while suffering from SAR. In these cases, modern antihistamines that much more slowly penetrate the blood-brain barrier are obviously drugs of choice.

The question remains whether there are any differences between the newer antihistamines' effects on leaning ability; and also, whether any one of them reduces the learning deficit associated with SAR. Loratadine and cetirizine are similarly efficacious for controlling symptoms of SAR. Yet clinical trials have generally shown that adult allergy patients more often report feelings of drowsiness and lack of concentration while taking cetirizine than loratadine. Only one psychometric study has compared cetirizine and loratadine effects on feelings of alertness and objectively measured performance (Ramaekers et al 1992). Yet the participants in that trial were healthy adult volunteers and their performance was measured in an task totally unlike anything undertaken by children (i.e. prolonged and monotonous automobile driving). Although cetirizine but not loratadine significantly affected both feelings of alertness and performance in a manner indicating the occurrence of sedation, these results can not be generalized for indicating a comparable difference in the drugs' effects in children.

The objectives of the present study were to compare the effects of cetirizine, loratadine and placebo on learning acquisition during training and retention upon later examination between matched, parallel groups of children suffering from SAR; and, to similarly compare those groups' performances, separately and combined, with that of another matched but untreated group of healthy children. This study was similar to the conducted earlier by Vuurman et al (1993) but differed from it in several important respects. Children across a wider age range (i.e. 10-14 yrs) were included to obtain larger groups. Antihistamine and placebo treatments began on the day prior to training for increasing possible differences among their effects. The earlier procedure allowed children to acquire learning at self determined rates by simply interacting with the computer simulation. No attempt was made to measure how rapidly each child proceeded or to compare rates of learning acquisition between groups. This time the procedure was the same except that self paced training was interrupted at regular intervals for measuring learning acquired until those times in separate simulation performance

tests. Though it was recognized that interpolated testing might affect the children's motivation to pursue training exercises more diligently than before, the benefit of additional information was thought to outweigh the risk of disparate and possibly contradictory results. Finally, two tests were applied midway through the training session for respectively assessing treatment effects on the children's attention and verbal memory. These were added to the original procedure in the hope of explaining possible differences in the groups' simulation learning performance as attributable to more fundamental deficits involving attention or memory, or both.

METHODS

*S*ubjects

Atopic and normal children were recruited by newspaper solicitations to their parents that specified the study objectives, inclusion criteria and other requirements in a general manner. This occurred during the winter months when it was assumed that the atopic children would be asymptomatic. Responding families were sent 'Information for Volunteers and their Parents', containing the telephone number of the person to contact if they wished to continue. Those who did received a medical history questionnaire to be completed by the child's parents before an interview with the study's Medical Supervisor. That interview was attended by the child and at least one parent. The child's medical history was reviewed and he/she was examined to determine if he/she satisfied the inclusion and exclusion criteria.

Inclusion criteria

- Gender: male or female
- Age: 10-14 years of age
- Weight: within t 15% of normal for the child's height and frame with a minimum requirement of 30 kg
- Binocular visual acuity : within .65 diopters of normal, corrected or uncorrected
- School attendance: 2! 16 hrs/wk of formal education within the Dutch educational system
- Allergy History: diagnosed seasonal allergic rhinitis requiring medical intervention during each of the preceding two pollen seasons (atopic children) or; no previous history of allergic rhinitis (normal children)
- Consent: written and witnessed informed consent by both the child and at least one parent.

Exclusion criteria:

- story of hypersensitivity to antihistamine drugs or multiple drug allergies.
- Overt cardiovascular, pulmonary, respiratory, metabolic, hepatic or renal disorders or a history of severe disorders of these types (An exception was made for mild asthma occurring in conjunction with SAR)
- Any sense organ or neurological disorder.
- Current participation in other drug trials.
- Use of astemizole within 30 days or of any other antihistamine within 48 hours preceding the beginning of trial medication.
- Use of an oral or nasal decongestant within 48 hours preceding the beginning of trial medication.
- Use of systemic corticosteroids.
- Resting systolic and diastolic blood pressures greater than 140 and 90 mm Hg.
- Resting heart rate below 50 or above 90 b.p.m..

The exclusion criteria regarding use of drugs other than study medication remained in force throughout the children's participation in the study. Children enrolled in the study included 93 atopics and 30 normals. Their mean ±SD ages at inclusion were 12.0 (1.4) yrs. Two 9 year old atopic children were included who would become 10 prior to treatment as was one atopic child whose 15th birthday coincided with the date of his enrolment.

Ethics

The study protocol was reviewed and approved by the standing Medical Ethics Committee of Maastricht University. The subjects were treated in full accordance with the Declaration of Helsinki through its latest modification (Hong Kong, 1989).

Design

The study followed an observer-blind 3leg, placebo-controled, matched parallel group design. Treatments administered to the respective atopic groups were as follows.

Loratadine	**10 mg**	**q.a.m. tablets,15 days**
Cetirizine	**10 mg**	**q.a.m. tablets,15 days**
Placebo	**10 mg**	**q.a.m. tablets,l5 days**

Drug treatments were prepared from the commercially available formulations of Claritine R and Zyrtec^{R} , respectively. The placebo tablets were identical in

appearance to the former. Treatments were packed and supplied by the sponsor in individual opaque bottles with unique labels displaying the following information: study number, subject number, administration information, storage instructions, name and telephone number of the Medical Supervisor. The Medical Supervisor was solely aware of the nature of the subjects' treatments throughout data collection and until code breaking. She was not involved in any evaluation procedure and did not communicate her knowledge of the individuals' treatments to investigators who were.

Laboratory and facilities

The clinical assessments were conducted in a learning laboratory at the Institute. This large room contained individual workstations for six subjects and a monitoring station for investigator. The subject's workstation consisted off chair and table upon which was mounted a stand-alone IBM AT/386 computer, keyboard and VGA color monitor. The investigator's workstation contained six computer monitors that separately replicated the imagery appearing on each of the subject's display. With these, the investigator was able to supervise the subject's progress and provide them with assistance, if needed. During pauses in the assessment routine, subjects were accommodated in another large room containing a dining area and light recreational facilities (i.e. color television with VCR, video tapes, books etc.).

Preliminary Activities

About 6 weeks prior to the expected beginning of the pollen season, all atopic and normal subjects were brought to the Institute in groups of 6 for familiarization with study personnel and procedures. The subjects' prior knowledge of computer keyboard operation was checked and in all cases found sufficient for allowing them to continue without instruction concerning its use. Shortly before the expected beginning of the allergy season (2-4 weeks), subjects returned to the Institute with their parents for assessing their knowledge related to the learning test using a standard questionnaire. Their intelligence quotients (IQs) were individually determined using the standard Dutch non-verbal IQ test (Snijders and Snijders-Oomen, 1988). At the conclusion of this session, parents of atopic children were instructed to telephone the investigators as soon as they began to show symptoms of SAR. Parents were told that the Medical Supervisor would visit the children during the evening of the same day to rate their symptoms and dispense study medication for use beginning the following morning.

Group matching for IQ and age followed an iterative procedure. When it was confirmed that an atopic subject was about to enter the study, his/her IQ score and age was categorized as being in one of the following 9 strata:

STRATUM	IQ	AGE yrs
I	< 115	< 11.5
II	< 115	11_1.5-13.0
III	< 115	> 13.0
1V	115-130	<11.5
V	115-130	11.5-13.0
V1	115 - 130	> 13.0
VII	> 130	< 11.5
VIII	> 130	11.5 - 13.0
IX	>130	>13.0

The first three subjects to become symptomatic were assigned randomization codes and medication by the Medical Supervisor for the placebo, cetirizine and loratadine groups (PLA, CET, LOR), respectively. Further assignments were made according to an algorithm that continually minimized the differences between the strata of subjects assigned to these three groups. Subjects comprising the normal group (NOR) were selected and called up from a pool of qualified volunteers so that their strata as closely as possible matched the atopic groups' while their numbers increased over the course of the study. Normal subjects who had undergone all preliminary activities were placed on stand-by and individually called to return for further activities on 1-day notice whenever it was known that only one atopic subject was about to do the same. This procedure was enacted to ensure that no atopic child would not have to undergo training and testing alone.

Treatment Phase

Day O: Onset of STIR.

The atopic subjects' parents telephoned the medical Supervisor for requesting her visit on the days their children showed the emergence of SAR symptoms. Upon arrival at the subject's home, the Medical Supervisor rated the presence and severity of his/her symptoms including, rhinorhea, sneezing, nasal and/or palato-pharyngeal pruritus, conjunctival pruritus, nasal congestion and mouth breathing. Each symptom was weighted for severity from 0-5 as follows: 0) absent; 1) very mild -hardly present; 2) mild-present but not distressing; 3)moderate-present but not interfering with daily activities; 4) severe-distressing and interfering; and 5)

very severe-prohibiting daily activities. A subject's weighted symptoms score had to be >_ 9 for his/her progression into the treatment phase. If not, the subject's parents were told to continue observing his/her condition and report any worsening, whereupon the evaluation would be repeated. The subjects assigned code and medication were then reserved for a week for awaiting developments. If the parents did not resume contact within that period, the code and medication were reassigned to another subject. Parents of a subject who qualified were given the assigned medication with the instruction to administer the first dose to the child between 08:00 and 09:00 h the following morning; i.e. on Day 1. They were told not to administer the second dose on Day 2 but rather give the bottle containing medication to the investigator who would arrive in the morning for transporting their child to the Institute.

Day 2: Training Session.
Atopic and normal subjects were transported to the Institute for Training, scheduled from 08.45 until 15.45h. Atopic children's symptoms were rated as before and each subject was given the second dose of his/her particular medication at 09:00h. Thereupon all children undertook the same series of activities as follows.

Time (h r)	Activity
09:00 - 09:15	Lecture on the simulation
09:15 - 09:45	Practice
09:45 - 10:00	1st simulation test 10:00 - 10:30 Practice
10:30 - 10:45	2nd simulation test 10:45 - 11:15 Practice
11:15 - 11:30	3rd simulation test 11:30-11:50 Memory test - immediate recall
11:50 - 12:15	Attention test
12:15 - 13:00	Lunch
13:00 – 13:15	Memory test delayed
13:15 – 13:45	Practice
13:45 - 14:00	4^{th} Simulation test
14:00 – 14:30	Practice
14:30 – 14:45	5^{th} Simulation test
14:45 - 15:15	Practice
15:15 - 15:30	6th simulation test

At the conclusion of these activities, atopic children's symptoms were again rated and all were taken to their homes. The children's oral medication was returned to the parents who were also provided with a topical antihistamine nasal spray (levocabastine 0.5 mg/ml, Levocab', Taxandria Pharmaceuticals). The instructions were to treat their children with one tablet of oral medication each morning as needed to control allergy symptoms; and, to administer the topical

antihistamine, as rescue medication, if the tablet failed to provide relief. Parents were to follow this procedure for the following 13 days (i.e. Days 3-15) and suspend it on Day 16 when the children were scheduled to return to the Institute.

Days 3-15: Waiting Period.
All subjects continued their normal living activities. Atopic children took their normal and rescue medication 'as needed'. If still failing to obtain relief from SAR symptoms they were allowed to contact the Medical Supervisor for authorization to change medication. As it happened, none did.

Day 16: Final Examination.
Subjects were met at their homes and transported to the Institute for the Examination between 16.00 and 17.00 h. Upon its completion they returned unused medication and were dismissed from the study by the Medical Supervisor.

Assessments

Didactic Simulation.
Subjects' learning acquisition during Training and retention at Examination were measured using the computer simulation 'Hunger in North Africa' (Leutner, 1989). It is one of the most widely known examples of an Intelligent Tutorial System (ITS). Such systems are used in primary and secondary schools as an adjunct to traditional teaching methods. An ITS possesses the advantage of demonstrating complex dynamic interactions among factors that are simply identified by name in textbooks. Students generally view an ITS as a complicated computer game. They are challenged to learn its operating principles so as to attain complete control over the simulation. This level of proficiency usually requires practice extending over several days, during which time, students are expected to learn concepts the ITS was designed to impart. 'Hunger in North Africa' was developed as an adjunct for teaching geography and cultural anthropology in German secondary schools. It casts the student in the role of a farmer attempting to subsist and if possible, prosper in an arid region. To begin, he/she is symbolically provided with a family comprised of productive and dependent members, ten plots of undeveloped land on sloping terrain, livestock and a small amount of money. The simulation is played by the year. At the beginning of each, the student is required to make up to 19 decisions and corresponding keyboard entries about cultivating different crops on each plot of land, developing that land (e.g. terracing or digging wells), managing the livestock, conserving or liquidating assets, mechanization, controlling family growth, etc. Each decision has both certain costs and potential benefits that continually and logically change as the simulation progresses. That progression occurs after each year's decisions are made and the student advances the

program. At these times an unpredictable factor (i.e. the weather) is added which has benign effects sometime but adverse ones usually. The extent to which the weather affects the student's status at the end of the year depends upon his/her prior decisions. Ignoring the interaction between a host of economic, ecological and meteorological factors, practically ensures that the student will survive no longer than 3-4 years. On the other hand, learning and implementing a strategy based on knowledge of these relationships insures indefinite survival, and even relative prosperity.

Subjects in the present study were introduced to the simulation with a lecture and demonstration of the opening procedure. They proceeded individually to practice the simulation for 30 minutes. During this period the program provided two kinds of assistance: online feedback that questioned each response indicating a dubious decision and access to tabular information concerning the known cost and potential benefit of every decision. Thereafter, the subjects' acquisition of learning was tested by restarting the program without its assisting functions and allowing them to proceed for as long as possible within a 15-minute limit. The $\log_e$ number of survival years was the parameter measured. This procedure was repeated through six practice/test cycles with a break between the 3`d and 4`^{h}. When subjects returned on Day 16, they simply repeated the simulation test, this time without prior practice, and the $\log_e$ number of years each survived was taken as his/her Knowledge Application Score (A). Two multiple-choice questionnaires were also given. The first measured the subjects recall of information in the table listing costs and benefits of decisions. The number of correct answers was taken as the subject's Factual Knowledge Score (F). The second was identical to the questionnaire used before training for assessing the subjects' prior knowledge of simulation concepts. The change in the number of questions correctly answered from the 1st to the 2nd repetition was taken as the subject's Conceptual Knowledge Score (C). Each subjects examination scores, A, F and C, were combined to yield his/her Composite Learning Score (L) according to the following equation:

$$L = 10 * \left(\frac{Ai - Ma}{SDa} + \frac{Fi - Mf}{SDf} + \frac{Ci - Mc}{SDc} \right)$$

where, Ai, Fi, Ci = the particular subject's (1) raw scores for parameter the respective Ma, Mf, Mc = the entire group's mean raw scores for the respective parameters SDa, SDf, SDc = the entire group's standard deviation of raw scores for the respective parameters.

Verbal Memory Test.

This is the standardized Dutch version (Brand and Jolles, 1985) of a well known method for assessing the amnestic effects of drugs. It was administered to

subjects individually and in isolation from the others during the break between the 3rd and 4th simulation practice/test cycles on Day 2. It began with the sequential presentation of 15 monosyllabic common nouns. Each word was shown on a computer display for 2 seconds while the subject read it aloud. When the series ended the subject verbally recalled as many words as possible and the number correct was recorded. The same list was then repeated in this manner four more times and the numbers correctly recalled were recorded after each repetition. The maximum number of correct responses on any trial (usually the last) was recorded as the subject's Immediate Recall Score. After a delay of 90 minutes, the subject named as many words as he/she could still recall, which was recorded as his/her Delayed Recall Score.

Attention Test.
This paper and pencil test was developed and validated by De Jong (1991) as an instrument for measuring achievement-related attention in school aged children. It was also administered during the break on Day2. The test transpired in two blocks lasting 12 and 8 minutes respectively. A separate sheet of paper was used for each. The first sheet displayed 15, 9x6 matrices of asterisks (*), each one led by a different 2-digit number in the top left corner. Six alternating minus (-) and plus (+) signs were randomly interspersed among the *'s and also 8 blank spaces. Subjects began the test by adding each * in sequence from left to right, top to bottom, to the number given at the corner. Upon coming to the first minus-sign they sequentially subtracted the following *'s until arriving at the first plus-sign. Then they resumed adding *'s until the next minus-sign whereupon the process was again reversed. They continued in this manner until coming to the end where they wrote the final tally. The blank spaces were merely to prevent subjects from adding or subtracting *'s, row-wise.

After completing all matrices on the first sheet, subjects proceeded to the second displaying 10 new 9x4 matrices. However, this time they were told that the alternating + and - signs had exactly the opposite meaning. That is, they were to subtract *'s after plus-signs and add them after minus signs. Otherwise their task was as before. Tallies from the first three matrices on the first sheet and the first two matrices on the second were not taken into account. The remaining 12+8=20 tallies were scored for accuracy and the sum of correct answers was taken as the Attention Score.

Statistical Analysis

Parameters recorded during Examination - Learning Application, Factual Learning, Conceptual Learning and the Composite Learning Scores - were considered as primary outcome variables. Survival scores ($\log_e$ years) in each of six consecutive as well as Immediate Recall, Delayed Recall and Attention Scores recorded during Training were the secondary outcome variables.

Each variable was analyzed in the same manner. A 4-way analysis of variance (ANOVA, independent-groups/ fixed effects model) was applied for testing the overall significance of mean differences between the three atopic groups and the normal control group. Detection of a significant ($p<.05$) overall difference was followed by exhaustive mean-pair comparisons using the Duncan Multiple Range Test with a $p=.05$ criterion level. Whether or not there were any significant differences between groups, a 2-way ANOVA was applied for testing the mean difference between the normal control group's scores and those from all atopic groups combined. The final ANOVA was for assessing the effect of SAR, irrespective of treatments.

In addition, the groups' ages and IQ-scores were compared in 4-way ANOVAs for confirming the adequacy of the matching procedure. A 2x4, x^2 contingency test was applied to the frequencies of male and female subjects in the four groups for similarly confirming that they were matched for gender.

RESULTS

Completers

All of the 93 atopic children who entered the treatment phase completed the study. None spontaneously complained of any adverse event that was not a common SAR symptom. Thirty normal children also completed the study. All subjects' demographic data are given in Table 1. Also summarized are the results of F and x^2 tests for determining whether the groups differed significantly with respect to the matching variables. As shown, there were no significant differences among groups' ages at enrolment, IQ scores or their respective male/female ratios.

GROUP	NOR	PLA	LOR	CET	$F_{3,119}$ =
N	30	31	31	31	
AGE (yrs)	12.1 ± 1.4	11.9 ± 1.4	12.0 ±1.4	12.1 ±1.4	0.22; ns
Range	(10.7-14.1)	(10.3-14.7)	(9.7-14.1)	(9.9-15.0)	
IQ	110 ± 12	107 ± 12	109 ± 11	109 ± 12	0.54; ns
Range	(79-127)	(83-125)	(85 -127)	(80-131)	
M/F	19/11	19/12	16/15	21/10	1.81; ns

Table 1. Mean ±SD (range) for subjects' ages and 10-scores, and gender ratios by groups; also, the results of F tests for differences between groups

Symptom Severity

Ratings of the atopic groups' symptoms on Days 0 and 2 are summarized in Table 2 along with the results of F-tests applied for assessing group differences at every point in time. As shown, mean symptom severity dropped for every group from the evening of Day 0 to the morning of Day 2, and further, to the afternoon measurement on the same day. Yet at none of these times did symptom severities differ significantly among groups.

GROUP	PLA	LOR	CET	$F_{3,19}$ =
Day 0 pm	14,8 ± 2,9	14.8 t 3.0	13.9 ± 3.4	0.95; ns
Range	(9-20)	(10-23)	(9-23)	
Day 2 am	10.6±4.7	10.6±4.7	8.9±6.0	1.15;ns
Range	(0-19)	(2-22)	(0-21)	
Day 2 pm	6.7±4.4	5.7±4.0	5.5±4.8	0.63;ns
Range	(0-17)	(0-17)	(0-17)	

Table 2. *Mean ± SD (range) for symptom severity ratings, by group; also, the results of F tests at each point in time*

Simulation Performance During Training.

Figure 1 shows geometric mean (± SEM) years of simulation survival over successive training sessions by group. The two continuous functions are for the normal group and all atopic groups, whereas the three atopic groups performances remained more or less stable at about the same low level of proficiency. The four groups' mean levels of performance did not differ significantly in any of the first four sessions ($F_{3,119} < 1.13$; $p > .34$); and, the difference among the three atopic groups' performances did not differ significantly in any session as measured in the Duncan Test. However, the overall difference in the groups' geometric mean survival was significant during sessions 5 and 6 ($F_{3,119} = 4{,}37, 3.85$; p=.006,.011). This was entirely attributable to the ascendancy of NOR over the three atopic groups. The former's performance was significantly (< .05) better than each of the latter's on both occasions. The significance of the mean difference between the normal and all of the atopic children combined was highly significant in both sessions($F_{1,121}$=12.92,11.71; p=.0005, .0008).

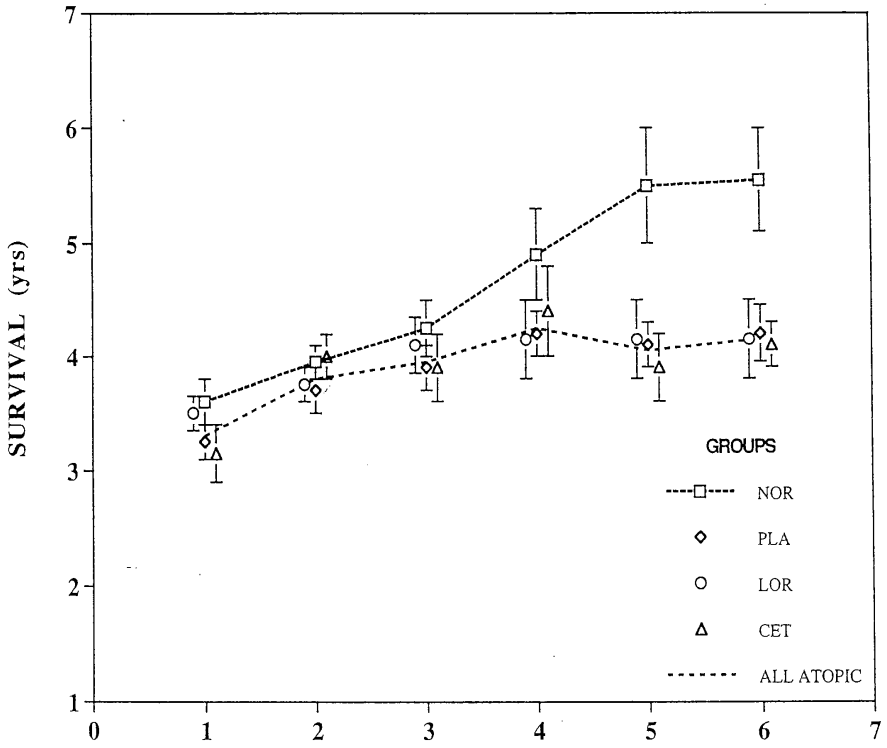

Figure 1. *Geometric mean* (f *SEM) survival values for each group at every time of testing during Training. Curves show geometric mean survival as a function of repeated training sessions for normal subjects and all atopic subjects combined.*

Memory Performance

Figure 2 shows the groups' mean (±SE) maximum Immediate (I) and Delayed (D) Recall Scores. Group differences in the first phase of the test were significant ($F_{3,119}$ = 2.84; p = .041). Although the three atopic groups' mean Immediate Recall were all lower than the normal controls', only the difference between LOR and NOR was significant ($p<.05$) in the Duncan Test. The 2-way comparison of Immediate Recall Scores between the normal children and all atopic children combined also yielded a significant result ($F_{1,121}$ = 5.88; p = .017). Mean Delayed Recall Scores followed a similar pattern, with that of the normal group's being higher than the others'. However, these differences were not significant in either the 4- or 2-way comparisons ($F_{3,119}$ = 0.43 & $F_{1,121}$ = 1.29).

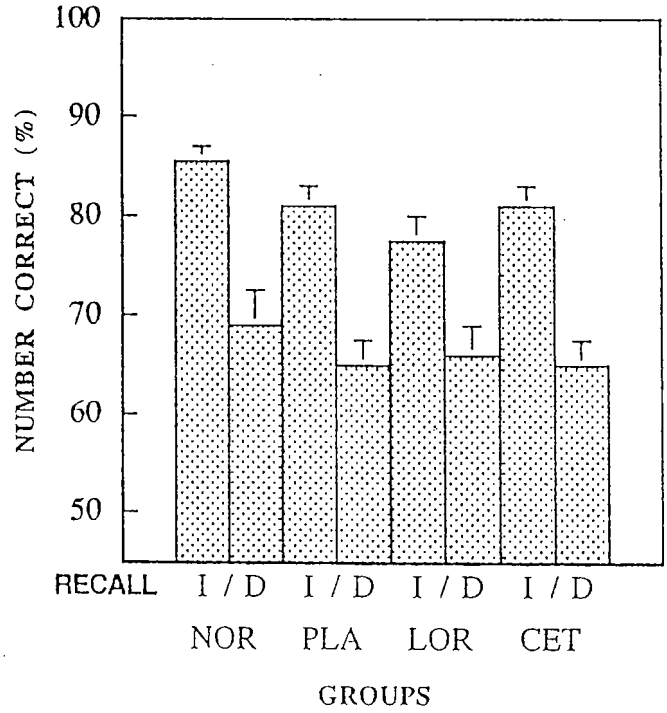

Figure 2 *. Mean (+ SEM) Immediate (1) and Delayed (D) Recall Scores as percentages* of full *scale for each group.*

Attention Performance

Figure 3 shows the groups' mean (+ SE) Attention Scores. Differences among groups were highly significant in both the 4- and 2-way comparisons ($F_{3,119}$ = 5.19; p _ .002 & $F_{1,121}$, = 15.18; p = .002). The normal controls scored significantly (p< .05) higher than every atopic group but the differences among the latter groups were not significant.

Examination

Although most of the atopic children were still suffering from SAR symptoms at the time of their arrival for the final examination, these were generally very mild. Only 11 (12 %) had symptom severity ratings as high or higher than the criterion for beginning treatment and 19 (20%) were asymptomatic. Mean severity ratings of 3.9, 4.8 and 3.0 for PLA, LOR and CET did not differ significantly ($F_{3,119}$ = 1.20).The groups' geometric or arithmetic mean (± SEM) scores for Knowledge Application (A), Factual Knowledge (F), change in Conceptual Knowledge (AC) and Composite Learning Scores (L) are given in Table 4. Also given are the results of statistical tests for differences among and between group mean values

for the 4- and 2-way comparisons. As indicated, none of those differences was significant.

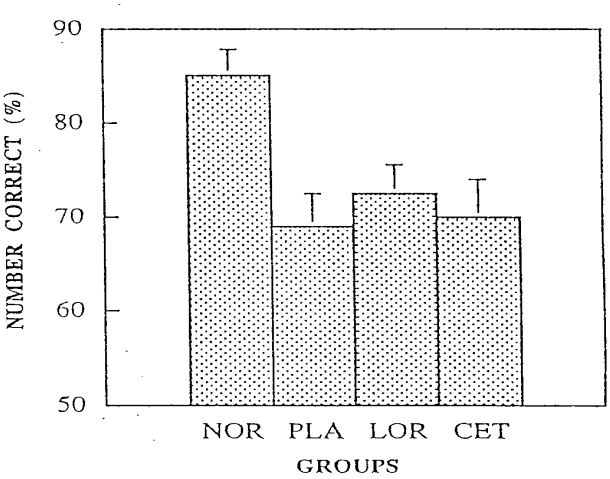

***Figure 3**.Mean (+ SEM) Attention Scores as percentages of full scale for each group*

SCORE	GROUPS				ANOVA			
	NOR	PLA	LOR	CET	4-way		2-way	
					$F_{3,119}$	P	$F_{1,119}$	P
A(yrs) M	4.77	4.61	4.90	4.56	0.22	(ns)	0.05	(ns)
+ SD	1.60	1.70	3.26	2.34				
- SD	1.20	1.24	1.96	1.55				
F M	22.7	21.2	21.6	21.1	0.82	(ns)	2.32	(ns)
t SD	3.9	4.4	4.2	5.3				
0 C M	7.6	6.9	6.0	6.5	0.93	(ns)	1.98	(ns)
f SD	4.2	4.4	3.5	3.5				
L M	155	149	149	147	0.73	(ns)	2.12	(ns)
t SD	18	22	23	23				

***Table 4**. Geometric mean (± SD) Knowledge Application (A) and arithmetic mean (± SD) Factual Knowledge(F), change in Conceptual Knowledge (A C) and Composite Learning (L) Scores for each group at Examination; also, with the results of ANOVA tests for group differences*

DISCUSSION

The four groups were closely matched with respect to age, non-verbal intelligence and the relative frequencies of both genders. There is no reason for supposing that the normal children were, a priori, any more capable of learning the didactic simulation than the atopic groups, separately or together. The only known difference between the normal and atopic children as they appeared for Training was that latter were suffering from allergic symptoms.

The atopic groups' severities of symptoms did not differ significantly before treatment and all showed about the same reduction in symptom severity when they appeared for Training. Little difference between the groups' symptom ratings was expected at that time since they had only been treated with a single dose of trial medication beforehand. The same lack of a significant differential effect of antihistamines and placebo after the first in a series of repeated doses is a common occurrence in clinical trials (e.g. Falliers et al, 1991).

Moreover, given the variable Dutch weather, it may be assumed that the airborne pollen concentration was particularly high on the days when the children's parents made contact to announce the onset of symptoms but generally lower over the days immediately thereafter. In any case, fluctuations in the weather did not abolish the childrens' symptoms: only 3 (3%) were found to be asymptomatic upon arrival for Training. Moreover the effects of SAR, if not its treatments, were readily apparent in every test applied during Training. The atopic children began simulation training showing as little proficiency as the normal controls. The formers' performance remained relatively poor over the six interpolated tests of simulation performance, whereas the controls' improved substantially after the third. However, all atopic groups' showed about the same deficiency in comparison to the controls; i.e. there was no evidence of any differential treatment effect on learning ability.

The short tests used for assessing memory and attention likewise discriminated between the normal controls and every atopic group but not among the latter according to their treatments. The atopic children scored slightly but significantly worse in the first part of the memory test. Those treated with loratadine were the poorest of all. However, all differences between the groups' scores in the second part of that test were not significant. Such findings are very unusual. Deficient immediate recall usually precedes an even greater deficiency in delayed recall. At least this is generally the case when both deficiencies are attributable to the amnesic properties of drugs (e.g. Vermeeren et al 1995). That the same did not occur in the present study makes it questionable whether the atopic children were suffering from any sort of memory impairment at all. Their relatively poor performance during the rapidly paced immediate recall phase could have simply reflected inattention and distraction due to SAR symptoms. These factors would be less likely to affect their performance during the delayed recall phase because then the subjects were under no time pressure to complete

this part of the test. Unless one is willing to entertain the alternative explanation that the normal controls ‘forgot’ the word list faster than the atopic children, this seems the most plausible explanation.

More striking evidence for adverse SAR effects on the children's mental functioning was obtained in the attention test. All three atopic groups completed it while performing at levels that were only about 80% of the normal controls'. Each of the mean differences was significant and the overall difference between atopic and normal children was very much so (p=.0002). Apparently, SAR reduces children's ability to sustain attention and continually update information in working memory. This could be a serious handicap in many academic pursuits (e.g. performing serial mathematical operations). The only other explanation is that the normal controls were innately better at this test than their atopic counterparts.

So far, the results seem logical and consistent. Most atopic children were still suffering from peripheral SAR symptoms at the time of Training even though these were not as severe as recorded two days earlier. Directly or indirectly, SAR strongly reduced the children's ability to sustain attention in the rapidly paced and mentally demanding counting test. That deficit explains why they performed more poorly than the controls in the first phase of the memory test. They may have simply been unable or unwilling to demonstrate that they had memorized the word list. That they did in fact memorize the words, as well as the controls, was shown later by the groups' similar abilities to spontaneously recall them. Something similar might have occurred in repeated attempts to control the simulation. Although the atopic children did not demonstrate the acquisition of learning over the day to the same extent as the controls, this does not mean that they actually learned less. Results obtained during Examination suggest that they learned as much about the simulation as the controls but were somehow unable to show it during Training.

The atopic children's simulation performance improved substantially from the end of Training to Examination, whereas the opposite occurred for the normal controls, resulting in no significant differences between the groups' final A-Scores. These results contradict those obtained by Vuurman et al (1993). Simulation performance during Training was not measured in the earlier study, but during Examination, the normal control, group's performance was clearly superior. Two major methodological differences existed between these studies which may account for the disparity in their results. Many of the children in the present study were older and all were more rigorously trained than their predecessors. Moreover, the children in the present study knew as well as the investigators how much or how little their simulation performance improved over repeated tests during Training. Though the investigators did not reveal any child's test results to any other, it would be quite natural if the children discussed the results among themselves. The knowledge of one's own scores, and possibly those of others, might have affected normal and atopic children's motivation

differently when they returned to perform the simulation for a final time. The normals, knowing they had done relatively well, may have been less motivated to achieve still higher scores than the atopic children who knew they had done poorly. This difference in motivation may reflect the way atopic children normally compensate for their temporary disability while suffering from allergic reactions in school.

Other results from Examination were reminiscent of those acquired earlier. Specifically, the normal controls' mean Factual and Conceptual Knowledge Scores, and therefore their Composite Learning Scores, were higher than any atopic group's. Although the differences were not significant, they are in line with the earlier conclusion that SAR causes a learning deficit with consequences that can be enduring.

No differences between the effects of loratadine and cetirizine, nor of either in comparison with placebo, were found throughout the study. Both drugs' effects on the learning ability of children suffering from SAR may in fact be comparable to placebo's. However it seems equally likely that some relatively minor differences exist, but due to the study's design or insensitivity of the tests, we were unable to measure them.

CONCLUSIONS

- Children's ability to sustain attention is adversely affected by SAR.
- This disability may or may not impair learning depending upon the extent to which the children are forced to follow the assigned program of instruction.
- When forced as by the conditions of this study, learning can occur normally even though the children's performance does nor reflect it at the time.
- If as in this study, children become aware of but are not penalized for performance deficiencies while suffering from SAR, they can compensate in later tests of performance proficiency.
- Neither loratadine nor cetirizine affected the process of learning acquisition or retention under the conditions of this study.

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Chapter 10

Pharmacopsychology: Quo Vadis ?

The pharmacopsychological studies described in this thesis were designed and carried out to evaluate the risks of drugs on two important activities in daily life: Car driving and Learning. A total of 102 volunteers took part in the driving and lab-studies, together covering over 45000 km in the over-the-road driving tests. In the learning laboratory 272 young patients suffering from hayfever and 115 controls participated in the computer-aided learning paradigm. While doing so both patients and healthy volunteers were treated with a variety of investigational drugs, alcohol, placebo or a combination of these compounds. All studies were designed as experimental investigations.

Besides the investigational anxiolytic drug studied in Chapter 5 (Saripidem) all other drugs studied shared the property that their use is very common and they are readily available as an OTC product in most countries. The antihistamines (except desloratadine) studied in this thesis are available without subscription in both Europe and North America, also for paediatric use. Mefloquine (Lariam®) is still the best antimalarial agent in some countries with drug resistance to alternative treatments and is used as a prophylactic by travellers to many Asian and African countries(Olliaro, 2003).

Any behavioural toxicity resulting from the drugs studied would therefore have both serious personal and socio-economic consequences(Lurie 1990, Hanrahan 2003, Rodriquez 2003). In the case of driving impairment these would directly result in injuries or even death of subjects involved. The consequences of behavioural toxicity on learning are less clear-cut as they are likely to emerge only later in the individuals' career, possibly as a lower level of academic achievement or diminished job opportunities(Breslin 1993)

Although at the biological level the mechanism of drug action is well documented for most drugs, predicting the consequences of it on behaviour is still far from perfect. The studies presented here have focused mainly on one very well described activity in daily life: driving. The methods used to evaluate the drug effects have shown to reliable and valid in showing basic impairing effects on vehicle control(O'Hanlon 1995). However, the applicability of the tests in predicting effects under 'real life' circumstances is still limited. Although actual over the road driving is used as a test there are still fundamental differences with normal driving. The possible consequences for the interpretation of behavioural changes deserve further attention. Furthermore, the effects measured and the explanation of the possible mechanism of action has been mainly from a information processing point of view, with psychometric concepts such as 'attention, effort and arousal' playing a key role.

Far less is known about the role of changing the psychological state of drivers with psychoactive drugs. A drug induced change in mood could directly alter driving behaviour, as with changing risk perception (Slovic 1987, Ivancic 2000). Changes in cognitive functioning are also a potential threat to safe driving. Also diminished 'executive control' will lead to impaired route planning and overview of complex traffic situations, again possibly comprising the drivers safety. Finally, the role of laboratory tests in predicting driving impairment deserves more attention, as they might provide a valuable aid to disentangle the complex behaviour of driving into a limited number of basic functions which are sensitive to psychoactive drug intervention.

1 Conclusions from the Driving Studies

1.1 Drugs, driving and performance on control tasks

The driving studies mentioned in this thesis all employed the 'over the road' driving paradigm as the primary method to evaluate drug effects. Complementary to this a variety of cognitive and psychomotor tests was used to evaluate specific skills and functions under drug conditions. The test battery consisted of tests that were selected to measure some aspect of driving separately i.e vigilance, psychomotor tracking, reaction time, memory etc. Results from these tests were expected to support results from the driving tests, pinpointing the function that was specifically affected by the drug under investigation.

Furthermore, in all driving studies a 'control drug' condition was used. This control drug had known impairing effects on the driving test, more specifically on the primary outcome variable SDLP (Standard Deviation of Lateral Position). This control drug was used to ensure the study procedure was sensitive enough to detect relevant results. In all driving studies this impairment by the control drug was found on SDLP but not consistently on the secondary measures of the driving test (speed, headway variability) or on the laboratory tests. The latter is a somewhat disappointing finding although not unique to the driving studies reported here (Galski 1997). However, one would at least expect a high correlation between basic laboratory measures such as tracking and SDLP. With only SDLP as a reproducible and reliable outcome variable, impairment of driving behaviour by drugs can only be partially explained in terms of a behavioural model.

More recent other studies report both low and high correlations between driving skills and various laboratory tests. Myers (2000) failed to predict on-road driving performance from a test battery consisting of tests for the measurement of visual organization, visual screening, divided attention, symbolic sign substitution and reaction time. DeRaedt (2001) claimed a validity of 85% in predicting driving ability in elderly subjects using a test battery consisting of the MMSE, Trail Making test and visual acuity tests. In an earlier review of a large

number of driving related laboratory studies Parrott (1991) points out the lack of uniformity concerning test selection across the research laboratories involved in traffic-safety research and the lack of a sound model upon which tests are selected. Since that study was published the situation has not improved much (Verster 2001).

It can therefore be concluded that there is still little consensus among researchers with respect to the task of modeling driver behaviour. This lack of progress in the field has led some researches to turn to alternative models that give more credit to recent achievements in cognitive psychology and neurobiology (Overskeid 2000, Fuller 2000).

1.2 The relationship between actual driving and laboratory tests

Using a pure performance model to study driving behaviour a one-to-one relationship between laboratory tests and actual driving parameters should be sought after. However, in most cases fundamental differences between the two prevent this from happening. Although laboratory tests are designed to measure driving related skills they transpire under different conditions compared to actual driving. The most important concerns the safety of the subjects while performing the test. During driving they are always subjected to a risk of being involved in a traffic accident. This is true even if the experimental setup has taken measures to minimize this by providing a safety officer in the car, avoiding dense traffic engagement and possible dangerous traffic situations. It therefore calls for some form of risk-perception and awareness, risk acceptance and risk evaluation by the subject, which does not play a role in a laboratory situations.

Most of the driving models based upon general information processing models discussed earlier like the AFM or resource models (Wickens 1981, Sanders 1986), Rothengather 1997, Reed 2002) do not include '*risk*' or other *subjective states of the driver* directly in their performance model. It can however be argued that there is a rationale for including human emotion into a driving performance model. This is given by the notion that car driving is characterized by constantly solving problems that involve thinking, choosing and deciding between different alternatives.

These alternative scenarios are characterized by different outcomes that each have an emotional value attached to it. It is this emotional dimension that makes it possible to choose between alternatives based on cognition (Vaa 2001). Or as Damasio (1994) puts it 'If there is no feeling, there is no possibility for evaluating the outcomes'. The performance on laboratory tests can therefore not be directly equated with corresponding (psychomotor) elements in car driving. A more wholistic model, incorporating environmental and psychological factors is needed to more fully understand this relationship.

1.3 Models of 'risk reduction' and their role in driving behaviour

Parallel to the traditional performance models of driving behaviour several alternative models have been developed since the early 1960's (Rothengather 1988). They recognize other factors as being important in the understanding of impaired driving ability and deserve further attention. The most prominent of these models are Taylors (1964) galvanic skin responses model, Näätänens Zero Risk model (1974) ,Wilde's Risk Homeostasis model (1982) and Fullers' Threat Avoidance Model (2001). Contrary to the performance models that focus on describing the nature of 'normal' driving in information processing terms these models are mainly used in studies where traffic safety is the main topic.

All the above models share the concept of *risk reduction*, based on the original notion of Näätänen et al.(1974) that drivers' main control mechanisms consists of risk avoidance. According to their view drivers adopt their behaviour in such a way that they subjectively perceive a 'zero risk' situation. According to the authors this would be a universal principle governing the behaviour of all drivers. Wilde(1982) disagreed with this point of view and argued that drivers engage in seeking a certain amount of risk (not equal to zero) and that the amount of risk is not universal but varies between drivers. Drivers adapt their behaviour constantly to maintain a certain risk level. This risk level or 'homeostasis' is set by a pay-off matrix in which costs and benefits of risky behaviour are contrasted with costs and benefits arising from cautious behaviour. This yields an individual target risk level. The driver will meet changes in the driving environment with changes in his behaviour in such a way to maintain his personal target risk level. This will be become higher if expected benefits from risky behaviour or costs of cautious behaviour increase and diminish if expected benefits from cautious behaviour or costs of risky behaviour increases.

Although the notion of risk reduction/adaptation is widely accepted (Moskowitz, 1992)there is still much debate as how the desired adaptation of the individual drivers' risk level comes about. A major problem with Wilde's model is how people actually perceive changes in costs and benefits. In the model these are numerical entities to be entered in the homeostasis equation. However, they are not described in psychological terms and are therefore not open to operationalization and subsequent testing. This seriously limits the application of the model in experimental research. Recently Vaa et al (2001) introduced the notion of 'target feeling' as replacing 'target risk'. He suggested that drivers set out to seek a certain way of driving that suit them well and gives them the most comfortable feeling. So drivers do not only want to avoid accidents but also seek a unique 'target feeling' These are defined and characterized by an 'emotional' dimension, either positive or negative. In such a way psychological concepts like Sensation, Joy/Pleasure, Pleasantness, Effort etc. are entered in the homeostasis model.

Avoiding accidents is no longer the only motivation for driving, fulfilling some emotional equilibrium plays an important role. If this is true it could provide some answers to the problems encountered in experimental driving studies as they are conducted in this thesis and elsewhere(Jans 1998, Crown and Marlow 2001, Verster 2001).

1.4 Evaluation of the risk reduction hypothesis.

In the three studies described here about 45000 km were covered by the 102 subjects without any accident occurring. However, on 7 occasions a driving test was prematurely stopped by either the safety officer accompanying the subject in the car or by the subjects themselves as continuing to drive was considered to be too dangerous. Surprisingly, after unblinding of the study medication this occurred under placebo condition 4 times. These subjects were all young healthy volunteers in excellent physical condition before engaging in the one hour lasting experiment. There was no apparent reason for this situation to arise unless one considers the circumstances under which the experiment took place. Subjects were not free to adopt their personal style of driving during the test but were instructed to comply with specific (low) speed, distance etc. Also the 'environment' was controlled: subjects were not allowed to speak, listen to the radio, drink, eat or smoke. Moreover their perceived risk level was most probably also influenced by the presence of a safety officer in the car who had access to the controls of the car too, providing an extra safety backup.

Taken together these factors could account for a sub optimal target feeling, resulting in inadequate driving, even under placebo conditions. An interesting question is why the subjects themselves sometimes decided to abort the experiment. Their subjective experience of exceeding their risk level is not likely to have been triggered by their actual driving performance. In that case the accompanying safety officer should have noticed the impairment beforehand. Also no excessive SDPL ('weaving') was detected on the logged data when it was checked later. Therefore a different internal stimulus or feeling must have caused this. This would support the notion that emotions or feelings are part of the risk monitoring process and provide subjects with an instrument to monitor danger and to evaluate and consider behavioural alternatives in given situations. Alternatively the subject could have been driving under 'controlled processing' conditions in order to comply with the directions of the driving supervisor and could not sustain the continuous allocation attention to adequately perform the test.

If one accepts this notion the role of laboratory tests as indicators or predictors of driving ability should be re-evaluated. The now often used chronometric approach (O'Hanlon, 1996), directly derived from performance models, no longer seems sufficient (Rothengather, 1992). Although it remains a useful framework to detect impairment on basic psychomotor functions such as reaction

time and visual functions it misses essential elements vital to actual driving. The same critique applies to 'extended' lab tests like driving simulators. For both ethical and practical reasons driving simulators have become very popular in the last decade of the previous century. Some have reached very high degrees of realism such as the DaimerBenz simulator in Berlin (Janke 1995, Cobain 1999) or the Arizona driving simulator (Willems 1997). Both the handling and environmental conditions are almost indistinguishable from over the road driving. However, here the risk perception of the task will be very different too. For one thing, it is perfectly safe to crash in a driving simulator, and in fact this often happens (Tijerina,1996*)* . On the other hand most subjects would never attempt this in a real car.

This leads us to the conclusion that to monitoring and evaluating driving related safety behaviour traditional psychomotor tests and test batteries, including simulators, tell us only part of the story and are therefore definitely not sufficient. What is further needed is a method to evaluate drug induced changes in risk perception and risk taking. As this can be seen as psychological construct that is not solely related to car driving it could be evaluated using instruments from other research fields like economics and social psychology (Louberge 2000, Llwellyn 2002)

1.5 Alternative methods and approaches for Risk Evaluation

The question to answer now is whether there are better alternatives ?. We would argue that in the ideal case driving behaviour should be monitored in actual 'risky' situations in which no constraint is placed on the subject. Not only the technical data of car handling such as SDLP speed etc should be monitored but also parameters indicating the subjects 'emotional state', attitude, expectations of the experiment and 'mental set'. Subjects are aware of the fact that they could be expecting an effect on their behaviour and even under placebo conditions this can lead to considerable changes in their performance (Kienle, 1996). Possible candidates to monitor some of these parameters come from psychophysiology. Well documented electrophysiological variables such as the Galvanic Skin Respons (GSR), Heart Rate(HR) and ElecroEncephaloGraphic (EEG) measures are related to both covert and overt emotions is a valid way. The relation between GSR and driving has been shown before in the study by Taylor(1964). EEG was measured during actual driving by Ramaekers (1995) but the interpretation of the results was done in general terms of 'arousal' and 'sedation'. No link was made with risk taking or risk perception. However using these methods within the framework of a Risk Homeostasis Model could appear to be useful in pharmacopsychological research. Combining performance data from the subject with psychophysiological measures would give a more complete picture of the influence of psychoactive drugs.

But not only should alternatives be sought in changing or expanding the method of over-the- road driving itself. A very important task for future research is to 'translate' the results from epidemiological to experimental research. Over the years drug epidemiological studies have identified many 'at risk' groups with a higher than average risk to be implicated in traffic accidents (i.e. novice drivers, elderly drivers, patient groups etc.). Experimental based research has almost exclusively relied on results from studies with healthy volunteers. In pharmacopsychological research the issue of healthy volunteers versus patient research is still a topic of continuous debate, and if one accepts a broader framework of safety related issues there are other characteristics that should be considered too, like age, experience, social status etc. This can provide more insight into the question why certain groups (i.e. young drivers) are more accident prone than others, as this would not be expected on the basis of any performance model.

An example comes from Jessor's Problem Behaviour Theory (PBT) Jessor (1989, 1993) that shows that young drivers have a different view of risk taking compared to older drivers: 'risk taking makes driving more fun'. Older drivers (>70 years) are also more at risk compared to the general population for a variety other causes (Winsum 1999). Therefore, demographic, social and personality variables like these and possible changes to them by drugs should be allowed to play a more prominent role in studying effects of drugs on driving. In a recent study Soderstrom et al (2001) investigated the relationship between car accidents leading to trauma centre admittance and a number of pre-accident risk factors. They found a strong but complex relationship between prior traffic violations, risk taking disposition, substance abuse and the admittance to a trauma centre. This again argues for a more refined look at 'the' driving population before generalized conclusions are drawn about effects of drugs.

Finally more effort should be put in research that elucidates the basic relationship between Pharmacokinetics and Pharmacodynamics. Except for the case of ethanol still very little is known about the relationship between drug concentration and impairment. Furthermore the recent developments in the field of Pharmacogenetics should be considered as a valuable source of possible information on enhanced risks of individuals with specific genetic predispositions leading to hypersensitivity to a particular drug. Pharmacogenetic profiling is already being done for the curative effects of drugs but certainly offer a possibility to evaluate and possibly predict adverse events, and behavioural toxicity in particular.

1.6 Future developments of the Driving model and Drugs & Driving research

The driving model that has been used in the research described in this thesis is a robust instrument to detect basic driving impairment. It could however be improved by implementing new measures and changing basic procedures:

- ***Less restrained driving conditions***. The driving tests as they are performed now are very restrictive as to the actual task it presents to the subject. Contrary to 'normal' driving the subject has no control over the actual route they are travelling, the speed of travel, concomitant behaviour (speaking, eating, smoking), or environmental stimuli that may be sought to 'arouse' them (radio). The important aspect of planning or 'executive control' is taken away from the subject and transferred to the co-driver. In doing so the nature of the task is fundamentally altered. Neuropsychological studies have show that subjects experiencing problems with planning or other cognitive functions are perfectly capable of performing complex tasks if the structure and control is provided for them (Fuster 1997) In this way important effects on driving caused by the experimental treatment might go unnoticed. We therefore argue that the test should be changed in such a way that subjects are only instructed to 'safely travel from A to B' and drive in a more natural way. By changing the nature of the task not only basic car handling variables such as SDLP and speed but also other variables important to driving can be measured and monitored by the safety officer to yield a *driving quality* measure.
- ***Measuring physiological variables***. Direct measurement of basic physiological variables can provide information about the condition or state the condition the subject is in while performing the task (Papillo, 1990) . More specifically, the *arousal* level of the subject while driving and the amount of *attention* devoted to the task can be quantified. Although the latter cannot be defined in terms of physiological parameter there is a high correlation with derived parameters like heart rate variability. Not only continuous (psycho)physiological variables like heart rate, blood pressure or skin conductance could be used but also direct reactions of the CNS to environmental stimuli. This could be done by employing Event Related Potential paradigms while measuring ongoing brain activity during driving.
- ***Improved laboratory task battery***. The laboratory tasks used so far focus mainly on behaviour directly linked to operating the vehicle: Reaction time, Vigilance, Tracking etc. An effort should be made to determine the effects of drugs on higher cognitive functions and 'emotional states' which govern the attitude of the driver while engaging in traffic: Risk taking and Risk perception, anticipation of traffic situations, route planning etc. Translated into terms of a psychological model this would mean more emphasis on tests measuring executive functioning: Both divided and focussed attention play a crucial role in evaluating traffic situations as the information stream arriving from the had to be filtered for relevant information while yet all potential new information has to be scanned for usefulness. But also other sub processes are likely candidates: Shifting, Inhibition, Planning etc.

In the design of driving studies themselves two important improvements can be made.

- ***Implementation of 'Worst case' testing designs.*** Most of the studies published over the last few years have a very limited range of drug plasma levels that are tested. Drugs are seldom tested at more than twice the recommended therapeutic dose and almost always on healthy volunteers with an average body mass. Without exception volunteers are physically fit and, besides low doses of alcohol, are not taking any other psychoactive medication. This is not a realistic scenario as there is more variance in the general population, leading to higher drug levels under less favourable conditions. Therefore it would be desirable to move towards 'worst case' testing that does more justice to the circumstances encountered in real life. Subjects entering the study should not be excluded on the basis of physical characteristics such as body weight, impaired vision or hearing, concomitant psychoactive medication or physical handicaps that do not interfere with driving per se. This of course provided the study itself would not put them at risk and they would be taking the medication under investigation 'in real life' if needed for medical purposes. However, using a more diverse population would certainly increase the effort needed to design and manage such a multiple n=1 study but the results would be more meaningful than the 'average' impairing effects reported now.

- ***Studies with special groups.*** The debate of using either patients or healthy volunteers in testing side effects has been ongoing for many years and has yielded valid arguments for both positions favouring either group (Amori 1989, Ho, 1994). Although ultimately the target population for which pharmacopsychological studies are done consists of patients, defined here as anybody under the influence of a psychoactive substance while driving, the use of healthy volunteers has many advantages. Certainly if there is to be a further diversification within the studied population the use of healthy volunteers becomes inevitable. There are many groups for which not enough patients can be identified or recruited to perform the study. The need to study these 'special groups' for instance people taking a new anti-epileptic medication, could arise from epidemiological data, indicating that certain population characteristics could contribute to a higher risk associated with a certain drug (Cox 2000). By performing a controlled study with such a group the correlational relationship found by the epidemiological approach can be altered to a casual one. These special groups can vary by drug but certainly special interest should be given to the elderly (Parker 2000, Daigneault 2003) , the young and inexperienced (Arnett 1997, McKnight 2003), and subjects with other chronic medicinal drug use.

- **Special interest should be given to the elderly driver**. Medication use increases with age. For example, Kaba et al., (2000) found that in Austria, 50-59 year olds consume 27 packages of medication, 60-69 year olds consume 38 packages and the 70-79 consume 54 packages a year. With the population ageing in industrialized countries, the current trend of medicine-related impaired driving and fatalities will only increase. Kaba et al., (2000) found from 1992 to 1996 a 25% increase for cardiovascular therapy and a 15% increase for psychiatric medications. Their most prescribed medications were antihypertensives (17.9%), cardiovascular (10.8%) and psychiatric (8.5%) medications. Most likely these trends are similar in other industrialized countries. Moreover, increased medical problems, reduced cognitive abilities and motor functioning such as reaction times among the elderly will only compound the problem. In addition, many elderly are multiple medication users. The risk of injuries, not only due to motor vehicle injuries but as pedestrians, or due to falls can only increase and research is needed to monitor these trends in relation to medicinal drug use. For example, Odell (2000) reviewing coroner's records for drivers aged over 70 who died in crashes between 1996-1997 in Canada found that many drivers were taking medications that could have affected their driving skills.

Finally a more prominent role of pharmacopsychology in the process of new drug development should be considered. There is no legal obligation yet to test new drugs for possible effects on driving and the majority of studies reported over the last 10 years have been initiated by the pharmaceutical industry. This has led to designs and procedures of which the results are not always comparable and are sometimes biased to favour the product under investigation. Test batteries and test procedures used are very different between laboratories(Heikkilla 2000) claiming to find effects on the same psychological variable. Even the application of different versions of the same test, like the Word Learning Test (Brand 1985) can lead to different results due to procedural differences in administration. More standardized study designs would overcome many of these problems and make results more comparable. Also it could be argued to have at least a 'core' set of tests or evaluations of drug effects before the presence (or absence) of an effect on a particular psychological function could be claimed.

2 Conclusions from the learning studies

The studies described here with the 'learning model' were set out to find evidence for a relationship between Seasonal Allergic Rhinitis and disturbed cognitive functioning, with an emphasis on 'learning'. Juniper and Guyatt (1991) had demonstrated that SAR patients not only suffer from disease related symptoms but also frequently report fatigue, malaise and cognitive problems

such as a diminished concentration span and disturbed memory. As the target population for the first study comprised of elementary school children an effort was made to find a valid test battery to investigate this relationship and the altering effect on 'learning' of an antihistamine drug. Although many well documented and sensitive tests existed to measure various elements of cognitive performance (Lezak 1995, Spreen and Strauss 1991) no usable test battery was found that could evaluate acute effects on scholastic learning. After an extensive literature search the simulation game 'Hunger in the Sahel' (Leutner 1989) was adapted in order to be used as an evaluation tool. The subsequent studies that were carried out and described here were for the most part successful in showing the impairing effects of Allergic Rhinitis.

The effects of the antihistamine drugs on performance in the studies reported here was not always conclusive. The results are still cited although the method has not been used in other pharmacopsychological studies. However, in a broader context, a growing body of research has focused on the negative impact of allergic rhinitis on quality of life, personal safety, and performance at school and work (Settipane 1999, Meltzer 1997, Baiardini 2003) and not only on the relatively restricted area of learning. Most if not all studies all rely on batteries of (neuro)psychological tests (Kay 2000, Spaeth 1996, Kremer 2002) or on teacher or parent rated questionnaires (Juniper 1994). The methods and tests used in these studies vary greatly as do the conclusions. Marshall (2000) concluded that allergic reactions to ragweed pollen causes significant cognitive difficulties in a subgroup of patients, while Bender (2001) found that learning and reaction time in children attending a laboratory school were not significantly affected by rhinitis or two antihistamine drugs. Kremer (2002) found that rhinitis was significantly related to perceived but not to objective cognitive functioning. Interestingly this discrepancy was explained by the psychological construct 'effort'. Patients would be able to sustain the same level of performance as controls, but only for a short period of time.

This would favour our original approach of assessing cognitive impairment as used in learning studies, as the 'time on task' was at least 3 hours as opposed to only very limited time it takes to complete isolated (neuro)psychological tests. But the results and conclusions of most of the recently published studies are hard to compare due to the variation in methods and subjects used (Parrot, 2000). Overall it can be concluded that much still needs to be done to first unravel the complex relationship between allergy and cognition before any effect of drugs can be explained in pharmacopsychological terms, as most of the cited studies above also mention in discussing their results.

3 New challenges for Pharmacopsychology.

Almost without exception pharmacopsychological studies focus on the *adverse* effects or lack of them on a variety of psychomotor and cognitive

functions. Very few studies are reported on drugs that *improve* these functions either directly in healthy volunteers or indirectly by correcting or counteracting the condition that caused the impairment (Riedel 1996, Robbins 1997, Hogervorst 1999, Mascord 1997). Usually these drugs are so called psycho-stimulants and their use has dramatically increased over the last 15 years (Cherland 1999, de Bruin 2001). Drugs like Caffeine, Ginkgo Biloba, Pseudoephedrine and various other food supplements are increasing in popularity as a way to improve cognitive functioning in normal healthy volunteers. Their therapeutic use is still debatable although some studies have shown positive effects on conditions like age related mild cognitive impairment (Ihl, 2003).

The most commonly used psychostimulant drug however is methylphenidate (MPD, Ritalin®) and to a lesser extent dextroamphetamine (DEX, Dexedrine®) These drugs are prescribed to children and also increasingly to adults suffering from Attention Deficit Hyperactivity Disorder(ADHD). Although MPD and DEX are stimulant drugs they have a paradoxal effect on ADHD, suppressing the hyperactivity to a certain degree. Over the years different mechanisms of action have been proposed through which stimulants achieve their therapeutic effect. Gaultieri (1983) explained the effect through a stabilizing effect stimulants have on arousal and attention. Haenlein(1987) explained the effects by a change in motivation to persist in ongoing activity, and increase the span of attention on ongoing behaviour. Presently there is consensus that these drugs mainly have an effect on impulse regulation (Epstien 2003, Denney 2001).

Although clinically effective, the use of MPD in the treatment of ADHD however is not without debate. As MPD is a powerful stimulant it is also a potential drug of abuse (Kollins 2003). The overall annual rate of stimulant medication used by children has considerably increased over the last few years and is a growing concern (Greenhill, 2003). In the US prescriptions of MPD to children under 18 have increased from 0.6 per 100 persons in 1987 to 2.4 in 1996 (Zito 2000). Although a recent study (Schirm 2001) showed that the prevalence of prescribing stimulant medication in the Netherlands was much lower (0.74 per 100 persons) the same increase rate was seen here over the last ten years. Also MPD is being administered to increasing numbers of young children (<7 years). Given this large and still increasing prevalence of stimulant drug use it is important to find alternative drug therapies.

New drugs like Atomoxitine (Straterra®) and Dexmethylphenidate (Focalin®) are promising alternatives for the indication of ADHD (Kollins 2003). Just as in the development of new drugs for other indications pharmacopsychology can play an important role. Given the fact that the dopamine system is implicated in ADHD (Solanto 2003), these drugs will in one way or the other interact with that neurotransmitter system (Overtoom 2003). From a pharmacopsychological point of view specific behavioural tests known to be sensitive to dopaminergic manipulation can be used to evaluate and predict the clinical efficacy of these

drugs. Combining this approach with clinical neuropsychological observations will also give a better understanding of the origin of this developmental disorder.

4 Conclusions

The reason to prescribe and take medicinal drugs is to cure patients from disease or to improve functions that are suboptimal according to their own perception or that of the physician treating them. Ultimately the common goal is to improve quality of life, either directly or in the long run. The development of drugs has accelerated dramatically over the last few decades and more drugs become available to patients every day. The prime target of this development has always been to correct the disease or condition of the patient, with efficacy of the drug as the central issue.

No drug however is without (negative) side effects which often have little relation with the disease itself, but almost without exception always on the final goal of the treatment: quality of life. Determining, investigating and documenting these side effects has changed dramatically over the last few decades, and increasingly more attention has been given to the first principle of medical treatment: 'To do no harm'. Up to the 70's of the last century these harmful effects or 'toxicity' of drugs was only evaluated on a biological level, with research mainly focussing on basic functions of the body. Gradually there was an increasing awareness that side effects of drugs could be harmful through behavioural changes. Epidemiological studies prompted the pharmaceutical industry to pay more attention to 'behavioural toxicity' of existing and newly developed drugs.

The studies described in this thesis are a direct consequence of this increasing awareness. All studies were initiated and funded by the pharmaceutical Industry. A shift can be seen in the role of this pharmacopsychological research: Most of the early study's were carried out in a late phase of drug development, or even after the drug was launched on the market. Nowadays, behavioural studies are already carried out in the early stages (phase I and II), and behavioural assessments play an important role in the early stages of development. The type of research as described, 'pharmaco-psychology', with its emphasis on cognitive performance, behavioral testing and 'mental set' will be developed further, and ideally will become a mandatory part of drug development and registration.

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Samenvatting

Dit proefschrift beschrijft een aantal studies die uitgevoerd zijn naar de bijwerkingen van geneesmiddelen op gedrag. De benadering is vanuit een farmacopsychologisch perspectief. Hierin wordt uitgegaan van de het gedrag als *afhankelijke* variabele en het middel waarmee de gedrag beïnvloed wordt als *onafhankelijke* variabele. Omdat in deze benadering de nadruk ligt op het gedrag is het mogelijk om de gevonden effecten te verklaren in de context van een bestaande theorie of (neuro)psychologisch kader. In tegenstelling tot een psycho-farmacalogische benadering kunnen gedragsveranderingen door geneesmiddelen voorspeld worden in de farmacopsychologie. Wel vereist dit fundamentele kennis over menselijk gedrag alsook de neurochemische basis die eraan ten grondslag ligt. De basis hiervoor werd in de jaren 70 en 80 van de vorige eeuw gelegd waarbij voortschrijdende kennis over neurotransmitter systemen en beter inzicht in neuronaal functioneren dmv nieuwe imaging technieken leidden tot het ontwikkelen van modellen die neuronale activiteit en gedrag koppelden. In dit manuscript staan twee aspecten van gedrag centraal: Psychomotoriek, met daarbij in het bijzonder de effecten van geneesmiddelen op autorijden, en Cognitie, met daarbij de effecten op kennis vergaren door kinderen in een 'leertaak'. Er worden een aantal op zichzelf staande experimentele studies beschreven, voorafgegaan door inleiding over psychologische gedragsmodellen die van waarde zijn in het domein van toegepaste farmacopsychologie

Hoofdstuk 1 gaat eerst in op een aantal historische achtergronden van het systematisch onderzoeken van de gevolgen en effectiviteit van (genees)middelen die gebruikt worden om gedrag te beïnvloeden. Het gebruik van middelen zoals opium, hellebore, rauwolfia, alruin en belladonna was al sinds mensenheugenis in veel culturen gebruikelijk. Op het einde van de negentiende eeuw trad er een plotselinge toename op van nieuwe middelen die dankzij de opkomst van de scheikunde gemaakt konden worden. Er was in het begin van de vorige eeuw echter nog geen regelgeving wat betreft het controleren op toxiciteit van deze nieuwe middelen. Het duurde tot aan de tweede wereldoorlog voordat er in de Verenigde Staten vanuit de overheid eisen werden gesteld aan de veiligheid van nieuwe medicijnen. Dit na een aantal ernstige incidenten waarbij veel mensen het leven lieten zoals de dood van meer dan 110 kinderen die stierven aan vergiftiging door diethylene glycol, dat als oplosmiddel voor sulfanilamide werd gebruikt.

Een aantal jaren later werd Chlorpromazine, het eerste medicament met een actieve psychoactieve werking op de markt gebracht, spoedig gevolgd door een aantal gelijksoortige middelen. Dit luidde het ontstaan van psychofarmacologie in als een onderzoeksdiscipline die zich bevond op het raakvlak van Psychiatrie en Psychologie. In het begin was de aandacht met name gericht op klinische effectiviteit en veel minder op bijwerkingen. Naarmate er meer alternatieven op

de markt kwamen voor dezelfde medische indicatie werd het profiel van bijwerkingen van ieder middel steeds belangrijker. Met name gold deze aandacht voor bijwerkingen op gedrag. De farmacopsychologie ontwikkelde zich naarmate er meer belangstelling ontstond voor geneesmiddelen als instrument om gedrag te beïnvloeden. Twee richtingen kunnen daarbij onderscheiden worden: *Theoretische farmacopsychologie,* waarin genees-middelen gebruikt worden om basale psychologische en psychomotorische processen te bestuderen, en *Toegepaste farmacopsychologie*, waarbij een (bijwerkingprofiel) van een geneesmiddel op gedrag in kaart gebracht kan worden. De onderzoeken in dit proefschrift houden zich alleen met de laatst genoemde richting bezig.

Om de bijwerking van geneesmiddelen op biologische functies te bepalen zijn er een aantal goed gevalideerde en betrouwbare procedures bekend, met duidelijk omschreven klinische 'endpoints'. Het bepalen van bijwerkingen en de mogelijke negatieve gevolgen van geneesmiddelen op gedrag is veel moeilijker. Dit komt omdat er slechts zelden een duidelijke relatie is tussen de uitkomst van een procedure of test die deze vermeende bijwerkingen bepaald en het uiteindelijke 'werkelijke' gedrag in het dagelijkse leven. En vaak is de duiding van de werking van een middel grotendeels afhankelijk van de omstandigheden waarin een individu zich bevind. Een voorbeeld daarvan is alcohol. Indien met mate genoten in een kroeg of restaurant kan het een onschuldig middel zijn of zelfs positief bijdragen aan het gedrag. Indien dezelfde persoon met dezelfde hoeveelheid alcohol aan het verkeer deelneemt ontstaat er een andere situatie, en kan de werking als een ernstige bijwerking gezien worden.

Omdat de gevolgen van bijwerkingen op gedrag zich niet beperken tot het eigen lichaam bestaat er wetgeving om het gebruik in bepaalde omstandigheden te reguleren. Deze wetgeving is echter zeer summier en beperkt zich in de meeste landen tot het verbieden van deelname aan 'gevaarlijke' activiteiten zoals autorijden of het bedienen van zware machines. Bijwerkingen op bijvoorbeeld cognitie of stemming zijn veel moeilijker in verband te brengen met negatieve consequenties voor een individu of groep patiënten. Toch kan dit voor individuen of groepen patiënten wel degelijk gevolgen hebben. Vaak ook is het echter moeilijk te bepalen of de effecten op het gedrag worden veroorzaakt door het gebruikte geneesmiddel of dat het een gevolg is van de aandoening waarvoor het middel genomen wordt. Het ontbreken van gevalideerde onderzoeksmethoden is hieraan mede debet.

Het ontwikkelen van betrouwbare en valide onderzoeksmethoden is een voorwaarde om farmacopsychologie verder te ontwikkelen en een plaats te geven in het ontwikkel proces van nieuwe geneesmiddelen. Hiervoor moeten deugdelijke gedragsmodellen worden opgesteld waaruit toetsbare hypothesen kunnen worden ontleent die in onderzoek gebruikt kunnen worden. Vanuit de Psychologie en met name de psychologische functieleer en Ergonomie zijn er een aantal modellen bekend die zich hiervoor goed lenen. Deze kunnen in grote lijnen worden verdeeld in twee stromingen: *Structurele* modellen en *Capaciteits*

modellen. Beide zien gedrag als het verwerken van informatie. De effecten van (genees)middelen worden door beide soort modellen op een andere manier verklaard, en naast strikt theoretische modellen van gedrag zijn er een aantal meer praktische modellen ontwikkeld die kenmerken van beide stromingen hebben.

Voor autorijden zijn er vanuit een aantal wetenschappelijke disciplines verschillende modellen ontwikkeld. Hierbij zijn, per model, een aantal parameters gedefinieerd die in verschillende psychomotorische testen zijn verwerkt om effecten van diverse achtergronden te kunnen meten. Deze testen variëren van simpele reactietijd taken tot ingewikkelde simulator opstellingen, afhankelijk van het doel waarvoor ze gebruikt worden. De meest realistische is de rijtest die ontwikkeld werd in de jaren 80 van de vorige eeuw en die ook in de hier beschreven experimenten is gebruikt. De test is tot heden de meest gevoelige manier gebleken om effecten van (genees)middelen op gedrag te meten, maar heeft een aantal beperkingen omdat niet alle aspecten van autorijden gemeten worden. In het afsluitende hoofdstuk 10 wordt hier verder aandacht aan besteed.

Een tweede gedragscategorie waaraan aandacht besteed wordt is Cognitie, en in het bijzonder het vergaren en zich eigen maken van nieuwe informatie. Scholing is veruit de belangrijkste activiteit van westerse kinderen in de leeftijd van 6 tot 18 jaar. Ook deze categorie kinderen gebruikt medicijnen om ziekten of aandoeningen te behandelen. Negatieve effecten van geneesmiddelen op schoolprestaties kunnen voor individuen en groepen patiënten grote gevolgen hebben voor hun verdere maatschappelijk carrière. Er is hierover weinig bekend en alleen epidemiologische gegevens signaleren een aantal mogelijke problemen. Maar ook hier zijn de effecten van het geneesmiddel weer moeilijk te scheiden van de mogelijke effecten van de ziekte.In dit proefschrift word een experimentele procedure beschreven die het proces van leren en de effecten daarop van farmaca in kaart tracht te brengen middels een simulatie spel.

Hoofdstuk 2 beschrijft een experimentele studie waarbij de effecten van het anti-histaminicum Desloratadine op autorijden geëvalueerd wordt. Antihistaminica worden gebruikt bij de behandeling van allergieën zoals hooikoorts. De werking berust op het blokkeren van de werking van Histamine, een neurotransmitter. Behalve de gewenste werking op het perifere Histamine systeem dringen met name de oudere antihistaminica ook door in het centrale zenuwstelsel en veroorzaken slaperigheid (sedatie). Dit kan gevaarlijk zijn bij het taken zoals autorijden. De nieuwere middelen zijn zo ontwikkeld dat zij het centrale zenuwstelsel veel slechter bereiken waardoor deze bijwerking minder prominent zou zijn. Om dit te onderzoeken werd Desloratadine vergeleken met een ‘ouder’ antihistaminicum diphenhydramine en placebo. Achttien gezonde vrijwilligers namen deel aan een tweetal rijtesten op de openbare weg en een aansluitende batterij van laboratorium testen terwijl zij onder invloed waren van deze middelen. Zoals voorspeld presteerden de deelnemers slechter (onveiliger) nadat

zij het oude middel (diphenhydramine) hadden genomen in vergelijking tot het nieuwe (desloratadine) en placebo. De meest duidelijke effecten waren te zien op de rijtest en in mindere mate op de laboratoriumtesten. Geconcludeerd kon worden dat bij gelijke klinische effecten Desloratadine de voorkeur geniet boven oudere middelen zoals Diphenhydramine.

Hoofdstuk 3 beschrijft een rijstudie uitgevoerd om de effecten te onderzoeken van Mefloquine (Lariam®) een profylactisch middel tegen Malaria. Mefloquine heeft geen farmacologisch profiel op grond waarvan verwacht kon worden dat het enig effect zou hebben op psychomotoriek. Toch werd in sommige gevallen melding gemaakt van mogelijk ernstige bijwerkingen zoals psychosen, verwardheid en depressie. Omdat het middel op grote schaal werd ingezet onder militairen die betrokken waren bij de vredesmissies in Cambodja was er behoefte om mogelijke risico's ervan op gedrag beter in kaart te brengen. In een rijstudie waaraan 40 mannelijke en vrouwelijke vrijwilligers deelnamen werd het middel gedurende een maand volgens een gebruikelijk doserings schema toegediend. Op de eerste dag en ook drie en vier weken na het begin van de dosering werden mogelijke effecten geëvalueerd. Op de laatste dag werd bovendien gezocht naar een mogelijk interactie effect met alcohol. Vermoed werd dat Mefloquine mogelijk de negatieve effecten van alcohol zou versterken waardoor op zich onschuldige hoeveelheden alcohol in het bloed wel ernstige effecten zouden krijgen. De uitkomsten waren enigszins verassend omdat in tegenstelling tot hetgeen verwacht werd Mefloquine geen negatief effect had op autorijden maar juist een verbetering liet zien. Met name kwam dit naar voren in de conditie waarin er ook alcohol gegeven werd.

Hoofdstuk 4 beschrijft een verdere analyse van de Mefloquine rijstudie uit Hoofdstuk 3. Het positieve effect van Mefloquine op rijgedrag dat werd gevonden was aanleiding om een verdere exploratieve analyse te verrichten. Met name toonde deze analyse aan dat de effecten van Mefloquine zich tijdens de rijtest manifesteerden en een positief invloed hadden op de prestaties als er gelijktijdig ook een lage dosering alcohol werd gegeven. Er trad dan een provigilantie effect op

Hoofdstuk 5 beschrijft de effecten van 4 verschillende doseringen van een 2de generatie antihistaminicum op rijgedrag en een aantal psychomotorische functies gemeten met laboratorium tests. 24 vrijwilligers werden elk in totaal 6 maal getest, met 4 doseringen van mizolastine en daarbij ook met clemastine (een referentiemiddel) en placebo. Het gebruik van 4 verschillende doseringen geeft de mogelijkheid om een dose-effect relatie voor bijwerkingen te onderzoeken. Bijna zonder uitzonderingen worden geneesmiddelen in een enkele dosering voorgeschreven. Maar gelet op de spreiding in de bevolking wat betreft

lichaamsgewicht kunnen de werkelijke concentraties van een geneesmiddel in het bloed makkelijk een factor twee tot drie verschillen tussen individuen. Ook kan met een dergelijke opzet beter onderzocht worden of een middel helemaal geen effect heeft op psychomotorisch functioneren dan wel of er sprake is van een gradueel verloop van het effect, dat zich pas bij hogere doseringen als die klinisch voorgeschreven worden uit. In dit onderzoek bleek de klinische dosering van Mizolastine marginale effecten te hebben die dankzij de gegevens van de andere doseringen in een beter perspectief geplaatst konden worden..

Hoofdstuk 6 beschrijft de effecten op psychomotorisch functioneren van 3 doseringen van een middel dat in fase II van de ontwikkeling was als nieuw Anxiolyticum. Op grond van dier onderzoek en chemisch-biologische eigenschappen van het middel werd vooraf voorspeld dat het zich zou gedragen als een partiële Benzodiazepine agonist. Het middel Saripidem hoort tot de klasse van imidazopyridines en heeft een farmacologisch profiel dat nauw aansluit bij Benzodiazepine. De unieke eigenschap van het middel zou zijn dat het bij lagere doseringen wel de anxiolytische effecten heeft van een Benzodiazepine, maar dat de sedatieve effecten die wel gezien worden bij Benzodiazepine pas bij veel hogere doseringen optreden. In eerdere studie was de anxiolytische werking bij lagere doseringen van Saripidem al aangetoond. In deze studie werden doseringen tot 3x hoger getest op een uitgebreide batterij van laboratorium testen. Geconcludeerd werd dat het middel inderdaad het profiel had van een partiële Benzodiazepine agonist. Sederende effecten traden pas op bij hogere doseringen.

Hoofdstuk 7 beschrijft een studie waarin de effecten van hooikoorts en antihistaminica op het leergedrag van kinderen onderwerp van studie is. Ongeveer 10% van de schoolgaande kinderen heeft in het voorjaar last van seizoensgebonden allergische rhinitis (SAR) ofwel hooikoorts. Dit treed doorgaans in het voorjaar op en duurt vaak tot in de periode waarin ook belangrijke schoolprestaties geleverd moeten worden voor de overgang naar een volgend leerjaar of in het kader van examens. Dat SAR een negatief effect heeft op het functioneren van kinderen werd al eerder onderkend en heeft in sommige landen zoals in Scandinavië geleid tot maatregelen om dit the compenseren. Er waren echter geen objectieve gegevens bekend over de effecten op prestaties tijdens het leerproces, of eventuele invloeden die hooikoorts medicatie hier op zou hebben. In deze studie werd voor het eerst een nieuwe evaluatie techniek gebruikt om de effecten te meten. Een eerder voor andere doeleinden ontwikkeld simulatie programma werd geschikt gemaakt voor de doelgroep van 8-12 jarige kinderen. Het simulatie programma werd met een computer aangeboden in een klassikale situatie, waarbij hooikoorts patiënten en een niet behandelde controlegroep een dag lang werden getraind om als boer op een ‘virtuele’ boerderij in Afrika te kunnen overleven. Het vergaren en onthouden van feitelijke kennis en het ontwikkelen van strategische inzichten was het voornaamste doel

van het programma. De hooikoorts patiënten werden tijdens deze training voor hun symptomen behandeld met ofwel een oud en sederend middel (diphenhydramine) of met een nieuw, minder sederend middel (Loratidine) of placebo. De effecten werden twee weken na de deze training gemeten toen alle kinderen vrij van symptomen waren en nogmaals werden getest op feitelijke kennis van het programma en kunde om de simulatie zo lang mogelijk te laten verlopen. Uit de resultaten bleek dat hooikoorts een negatief effect heeft op het vergaren en onthouden van nieuwe kennis, en dat dit deels wordt opgeheven door indien de patiënt behandeld wordt met Loratidine en verergert na behandeling met Diphenhydramine.

Hoofdstuk 8 beschrijft een tweede studie gebaseerd op hetzelfde paradigma als in het vorige hoofdstuk. Een aantal vragen die na aanleiding van het vorige onderzoek naar voren kwamen werden in de opzet meegenomen. De populatie patiënten die aan het onderzoek meewerkten was ouder, en in de leeftijdscategorie van studenten en HBO'ers (16-25 jaar). Een van de belangrijkste punten van kritiek op de eerste studie was dat er slechts naar de effecten van de eerste dag gekeken werd. In deze studie werden patiënten en gezonde vrijwilligers op drie opeenvolgende avonden getraind met het simulatieprogramma. In totaal namen 67 patiënten en 28 op leeftijd en opleiding gematchde gezonde vrijwilligers deel aan het onderzoek. De onderzochte hooikoortsmiddelen verschilden met het eerste onderzoek. Naast diphen-hydramine en placebo werd er nu een combinatie van acrivastine en pseudoephedrine gebruikt (Semprex-D®) om de symptomen te bestrijden en eventuele bijwerkingen te bestuderen. Ook uit deze studie bleek dat hooikoorts op zich een negatief effect had op leerprestaties, en dat dit effect niet direct verdwenen was als de symptomen bestreden werden met antihistaminica. Ook werd bevestigd dat Diphenhydramine de leerprestaties verder deed verslechteren.

Hoofdstuk 9 beschrijft een derde studie gebaseerd op het simulatie programma met 123 jonge (10-14) jarige hooikoorts patiënten en gezonde vrijwilligers. Deze studie verschilde op een aantal punten van de vorige twee. Er werd in deze studie alleen een vergelijking gemaakt tussen de effecten van twee 'nieuwe' hooikoorts middelen. Loratidine en Cetirizine. Wel was er een placebo conditie maar geen vergelijking met een ouder, sederend antihistaminicum zoals in de vorige studies. Ook het simulatie programma was aangepast en het aantal uren training met het programma was veel groter vergeleken met de vorige twee studies. De resultaten waren niet eenduidig. Tijdens de leerfase werd er een duidelijk verschil in presteren gevonden tussen de patiënten groep en de gezonde vrijwilligers, maar dit was niet terug te vinden bij de 'follow up' twee weken later. Op dat tijdstip presteerden de patiënten beter als tijdens training en de normale controles juist slechter. Er werd voor deze discrepantie met de vorige twee studies geen directe

verklaring gevonden. Wel was waarschijnlijk dat de intensiviteit van de training debet was aan het verdwijnen of tenminste kleiner worden van de effecten.

Hoofdstuk 10. In dit afsluitende hoofdstuk worden een aantal conclusies getrokken uit de gezamenlijke resultaten van de rij en leerstudies. Er worden verder aanbevelingen gedaan hoe deze in de toekomst verder ontwikkeld en aangevuld kunnen worden.

Wat betreft de rijstudies wordt er een ontwikkeling gesignaleerd die rijgedrag in een breder kader plaatst dan alleen een 'performance' perspectief. Modellen die zich bezig houden met risico gedrag lijken een goede aanvulling te zijn om rijgedrag en de mogelijke effecten van psychofarmaca te beschrijven. Met name zou het inzicht in risico perceptie en risico acceptatie door automobilisten een aanvulling betekenen om het autorijden als 'geheel' beter te kunnen beschrijven. Directe gevolgen voor de opzet van rijonderzoek zijn dat de aard van de taak beter moet aansluiten bij de werkelijke situatie waarin de automobilist zich kan bevinden. Met name moet de rijtesten meer ruimte laten voor 'executive control' van de proefpersonen, in de vorm van verantwoordelijkheid voor route planning, snelheid en dergelijke.

De rol van farmacopsychologie in onderzoek en ontwikkeling van (genees) middelen lijkt definitief gevestigd, blijkens het gestaag toenemende aantal onderzoeken dat de laatste jaren is gepubliceerd. Het onderzoeksgebied beperkt zich ook niet langer tot de negatieve bijwerkingen op gedrag maar ook tot onderzoek van middelen waarvan de effecten op gedrag juist positief zijn, zoals middelen tegen gedragsproblemen met kinderen (ADHD) of middelen tegen cognitieve achteruitgang bij ouderen. Ook wat betreft regelgeving met betrekking tot het gebruik van bepaalde (genees)middelen zal farmacopsychologie een steeds grotere rol gaan spelen

Summary

This thesis describes a number of studies investigating the side effects of medicinal drugs on behavior from a pharmacopsychological perspective. Behavior is the *dependant* variable that is being manipulated by drugs an *independent* variable. Because it focuses on behavior and not on the drug itself, a much more refined study of the behavioral effects can be made and evaluated within an existing psychological theory or (neuro)psychological framework. Therefore, given a drug with a known chemical profile one should be able to predict the effects on distinct behavioral functions. Contrary to the psycho-pharmacological approach, behavioral effects can be *predicted* in pharmaco-psychology. However, this requires a fundamental understanding of human behavior and its neurochemical basis. Over the last decades much progress has been made in this domain but knowledge is still far from complete. The theoretical background for it has been developed in cognitive psychology in the 70's and 80's of the last century. Aided by the expanding knowledge of neurotransmitter systems and using new neuroimaging techniques, models were developed linking biological functioning with overt behavior. This thesis describes a series of eight experimental studies that investigate the feasibility of this approach in two distinct but specific behavioral domains: *motor* and *cognitive* performance. Motor performance in these studies is operationaliszed in terms of car driving in a specially instrumented vehicle. Cognitive performance is studied in 'learning', operationaliszed as performance in a well controlled classroom situation. Before the presentation of the studies a number of psychological performance models are presented and their value for applied pharmacopsychology is discussed.

Chapter 1 first presents the historical background of systematic research into efficacy and side effects of psychoactive compounds:

For thousands of years and in all cultures humans have used drugs such as rauwolfia, belladonna and hashish for medicinal, recreational and religious purposes. The advancement of chemistry in the 19th century made it possible to synthesize new compounds with curative potentials. Many new compounds were marketed as a drug with little or no basic testing regarding safety or efficacy. However, drug prescription and development became subject to regulation after a few drug-related disasters such as the death of over 100 children taking sulphanilamide dissolved in diethylene glycol, a toxic solvent.

The synthesis of Chlorpromazine as the first drug to be useful in the treatment of mental disorders marked the birth of *psychopharmacology* as a rapidly growing scientific discipline in the early 1950's. Besides an interest in clinical efficacy of new drugs, attention was now also given to the accompanying unintended or 'side-effects' of drugs. Evaluation of effects of new drugs on behavior, mood and cognition were more often carried out routinely in the

process of drug development. In the 1970's psychopharmacology to lines of research emerged: *psychopharmacology* which sets out to understand the neurochemical action of drugs that yield a specific behavioral effect and had a biological approach, and *pharmacopsychology*, that focuses more on the psychological effects and behavioral consequences of drugs.

Research in the field of pharmacopsychology can be divided in two main areas: The first, *theoretical pharmacopsychology*, uses drugs as tools to study basic psychological and psychomotor processes. Not the drug, but the behavior is the main object of study. The second, *applied pharmacopsychology*, seeks to elucidate the profile of CNS action of new drugs in terms of (un)wanted changes in behavior. This thesis addresses only in the latter area.

In the process of developing new drugs strict requirements are made as to the 'biological' safety of a drug, with validated procedures and predefined clinical endpoints. Contrary to this the process of defining the 'behavioral' safety of a drug is much less clear. This is because behavioral tests usually measure a surrogate end point and the relevance of the measured effects will ultimately depend on the relationship to daily life tasks or on their predictive value for an increased risk of accidents. The 'behavioral toxicity' of a drug also depends to a great extent on the situation the subject is in. For example, low amounts of alcohol could have positive effects social interactions in a crowd, while the same amount could prove to be dangerous when engaging in traffic.

The law only prohibits the use of a few medicinal drug in traffic and leaves this responsibility for most psychoactive drugs to the individual patient, although it does issue a warning on drugs that are suspected to interfere with 'reaction speed' and should therefore not be used while operating potentially dangerous machinery and car driving. The question of toxicity is much less clear for drug effects on cognition or learning. Although individual cognitive functions can be evaluated by neuropsychological tests, establishing serious detrimental effects in daily life is much more difficult. Besides that and contrary to the case of psychomotor impairment it is also commonly thought that the disease itself the drugs are being taken for also influences cognitive functioning. However, separating the effects of disease and drugs has so far proven to be an almost impossible task.

Developing valid and reliable models to predict drug effects on behavior are a prerequisite for pharmacopsychological research. Two main lines have been developed within using a cognitive approach of human behavior, each with distinct assumptions about the nature of 'the information flow' in human information processing: *Structural models*, emphasizing the flow of information through a number of discrete or continuous 'stages' of processing, and *Resource models*, in which different tasks and task aspects compete for a limited amount of processing capacity. The effects of dugs on behavior are explained differently by both models, and next to strict theoretical models a number of more practical ones have been

proposed, aiming to explain specific (sub)domains of behavior. These models often have characteristics of both lines.

Models of driving behavior have a different (task oriented) approach compared to pure theoretical human performance models although they share many concepts and include general information processing, zero-risk, threat avoidance and trait models. Most of these task oriented models are based on the original classification of Janssen (1979). This classification is based on an Additive Factor Method model with three distinct levels of processing information: A basic *operational level*, *a tactical level*, *and a Strategic level.* However, the lack of a well–conceptualized theory and model of car driving hampers the translation from laboratory to real-life and limits the implications of the results. A way to circumvent this problem is to closely mimic real-life under laboratory conditions and 'simulate' the actual real-life task. This has been done very successfully in some areas like piloting an aircraft and although driving skills seem to be easier to master than flying skills the use of driving simulators is more problematic and has serious limitations.

A second behavioral domain that is addressed in this thesis is Cognition, and more in particular Learning of new and complex information. A child typically spends up to 30 hours a week and 40 week per annum in school, making it by far the most important activity children engage in. However, very little is known about the effect of medicinal drugs on scholastic achievement although systematic disruption of the learning process by drugs or other sources could have serious consequences for the individual. There is no valid instrument to evaluate drug effects on the process of formal learning in an experimental way but epidemiological data suggest there could be a problem with certain classes of psychoactive drugs. Again, the effects of the disease are difficult to separate from the effects of the drugs taken to cure it. Nevertheless a series of studies is presented in which an experimental procedure has been used to investigate possible negative side effects of medicinal drugs on children's learning.

Chapter 2 describes a driving study with Desloratadine, a new antihistamine , and Diphenhydramine, an older antihistamine. The latter and other first generation antihistamines taken for relief of allergic rhinitis are sedating and pose serious health risks when driving cars or operating machinery. Desloratadine is a potent, selective, histamine H_1-receptor that does not easily cross the blood–brain barrier believed to be nonsedating at therapeutic doses and consequently not affecting driving or psychomotor performance. The study compared the acute effects of desloratadine, relative to placebo and diphenhydramine (as an active control), on healthy subjects' performance using standard over-the-road driving tests as well as conventional psychometric tests. Eighteen men and women received a single dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo in each period of this randomized, double-blind, 3-way crossover study. Two hours post dosing, subjects operated a specially instrumented vehicle in tests lasting 90 minutes

designed to measure their ability to maintain constant speed and lateral position, follow another vehicle at constant distance, and respond to brake signals. Afterward, a full battery of psychometric tests was administered. There were no significant differences between desloratadine and placebo in standard deviation of lateral position (SDLP), the primary outcome variable; however, diphenhydramine treatment significantly increased SDLP. Brake Reaction Time was significantly faster after desloratadine than diphenhydramine. The majority of psychometric tests showed no significant differences among treatments and was concluded that Desloratadine administered in a therapeutical dose does not impair driving performance.

Chapter 3 This study investigated whether mefloquine (Lariam®), a quinoline antimalarial drug, affects psychomotor and actual driving performance when given in a prophylactic regimen, alone or in combination with alcohol. Forty male and female volunteers were randomly assigned in equal numbers to two groups. They were respectively treated for one month with mefloquine and placebo, double-blind. The drug was taken in 250 mg doses on the evenings of days 1, 2, 3, 8, 15, 22 and 29. Testing occurred on days 4, 23 and 30, the latter after repeated alcohol doses sufficient for sustaining blood concentration at about .35 mg/ml. Two actual driving tests were used for measuring prolonged (1h) road tracking and car following performance, respectively. Critical Flicker/Fusion Frequency (CFF), critical instability tracking and body sway were also measured in laboratory tests. mefloquine caused no significant impairment in any test at any time relative to placebo. Instead, mefloquine significantly improved road tracking performance on day 4. A significant interaction between prior treatment and alcohol was found in the body sway test; i.e. alcohol-induced changes were less after mefloquine than placebo. Both driving tests and the CFF test demonstrated their sensitivities by showing significant overall alcohol effects but did not discriminate between prior treatments. The conclusion was that mefloquine did not impair driving performance but rather improved it in the longer test to suggest that the drug possesses psycho stimulating properties.

Chapter 4 describes the results of a reanalysis of data from the previous published study comparing the effects of mefloquine and placebo on actual driving performance in a standardized test. The previous analysis showed that mefloquine produced significantly superior total-test driving performance on day 4 but on neither of the subsequent test-days. The present analysis revealed that mefloquine also significantly altered driving performance while the test was in progress on day 30. Specially, performance progressively deteriorated after the combination of placebo and alcohol but began the same way and then recovered after mefloquine and alcohol. The persistence of mefloquine's provigilance effect over a month of treatment was thereby demonstrated.

Chapter 5 describes the acute effect of doses of mizolastine 5,10,20 and 40 mg, an active control (clemastine 2 mc) and placebo on actual car driving and psychomotor performance. Twenty four healthy volunteers were treated according to a double blind 6-way cross-over design. In the driving test, lasting about 1 h, lateral position control and speed were continuously measured; the psychomotor test battery, lasting 50 minutes, comprised critical flicker-fusion frequency, critical instability tracking, divided attention, memory search and choice reaction time, and vigilance studies; and mood changes and possible adverse effects were rated on visual analogue scales. The results showed a dose-response relationship: Mizolastine 40 and 20 mg impaired driving and psychomotor performance. The effect of mizolastine 40 mg was strongly correlated with that of clemastine (r=0.78) and was comparable to the effect of a blood ethanol level of 0.8 ml^{-1}.Mozolastine 5 mg and 10 mg did not have a significant effect on driving performance and psychomotor tests. It was concluded that at a 10mg dose of mizolastine, the therapeutic dose, it could be considered a safe antihistamine, although individual adverse reactions cannot be completely ruled out.

Chapter 6 describes a laboratory study with Saripidem. This drug, an imidazopyridine with selective affinity for central benzodiazepine receptors (BZR) acts as a partial BZR agonist in animals. The pharmacodynamic effects of single oral doses of saripidem (10,20 and 30 mg) on psychomotor performance and memory in 20 healthy volunteers were compared to those of placebo and diazepam 10 mg. Psychomotor functions and sedation were assessed using both objective tests and visual analogue scales, before and up to 4.5 hours post dosing. Short term and long term memory of a word list was evaluated. The results indicated that saripidem 10 mg was devoid of any impairing effect. Saripidem 20 and 30 mg impaired psychomotor performance to the same extent from 0.5 - 1.5 hours and disturbed memory one hour post dosing but less pronounced than diazepam 10 mg. The results of the study suggest partial BZR agonistic properties of saripidem in man.

Chapter 7 describes a study in which children suffering from seasonal allergic rhinitis and matched normals were instructed on the use of a didactic computer simulation in a realistic classroom situation. Groups of atopic children received different treatments before instruction; i.e., sedating (diphenhydramine HCL) or nonsedating (loratadine) antihistamines or placebo. All returned after 2 weeks for an examination measuring factual and conceptual knowledge and the application of a learned strategy. Examination results showed large and consistent impairing effects of the allergic reaction on prior learning. Both the placebo and diphenhydramine groups learned significantly less than normal controls. The loratadine group's learning performance was superior to either of the other atopic groups' but still inferior to the normals'. Our conclusions are that the allergic reaction reduces

learning ability in children and that this effect is partially counteracted by treatment with loratadine and aggravated by diphenhydramine.

Chapter 8 describes a study to test the hypothesis that learning ability was impaired in patients with seasonal allergic rhinitis relative to untreated individuals and to evaluate a combination compound (acrivastine 8mg + pseudoephedrine 60 mg) for attenuation of the learning impairment in these patients. Sixty-seven young adults suffering from seasonal allergic rhinitis and 28 matched controls were trained on didactic simulation for three consecutive days. Atopic subjects were treated differentially during training according to a double-blind, randomized parallel group design with either diphenhydramine hydrochloride 50 mg, a combination compound (acrivastine 8 mg + pseudoephedrine 60 mg, A+P) or placebo, administered qd. After training, all atopic subjects were maintained on A+P treatment for 14 days at which time all groups returned for examination. Mean performance at the end of training was worse for all atopic subjects combined compared to normals. Subjects treated with diphenhydramine performed significantly worse than either normals or those treated with A+P. At the examination, the diphenhydramine group's performance differed significantly from those of the normal and A+P groups. The study supported previous findings that allergy symptoms reduce learning ability which is further reduced by diphenhydramine. Atopic subjects with allergies treated with acrivastine + pseudoephedrine learned as well as normal subject.

Chapter 9 describes a third study employing the didactic simulation paradigm to evaluate learning impairment in young patients suffering from SAR. The objectives of this study were: (1) to confirm that learning ability is impaired in paediatric patients with seasonal allergic rhinitis (SAR) relative to untreated normal children, and (2) to compare differences in learning ability between groups of patients suffering from SAR and treated with loratadine 10 mg, cetirizine 10 mg and placebo. The study followed an observer-blind, matched parallel-group design with a design-external, untreated, normal control group. A total of 93 atopic children, equally divided between treatment groups, and 30 normal controls, participated in the study. The results showed a significant difference between the normal groups simulation performance and that of all the atopic groups combined during Training. Similarly, the normal group's performance in the attention test was significantly better than that of all of the atopic groups combined. However, there were no significant differences between the performances of the three atopic groups on any test. The discrepancy with earlier studies was explained by different training regimens during the study.

Chapter 10 presents the general conclusions from the studies presented in previous chapters. Suggestions are made how future research could benefit from the studies carried out here.

As for the driving studies a development is described in which driving behavior is placed in a broader context and not restricted to 'performance'. Models of behavior that describe the role of risk taking and risk perception are likely to make a significant contribution to unravelling the complex behavior of driving an automobile and the unwanted side effects on it caused by psychoactive drugs. Some possible flaws in the 'over the road' driving test are discussed and possible solutions to overcome them are proposed. More specific the idea of letting the driver exert more executive control during the test is presented as a target for future development of the field.

The conclusion is reached that the role of pharmacopsychology has now been firmly established. Not only the amount of research carried out is still growing, but also the nature of it. Besides the unwanted or side-effects of psychoactive drugs more attention is also given to positive effects on behavior, as in counteracting negative effects of ADHD in children or ameliorating the effects of Alzheimer's disease in the elderly.

Epiloog

Woorden van dank zijn hier zeker op zijn plaats. Voor bijdragen aan de totstandkoming van de verschillende hoofdstukken zijn diverse mensen natuurlijk als auteur reeds vermeld, maar er zijn vele anderen die een bijdragen hebben geleverd om dit project tot een goed einde te brengen.

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Curriculum Vitae

Eric Vuurman werd op 14 december 1953 geboren te Hilversum. Reeds op jonge leeftijd verhuisde hij naar Rhodesië (het huidige Zimbabwe) en later naar Zuid Afrika waar een deel van de lagere schooltijd werd doorgebracht. De middelbare schooltijd werd verdeeld over Breda, Johannesburg en ten slotte Oudenbosch waar in 1974 het Atheneum-B diploma werd behaald aan het Thomas More College. De daarop aansluitende studie Psychologie aan de Katholieke Hogeschool Tilburg werd in 1976 gedurende twee jaar onderbroken voor een tewerkstelling als Dienstweigeraar bij de Staatsdrukkerij in Den Haag en het Arbeidsbureau te Eindhoven Het doctoraal diploma werd in1984 behaald met als hoofdvakken Fysiologische Psychologie en Functieleer. Van 1984 tot 1989 was hij werkzaam als onderzoeker op het *Instituut voor Revalidatievraagstukken* te Hoensbroek. Daarna volgde een aanstelling als onderzoeker bij het *Instituut voor Geneesmiddelen, Veiligheid en Gedrag*, dat later overging in het *Instituut voor Humane Psychofarmacologie*. Vanaf 1994 is hij als Universitair Docent verbonden aan de Universiteit Maastricht, vakgroep neuropsychologie.