Sedating and stimulating antihistamines: old problems and new insights

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**SEDATING AND STIMULATING
ANTIHISTAMINES;
OLD PROBLEMS AND NEW INSIGHTS**

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CONTENTS

Chapter 1	General introduction	9
Chapter 2	A dose ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo	23
Chapter 3	Repeated-dose effects of mequitazine, cetirizine and dexchlorpheniramine on driving and psychomotor performance	45
Chapter 4	Stimulating effects of H1-antagonists	61
Chapter 5	Stimulating effects of fexofenadine under high workload conditions. A combined neurophysiological and behavioral approach	81
Chapter 6	Effects of a high dose of fexofenadine on cognitive function and motor impulsivity	101
Chapter 7	Fexofenadine's potential to inhibit dopamine reuptake in healthy volunteers: a SPECT study	115
Chapter 8	General discussion	125
Summary		137
Samenvatting		145
Dankwoord		153
Curriculum Vitae		159
Publications		163

General introduction

CHAPTER 1

As much as 20% to 30% of the population is estimated to suffer from allergic conditions such as allergic rhinitis, hay fever or urticaria (Nathan, Meltzer, Selner, & Storms, 1997; Steerenberg et al., 2000). Allergic conditions do not only affect the patients' health but also have a detrimental impact on a patient's quality of life (Meltzer, Nathan, Selner, & Storms, 1997; Kremer, den Hartog, & Jolles, 2002). Allergy patients may experience impairment in their work, their sleep, and their social life (Meltzer et al., 1997; Craig, McCann, Gurevich, & Davies, 2004). Due to their condition, allergy patients also pay more visits to physicians and use more medication, which creates an extra financial load. An American survey estimated the mean cost per patient per year to be \$56 for prescription medication, and another \$56 for nonprescription medication (Storms, Meltzer, Nathan, & Selner, 1997). Oral antihistamines are the first-line medications for treating allergic conditions and in 2002, 2.5 million prescriptions for oral antihistamines were processed by pharmacists in The Netherlands, with a total turnover of 50 million euros (Stichting Farmaceutische Kengetallen, 2003). The impact of this condition on the health care system and society is consequently significant (Blais, 2000; Burton, Conti, Chen, Schultz, & Edington, 2001; Weiss, Haus, & Iikura, 2004). The total cost of allergies for society does not only include the direct costs of treatment, but also indirect costs due to loss of work productivity and absenteeism.

The most important concern of patients with allergies is to get quick relief from annoying symptoms, such as itching, sneezing, teary eyes or a running nose, without experiencing undesirable side effects. Antihistamines or H1-antagonists are highly effective and act fast in relieving the symptoms in most patients. However, the majority of patients report side effects when using these antihistamines. The most frequently reported side effects include gastro-intestinal complaints, dry mouth but most importantly drowsiness. This drowsiness can be so serious that it affects patients' daily activities, like studying, working or car driving. So, although there is a relief of symptoms, the inconvenience of adverse effects may be more troubling than suffering from the untreated condition and eventually patients may prefer to stop the treatment because of the discomfort.

It has been repeatedly demonstrated that there is a clear relationship between antihistamines and sedation or drowsiness. However, it has also been demonstrated that large differences exist between individual antihistamines; some causing excessive sedation, some causing no sedation at all and some even producing activation. The present thesis focuses on pharmacodynamic differences between sedating antihistamines and tries to assess the pharmacological mechanism which distinguishes stimulating antihistamines from sedating antihistamines.

The present chapter gives an introduction on how antihistamines bring about their therapeutic action and how they act in the brain, as well as the peripheral and central function of histamine. Furthermore, this chapter will introduce and evaluate the classification of antihistamines into first and second generation antihistamines. At the end, the aims and outlines of this dissertation are outlined.

HISTAMINE

Histamine is an endogenous substance which is released when an allergic person comes into contact with an allergen. The first exposure of an allergen to the immune system causes IgE antibodies to be secreted and these attach to the cell surface of mast cells. Mast cells occur

in all body tissues but particularly in areas which are typical sites of allergic reactions, such as the skin, nose, throat, lungs, and the gastrointestinal tract. At a second encounter with the allergen, the allergen binds to the IgE antibodies, causing the mast cells to release histamine and other chemicals. Mast cells contain large amounts of histamine, and when released this causes the typical symptoms of allergies like rashes, a runny nose and teary eyes (Feldman, Meyer, & Quenzer, 1997; van Wijk & Vaessen, 2003).

Histamine also acts as a neurotransmitter in the CNS and is involved in several central processes such as arousal, cognition and homeostatic systems (Brown, Stevens, & Haas, 2001). Histamine-releasing neurons are located exclusively in the tuberomammillary nucleus of the posterior hypothalamus, a region which has repeatedly been demonstrated to be important in wakefulness (Lin, 2000; Saper, Chou, & Scammell, 2001). Histaminergic neurons project to almost all regions of the brain, especially to areas involved in sleep-wake control, i.e. the cortex, thalamus, preoptic/anterior hypothalamus (Panula, Yang, & Costa, 1984; Lin, 2000). Impairing neuronal histamine transmission causes increases in sleep while enhancement of histaminergic neurotransmission increases wakefulness (Monti et al., 1991; Lin, 2000). Other monoamine neurotransmitters, such as serotonin and noradrenaline are also important factors in the control of sleep and wakefulness. Together with histamine neurons, these neurons have been found to fire actively during wakefulness and stop firing during REM sleep (Saper et al., 2001).

At present, there are three types of histamine receptors identified; H1, H2 and H3. All three receptors have been found in the brain and periphery (Hill et al., 1997). H1-receptors are the main target for treatment of allergies and are found in several peripheral tissues, including the smooth muscle from the airways and the gastrointestinal tract. Peripheral H2-receptors are mainly found in gastric cells and have a potent effect on gastric acid secretion. The recently discovered H3-receptor has also been found peripherally where it influences peripheral neurotransmission (e.g. in the gastrointestinal tract and the cardiovascular system). The central H3-receptor is an auto- and heteroreceptor, in that it influences its own neurotransmission as well as that of other neurotransmitter. By blocking the H3-receptor, H3-antagonists cause an increase in histamine levels and this has been related to improvements in cognitive functions such as learning and memory in animals (Prast, Argyriou, & Philippu, 1996; Ligneau et al., 1998).

ANTIHISTAMINES

Antihistamines' main target for achieving their therapeutic effect is the peripheral H1 histamine receptor. Most antihistamines are selective for the H1-receptors and have little effect on the H2 or H3 histamine receptors. Besides H1-receptor blockade, nearly all antihistamines produce weak to pronounced blockade of cholinergic, serotonergic and adrenergic neurotransmission (Snyder & Snowman, 1987; Simons, 1989).

The group of antihistamines includes chemically different compounds which all share the pharmacological capacity to prevent histamine from binding at its receptor and consequently diminish the symptoms of allergies. Most antihistamines are rapidly absorbed after oral administration and generally give relief of symptoms within 1 to 2 hours. The elimination half-life of antihistamines varies considerably, ranging from a couple of hours to a few days (Simons, Simons, Chung, & Yeh, 1987; Gonzalez & Estes, 1998; Slater, Zechnich, & Haxby, 1999; Golightly & Greos, 2005).

A distinction between first and second generation antihistamines is generally made. This division was initially made to distinguish sedating from non-sedating antihistamines.

THE FIRST GENERATION

First generation antihistamines readily cross the blood brain barrier and bind to H₁-receptors in the CNS (Quach, Duchemin, Rose, & Schwartz, 1979; Nicholson et al., 1991). As a result, these drugs cause somnolence and various studies demonstrated a correlation between the amount of H₁-occupancy and the sedative properties of antihistamines (Rose, Quach, Llorens, & Schwartz, 1982; Tagawa et al., 2001; Tashiro et al., 2002). The sedating effect of first generation antihistamines is such that some of them are even prescribed as sleeping aids. But of course, when used as a treatment for allergies, the sedative side effects are unwanted, especially when they interfere with patient's daily functioning. Over the years, it has become evident that the use of first generation antihistamines is related to a decrease in work productivity (Burton et al., 2001), increased absenteeism from work or school (McLoughlin et al., 1983; McMenamin, 1994) and also with an increased risk at traffic accidents (Cimbura, Lucas, Bennett, Warren, & Simpson, 1982; Ray, Fought, & Decker, 1992; Leveille et al., 1994) and occupational injuries (Gilmore, Alexander, Mueller, & Rivara, 1996).

First generation antihistamines include drugs such as diphenhydramine, clemastine, chlorpheniramine and triprolidine, and are in most countries available without a prescription (over the counter). Because they are freely available and usually inexpensive, there are still a lot of patients who use these sedating drugs, even though less sedating antihistamines are now available.

THE SECOND GENERATION

In the 1980's, new antihistamines were developed, which were less sedating. These second generation antihistamines are as effective as the first generation in treating allergic rhinitis. It has been suggested that these drugs are less sedating because they do not cross the blood brain barrier as easily (Passalacqua et al., 1996; Tashiro et al., 2002). They are often called 'non-sedating' antihistamines, but several studies have demonstrated that this term is not fully justified. Although they are clearly less sedating than first generation antihistamines, patients occasionally report sedative side effects when treated with second generation antihistamines, especially when the therapeutic dose is exceeded (Mann, Pearce, Dunn, & Shakir, 2000; Casale et al., 2003). Experimental studies have also demonstrated that this generation of antihistamines has the potential to impair subjects' performance on several tasks such as cognitive, attention and driving tasks (O'Hanlon & Ramaekers, 1995; Bender, Berning, Dudden, Milgrom, & Tran, 2003).

There is a wide variety in the chemical structure of second generation antihistamines available, and every now and then, new drugs are developed and introduced on the market. One second generation antihistamine that is frequently used, and is discussed in this dissertation, is cetirizine. Cetirizine has been reported to be highly effective in reducing patients' symptoms. The reports on its sedative effects are often inconsistent, however. Patients report drowsiness after treatment with cetirizine in most studies (Meltzer, Weiler, & Widlitz, 1996; Mann et al., 2000; Salmun et al., 2000) but not in others (Gengo,

Dabronzo, Yurchak, Love, & Miller, 1987; Gengo & Gabos, 1987). Also objective measures result in conflicting findings for cetirizine; with most studies reporting that cetirizine had no impairing effect on psychomotor performance, cognition and driving performance (Seidel, Cohen, Bliwise, & Dement, 1987; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992; Walsh, Muehlbach, & Schweitzer, 1992; Schweitzer, Muehlbach, & Walsh, 1994; Hindmarch, Johnson, Meadows, Kirkpatrick, & Shamsi, 2001; Shamsi, Kimber, & Hindmarch, 2001), while others did find that these functions were impaired (Ramaekers, Uiterwijk, & O'Hanlon, 1992; Nicholson & Turner, 1998; Vermeeren, Ramaekers, & O'Hanlon, 2002). Other second generation antihistamines such as acrivastine, terfenadine, loratadine, ebastine and mizolastine have all been tested frequently and have shown to cause impairment but mostly only after higher than their therapeutic dose (Mann et al., 2000; Bender et al., 2003).

RECENT DEVELOPMENTS

The group of antihistamines consists of a wide variety of compounds with different pharmacokinetic and pharmacodynamic properties. As described above, the most often used classification is based on the presence or absence of sedation. However, it has been repeatedly demonstrated that this classification is not that clear-cut.

Recently, new antihistamines have been developed from existing compounds. These new antihistamines, fexofenadine, levocetirizine and desloratadine are the active metabolites of terfenadine, cetirizine and loratadine and were found to be as efficient as other antihistamines. Up till now, no signs of impairment have been demonstrated for these antihistamines, even after higher than their therapeutic dose (Hindmarch, Shamsi, Stanley, & Fairweather, 1999; Nicholson, Stone, Turner, & Mills, 2000; Weiler et al., 2000; Hindmarch et al., 2001; Bower et al., 2003; Monroe et al., 2003; Verster, de Weert et al., 2003; Verster, Volkerts et al., 2003; Valk, Van Roon, Simons, & Rikken, 2004). In some studies, fexofenadine and desloratadine even had mild stimulating effects (Vermeeren & O'Hanlon, 1998; Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004). Together, these findings suggest that the active metabolites are less sedating than the parent compounds.

Because fexofenadine, desloratadine and levocetirizine are relatively free of sedative effects, they might be preferred by patients over first and probably also over second generation antihistamines. These antihistamines are not yet classified as a distinctive group, but some researchers have suggested to group them in a new category; the third generation antihistamines.

AIM OF THE DISSERTATION

This dissertation focuses on the psychoactive effects of antihistamines. The most often reported psychoactive effect of antihistamines is sedation or drowsiness. These sedating effects of antihistamines are consistent with the role of histamine in arousal processes and by blocking H1-receptors, antihistamines interact with these processes. In order to get a full view of the sedating potential of antihistamines, they need to be tested extensively using sensitive methods. In addition, it is necessary to examine whether effects are dose dependent and persistent over time.

Stimulating effects of H1-antagonists are less well known and seem in conflict with the

idea that blockade of the histamine receptors causes sedation. Nonetheless, several studies have reported stimulating effects of antihistamines such as terfenadine and fexofenadine. In the present dissertation, reports of stimulating effects of antihistamines are collected and reviewed. Furthermore, high workload tasks and electrophysiological measures are used to find further evidence of a stimulating effect of antihistamines. Eventually, the pharmacological mechanism responsible for the stimulating effect of antihistamines is explored.

OUTLINE OF THE DISSERTATION

In *chapter 2* and *chapter 3*, it is investigated whether a so-called 'non-sedating' antihistamine does affect cognitive function and actual driving performance as compared to placebo. *Chapter 2*, in addition, tries to answer the question whether this antihistamine's sedating effects are dose dependent, while *chapter 3* examines if behavioral tolerance occurs after repeated dosing.

In *chapter 4*, all the evidence of antihistamines with stimulating effects is gathered and reviewed. Numerous studies demonstrating significant and non-significant better performance after treatment with fexofenadine, terfenadine, ebastine or desloratadine, were discussed. This chapter also explores several possible pharmacological mechanisms that could explain the stimulating effect of antihistamines.

In *chapter 5* it is hypothesized that stimulating effects of antihistamines are more prominent under high workload conditions and after high doses. Therefore, the effects of two doses of fexofenadine in healthy subjects are investigated in cognitive tasks with increasing workloads. In addition, event related potentials are measured during task performance in order to see if the underlying neurophysiological processes show evidence of stimulation.

In *chapter 6*, the hypothesis that a high dose of fexofenadine improves healthy subjects' psychomotor performance and affects impulsivity control is investigated. This chapter describes a between subject design study performed to compare the effects of 360 mg of fexofenadine with placebo.

In *chapter 7*, a hypothesis about the cause of the stimulating effect of fexofenadine is investigated. Using SPECT-scans, it is investigated whether fexofenadine causes a blocking of the dopamine transporter in the striatum of healthy volunteers.

In *chapter 8* a few general issues concerning research into antihistamines are discussed. In addition, the implications of the findings of this dissertation are put in a broader perspective and suggestions for further research are proposed.

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A dose-ranging study of the effects of mequitazine on actual driving, memory and psychomotor performance as compared to dexchlorpheniramine, cetirizine and placebo

CHAPTER 2

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ABSTRACT

Background: Mequitazine is a so called “non-sedative” second generation antihistamine even though it has never been firmly established that this drug’s sedative potential actually differs from that of the “sedative” first generation antihistamines.

Objective: The present study compares the sedative effects of 3 doses of mequitazine on actual driving, psychomotor performance and memory with those of a first and a second generation antihistamine.

Methods: 18 healthy volunteers received on separate days a single dose of 5, 10 and 15 mg mequitazine, 10 mg cetirizine, 6 mg dexchlorpheniramine and placebo. Drug effects were assessed using two actual driving tests (highway driving test and car following test), cognitive and psychometric tests (tracking, divided attention, memory, reasoning and CFF), pupil size and questionnaires.

Results: Highway driving data revealed an overall effect of Treatment on the Standard Deviation of Lateral Position (SDLP). Dexchlorpheniramine impaired driving performance as indicated by a significant rise in SDLP. Mequitazine significantly increased SDLP in a dose related manner, but the separate dose effects failed to reach statistical significance. Divided attention performance was also affected by Treatment. Reaction time (RT) during mequitazine treatments increased in a dose related manner and significantly differed from placebo at the highest dose. Subjects reported to be less alert after treatment with dexchlorpheniramine. Cetirizine did not affect performance in any of the tasks.

Conclusion: It was concluded that mequitazine is mildly sedating. The effects of mequitazine are comparable to those of other 2nd generation antihistamines, in that it causes mild driving impairment, particularly at higher doses.

INTRODUCTION

Histamine is an endogenous substance that is stored and released by mast cells in peripheral tissues. When histamine is released, it acts on various tissues, causing a variety of allergic reactions in hypersensitive people, e.g. allergic rhinitis, conjunctivitis and urticaria.

Histamine also functions as a neurotransmitter in the brain. The histaminergic neurons are primarily located in a small region of the posterior hypothalamus, called the tuberomammillary nucleus (Panula et al., 2000). These neurons project to various parts in the brain, primarily to the hypothalamus, medial septum and amygdala (Steinbusch, 1991; Panula et al., 2000). Histamine acts through the activation of three types of histamine receptors, H1, H2 and H3, and is involved in several brain functions, e.g. arousal and the sleep-wake cycle (Onodera, Yamatodani, Watanabe, & Wada, 1994). Several neurochemical studies have shown that the activity of the central histaminergic system increases during the active phase of rodents, cats and monkeys and decreases while asleep (Yamatodani et al., 1991; Onoe et al., 1992).

Antihistamines cause a relief of allergic symptoms by blocking peripheral histamine H1-receptors. However, some antihistamines are also able to cross the blood-brain barrier and block histaminergic and other neurotransmitter systems (e.g. serotonin, choline, noradrenaline) in the brain, and as a consequence produce sleepiness, fatigue and sedation (Snyder & Snowman, 1987; Passalacqua et al., 1996). These are considered to cause cognitive and psychomotor impairment observed in a range of studies on antihistamine effects on performance (Rombaut & Hindmarch, 1994; O'Hanlon & Ramaekers, 1995; Kay, 2000). In order to reduce the sedative potential of antihistamines, a host of research evolved devoted to developing novel antihistamines that do not cross the blood brain barrier, the so called 2nd generation antihistamines.

Terfenadine, astemizole and mequitazine were among the first compounds to be introduced as non-sedating 2nd generation antihistamines in the 1980's. Many studies showed that therapeutic doses of these and subsequent drugs did not cause sedation (Gervais, Gervais, De Beule, & Van der Bijl, 1975; Blamoutier, 1978; Muler & Blum, 1978; Van Wauwe et al., 1981; Woodward & Munro, 1982; Hindmarch & Easton, 1986). Consequently it was suggested that 2nd generation antihistamines are not able to cross the blood-brain barrier and do not interact with histamine brain receptors. However, the difference between 1st and 2nd generation antihistamines turned out to be less distinct. When given in higher doses, most 2nd generation antihistamines produced mild to moderate sedation and performance impairment as measured in tests of actual driving or psychomotor skills (O'Hanlon & Ramaekers, 1995; Shamsi & Hindmarch, 2000), suggesting that these drugs do cross the blood brain barrier. The latter notion was definitively confirmed in imaging studies showing that 2nd generation bind to H1-receptors in the brain in a dose related manner (Yanai, Okamura, Tagawa, Itoh, & Watanabe, 1999).

Mequitazine is a synthetic antihistamine selective for H1-receptors. In patients treated with mequitazine over longer periods, some minor anticholinergic effects (dry mouth, blurred vision) have also been reported (Beaumont, Hugonot, & Hugonot, 1986), indicating a small affinity for cholinergic receptors as well. Though mequitazine was one of the earliest 2nd generation antihistamines on the market, only few comparative studies were performed to actually establish its sedative properties. These studies generally demonstrated that therapeutic doses of mequitazine 5-10 mg produced no or less psychomotor impairment and subjective drowsiness as compared to 1st generation antihistamines

Chapter 2

(Gervais et al., 1975; Blamoutier, 1978; Muler & Blum, 1978; Caille, 1979; Hindmarch & Easton, 1986). Most studies, however, used only subjective tests, small sample sizes or a specific population.

The aim of the current study was to assess the dose related effects of mequitazine on cognition, psychomotor function and driving performance, and to compare them to those of a well established 1st and 2nd generation antihistamine, i.e. dexchlorpheniramine and cetirizine respectively. It was expected that mequitazine would not be completely free of sedative effects but that it would produce mild and dose related performance impairment.

MATERIALS AND METHODS

Subjects

Eighteen healthy volunteers (9 males and 9 females), aged between 21 and 44 years were recruited by means of newspaper advertisements. Subjects were first screened using a medical history and a driving experience questionnaire. Each qualified subject underwent a physical examination, an electrocardiogram was made and a blood sample was taken. Mean (SD) age was 32.5 (8.29) years and mean weight (SD) was 76.1 (7.78) kg.

Inclusion criteria were possession of a valid driver's license for at least 3 years, driving experience of at least 5000 km per year and being healthy according to the physical examination. Exclusion criteria were: history of major medical or psychiatric disorder, any non-corrected visual or psychomotor defect, unusual sensitivity to antihistamines, drug abuse, chronic use of medication except contraceptives, using no efficient contraception, pregnancy and lactation. After having received all necessary information, all participants gave their written consent. The study was approved by the Ethics committee of Maastricht University and subsequently carried out in accordance with the World Medical Associations Declaration of Helsinki (Edinburgh, 2000).

Drug administration

On separate days, participants received a single oral dose of each of the following: 5, 10 and 15 mg mequitazine; 10 mg cetirizine; 6 mg dexchlorpheniramine (repetabs) and placebo. Drugs and placebo were administered on 6 separate days, according to a placebo-controlled, double blind, 6-way latin square design. The washout period between treatment days was at least 7 days. Drugs and placebo were administered by means of a double dummy technique because of pharmacokinetic differences between individual drugs. Mequitazine and dexchlorpheniramine reach T_{max} at approximately the same time (i.e. between 3-4 hours) but cetirizine concentrations are already maximal at 1 hr after administration (Wood, John, Chasseaud, Yeh, & Chung, 1987; Ylitalo et al., 1989; Rimmer & Church, 1990; CVZ, 1999). Drugs and placebo were administered according to the following schedule in order to fixate time of testing around T_{max} in every treatment condition. In the mequitazine and dexchlorpheniramine conditions the active drugs were given at 11.00h and placebo at 13.00h; in the cetirizine condition placebo was given at 11.00h and the active drug at 13.00h. In the placebo condition, placebo was given at both times of administration.

Procedure

Subjects were individually trained one or two weeks prior to their first treatment condition to perform driving, cognitive and psychometric tests. Subjects were prohibited from consuming alcohol for 24h before testing. On test-days, subjects consumed breakfast at home. Consumption of caffeine containing beverages was prohibited and smoking was prohibited 30 minutes prior and during testing. Subjects were brought to the test site where drugs were administered. At 12.00h they received a standardized meal. The highway-driving test started at 14.00h and the car-following test at 15.00h or 15.30h. Psychometric tests were performed at 16.30h. At the end of the test day, participants were transported back home.

Highway-driving test

During the highway-driving test (O'Hanlon, Haak, Blaauw, & Riemersma, 1982), the subject's task is to operate a specially instrumented vehicle over a distance of 100km (61miles) on a primary highway. A licensed driving instructor, who can intervene if necessary by using duplicate controls, accompanies the subject during all tests. The subject is instructed to attempt to maintain a constant speed of 95km (58 miles) per hour and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. The subject is allowed to deviate from this procedure in order to pass slower vehicles. Halfway through the circuit, the subject drives off the highway and re-enters, travelling in the opposite direction. The vehicle's speed and lateral position relative to the left lane delineation are continuously recorded using an electro-optical device mounted at the rear of the car. These signals are digitally sampled at a rate of 4 Hz and stored on a computer disk onboard. The offline editing routine involves removal of all data segments that revealed signal loss, disturbance or overtaking manoeuvres. The remaining data are used to calculate means and standard deviations for lateral position (SDLP) and speed. The primary measure is the standard deviation of lateral position, which measures the continuous road tracking error. SDLP is a very reliable characteristic of individual driving performance: the test-retest reliability coefficient for unmedicated young and middle-aged drivers is $r = 0.85$. It has also proven sensitive to many sedating agents, including alcohol in blood concentrations (BAC) as low as 0.35 mg/ml (Ramaekers, Uiterwijk, & O'Hanlon, 1992; Vuurman et al., 1996).

Car-following test

The car-following test (Brookhuis, De Vries, & De Waard, 1993; Ramaekers & O'Hanlon, 1994; Ramaekers et al., 2002) involves the use of two vehicles driving behind each other on a secondary highway. The subject controls the following vehicle, while the investigator controls the leading car. A licensed driving instructor accompanies the subject in order to intervene when necessary. During the test the investigator in the leading car initiates sinusoidal speed changes. Between deceleration manoeuvres, the investigator in the leading car randomly lights up the break lights of his car while the speed of the car remains constant. Subjects are instructed to maintain a 15-30m distance to the leading car and to react as fast as possible to the break lights by removing his/her foot from the speed pedal. Test duration is about 25 minutes.

Phase delay, converted into a measure of time to speed adaptation (in ms), and break reaction time (in ms), are the primary outcome variables of this car-following test. Headway (in m) and standard deviation of headway (in m) are secondary parameters.

Chapter 2

Cognitive and Psychometric tests

• *Word Learning Task*

In this task (Rey, 1964), subjects are shown 15 words on a computer screen. The words appear on the screen for 2 seconds, one by one. All words are in Dutch, the native language of all subjects. Subjects are instructed to try and memorize these words, and to name as many as they can at the end of the list. This procedure is repeated five times. The highest score in these trials is the immediate recall score. After at least 30 minutes, the subject is asked to name as many words as he/she can, and this score is the delayed recall score. The number of words recalled in the delayed recall compared to the immediate recall is defined as the relative recall score. Finally, a list of 30 words is presented on the computer screen, comprising the original 15 words and 15 new words. The subject has to press a button when he/she recognizes a word that belonged to the original list of words. The recognition score comprises of the number of correct recognitions and correct rejections. Subjects were presented a different version of the task on each test-day.

• *Critical Tracking Task*

During this task the subject controls a triangle, which is displayed on a horizontal axis on a computer screen, by moving a joystick. An error signal causes the triangle to become increasingly unstable and therefore it tends to diverge from the centre of the axis. The subject has to make compensatory movements to null the error in order to keep the triangle in the middle. As the frequency of cursor deviations increases as a stochastic, linear function of time, the subject is required to make compensatory movements with a progressively higher frequency. Eventually his response frequency lags the error signal by 180°. At that point, the subject's response adds to, rather than subtracts from, the error and control is lost. The frequency at which control is lost is called the 'critical frequency' or ' λ_c ' (rad/sec). The test includes five trails; the average score is calculated after removing the highest and the lowest scores, and is the primary variable in this test (Jex, McDonnell, & Phatak, 1966).

• *Divided Attention Task*

In the Divided Attention Task (Moskowitz, 1973), the subject performs two tasks simultaneously. Firstly, the subject has to perform the same tracking task as described above, with the difficulty level fixed at 50% of his/her maximum capacity. Tracking error is measured as the difference in mm between the position of the cursor and the midpoint of the scale. The absolute mean tracking error over the entire test is taken as the final score in this subtask.

As a secondary task, the subject has to monitor 24 single-digit numbers (0-9), which are present in the four corners of the display. These numbers change asynchronously every 5 seconds. Inter-target time varies between 5 and 25 seconds. The subject reacts to the target number '2' by removing his foot as fast as possible from a pedal switch. Reaction times (msec) are recorded, and the mean reaction time is the variable in this subtask.

• *Syntactic Reasoning Task*

The Syntactic Reasoning Task measures higher mental processes using sentences of various levels of syntactic complexity (Baddeley, 1968). A sentence describing the order of the letters A and B is presented on the computer display, e.g. "A follows B". Each sentence is immediately followed by a combination of the two letters. The subject has to decide whether the order of the letters is correct according to the sentence and responds by pressing

the corresponding button as fast as possible. Thirty-two sentences are presented and in half of the cases the letter combination is correct according to the sentence. The level of difficulty of the sentences is varied, ranging from simple active sentences to more complicated sentences using passives, negatives and combinations. Number of correct responses and reaction times (msec) are the primary variables of this task.

• *Critical Flicker Fusion test*

If a light is repeatedly turned on and off, it is perceived as flickering. When it flickers at increasing frequency, it will finally appear to fuse into a continuous light even though it is actually still moving. The threshold, at which it is perceived as a steady light source, is called the Critical Flicker Fusion frequency (CFF). The Critical Flicker Fusion test is often used in psychopharmacology studies, and is seen as a measure of central nervous system arousal (Curran, 1990). CFF is sensitive to changes in pupil diameter, and pupil size is affected by neurotransmitters as serotonin, noradrenaline and acetylcholine (Sokolski, Nguyen, & DeMet, 2000; Schmitt, Riedel, Vuurman, Kruizinga, & Ramaekers, 2002). Therefore it is necessary to control for drug induced variations in pupil size by using an artificial pupil (Smith & Misiak, 1976).

In order to test if antihistamines have an effect on pupil size, pupil diameter is measured using a Remote Eyetracking Device (SensoMotoric Instruments, Berlin, Germany).

Subjective measures

Subjective measures were used on each test day to assess sleep quality, effect of treatments on driving and mood. In order to assess the quality of sleep of the past night, subject filled out the Groningen Sleep Quality Scale before treatment (Mulder-Hajonides van der Meulen, 1981). This questionnaire includes specific questions about the total amount of sleep, number of awakens and time needed to fall asleep, and 14 yes/no questions to score the number of complaints, ranging from 0 (good sleep) to 14 (the worst possible). Subjects predicted their driving ability prior to the highway driving test and subjective driving performance after completion of the test, using visual analogue scales (100mm). Before the psychometric tests, subjective evaluation of mood was assessed by means of a 16-item mood scale from which three factors are derived: alertness, contentedness and calmness (Bond & Lader, 1974). Mood scales were subjected to a square root transformation before entering statistical analyses to correct for positively skewed distributions.

STATISTICAL ANALYSIS

A power calculation revealed that a sample of 18 subjects was sufficient for providing a power of more than 90% for detecting a critical mean difference between drug and placebo of 2 cm in SDLP. Psychometric and driving parameters were analysed using an ANOVA with Subject, Treatment and Period as factors. Subsequently, analyses for comparing treatments with placebo were conducted, using simple contrasts with sequential Bonferonni correction. A polynomial contrast was used to test the significance of linear trends over the administered doses of mequitazine; 0, 5, 10 and 15 mg. The effects of gender on driving performance were analysed, using a model including Treatment, Period, Gender and Gender by Treatment. The Groningen Sleep Questionnaire and subjective driving ratings were not normally distributed and analysed by means of the non-parametric Friedman test to detect an overall difference between Treatments. These were followed by Wilcoxon's signed-

Chapter 2

	Mean $\pm$ SEM per treatment		
	Pla	Meq5	Meq10
<i>Actual driving tests</i>			
Standard Deviation of Lateral Position (cm)	19.7 $\pm$ 0.8 ^b	19.3 $\pm$ 0.8 ^b	20.7 $\pm$ 1.0 ^b
Standard Deviation of Speed (km/h)	1.95 $\pm$ 0.1	1.99 $\pm$ 0.1	1.97 $\pm$ 0.1
Break Reaction Time (msec)	482 $\pm$ 18	463 $\pm$ 17	490 $\pm$ 19
Time to Speed Adaptation (sec)	1.94 $\pm$ 0.3	1.80 $\pm$ 0.2	1.67 $\pm$ 0.2
Standard Deviation of Headway (m)	6.58 $\pm$ 1.1	5.89 $\pm$ 1.4	5.92 $\pm$ 0.9
<i>Critical Tracking task</i>			
Critical frequency (rad/sec)	3.81 $\pm$ 0.3	3.78 $\pm$ 0.3	3.72 $\pm$ 0.3
<i>Divided attention task</i>			
Tracking error (mm)	20.6 $\pm$ 1.0	21.4 $\pm$ 1.3	21.9 $\pm$ 1.3
Reaction time (msec)	1696 $\pm$ 67 ^b	1850 $\pm$ 98 ^b	1858 $\pm$ 105 ^b
<i>Word learning task</i>			
Immediate recall (#)	14.0 $\pm$ 0.3	13.7 $\pm$ 0.4	13.7 $\pm$ 0.3
Delayed recall (#)	12.3 $\pm$ 0.6	11.8 $\pm$ 0.6	11.6 $\pm$ 0.6
Relative recall (%)	87.5 $\pm$ 3.3	86.4 $\pm$ 3.4	84.0 $\pm$ 3.5
Recognition (#)	28.4 $\pm$ 0.3	28.6 $\pm$ 0.3	28.3 $\pm$ 0.4
Reaction time (msec)	678 $\pm$ 15	680 $\pm$ 14	688 $\pm$ 20
<i>Syntactic reasoning</i>			
Correct responses (#)	22.3 $\pm$ 1.5	23.3 $\pm$ 1.7	23.2 $\pm$ 1.4
Reaction time (msec)	1562 $\pm$ 96	1519 $\pm$ 107	1540 $\pm$ 110
<i>Critical Flicker Fusion (Hz)</i>	19.9 $\pm$ 0.7	19.5 $\pm$ 0.6	19.4 $\pm$ 0.7
<i>Pupil size (mm)</i>	5.20 $\pm$ 0.3	5.67 $\pm$ 0.2	5.56 $\pm$ 0.2

Table 1. Summary of results from the driving, psychomotor and cognitive tests. Treatments are placebo (PLA), mequitazine 5 mg (MEQ5), mequitazine 10 mg (MEQ10), mequitazine 15 mg (MEQ15), cetirizine (CET) and dexchlorpheniramine (DEX). ^a Drug- placebo differences after sequential Bonferroni correction with $p < .01$. ^b polynomial effect $p < .05$; NS: not significant.

ranked test to compare the effects of drugs and placebo. All statistical tests were conducted using SPSS (version 10.0).

RESULTS

Missing Data

In the car-following test, headway data of four subjects was partly lost due to technical problems on five separate occasions. In addition, no data from the syntactical reasoning test was collected on two occasions because of technical malfunctions. Subjects with incomplete data records were not entered into statistical analyses of standard deviation of headway (SDH) and all dependent measures of the syntactical reasoning task.

Meq15	Mean $\pm$ SEM per treatment		Treatment effect		
	Cet	Dex	F	Df	p
20.8 $\pm$ 1.0 ^b	19.1 $\pm$ 0.8	22.1 $\pm$ 1.0 ^a	6.32	5,80	<.001
2.08 $\pm$ 0.1	1.89 $\pm$ 0.1	2.12 $\pm$ 0.1	1.67	5,80	NS
483 $\pm$ 15	506 $\pm$ 22	478 $\pm$ 21	0.90	5,80	NS
1.93 $\pm$ 0.2	2.18 $\pm$ 0.2	1.86 $\pm$ 0.1	1.60	5,80	NS
6.14 $\pm$ 1.2	4.48 $\pm$ 0.7	5.94 $\pm$ 1.2	0.44	5,60	NS
3.68 $\pm$ 0.3	3.79 $\pm$ 0.3	3.89 $\pm$ 0.2	1.15	5,80	NS
22.0 $\pm$ 1.4	21.0 $\pm$ 1.5	22.1 $\pm$ 1.2	0.86	5,80	NS
1958 $\pm$ 84 ^{ab}	1804 $\pm$ 102	1784 $\pm$ 76	3.13	5,80	.013
13.8 $\pm$ 0.3	13.7 $\pm$ 0.3	13.9 $\pm$ 0.3	0.46	5,80	NS
11.6 $\pm$ 0.6	12.2 $\pm$ 0.5	12.1 $\pm$ 0.6	0.69	5,80	NS
83.5 $\pm$ 3.8	88.3 $\pm$ 3.0	87.1 $\pm$ 3.5	0.48	5,80	NS
28.3 $\pm$ 0.3	28.7 $\pm$ 0.3	28.7 $\pm$ 0.2	0.62	5,80	NS
691 $\pm$ 16	687 $\pm$ 16	681 $\pm$ 14	0.28	5,80	NS
23.6 $\pm$ 1.7	23.5 $\pm$ 1.4	22.6 $\pm$ 1.7	0.65	5,70	NS
1572 $\pm$ 107	1671 $\pm$ 106	1486 $\pm$ 121	1.40	5,70	NS
19.7 $\pm$ 0.7	19.4 $\pm$ 0.7	19.4 $\pm$ 0.7	0.79	5,80	NS
5.74 $\pm$ 0.3	5.60 $\pm$ 0.2	5.53 $\pm$ 0.2	1.11	5,80	NS

Failure to complete the driving test

One subject did not complete the highway driving tests after treatment with dexchlorpheniramine and mequitazine 15 mg. In the dexchlorpheniramine condition, the driving instructor decided to terminate the test, because the subject fell asleep. The subject himself chose to stop driving after treatment with mequitazine 15 mg, because he felt he was incapable of continuing. The respective rides were 98 and 65 % complete when the test was stopped. SDLP scores for these rides were calculated using data of the completed part.

Driving Tests

A summary of descriptive and quantitative statistical analysis of all driving parameters is given in Table 1. The overall effect of Treatment ($F_{5,80}=6.32$; $p<.001$) and Period ($F_{5,80}=4.42$; $p=.001$) on SDLP were highly significant. Contrasting each drug with placebo showed that SDLP significantly increased after treatment with dexchlorpheniramine ($F_{1,80}=13.73$; $p<.001$). SDLP scores were significantly higher in period 3, 5 and 6 compared to the first period ($F_{1,80}=13.51$; $p<.001$; $F_{1,80}=9.41$; $p<.016$; $F_{1,80}=10.35$; $p<.0125$). No interaction was found between Treatment and Period. Mean (SEM) Standard Deviation of Lateral Position (SDLP) in each condition is shown in Figure 1. The polynomial contrast showed that SDLP increased in a linear fashion as a function of dose of mequitazine ($F_{3,46}=6.87$; $p=.012$).

	Mean $\pm$ SEM per treatment		
	Pla	Meq5	Meq10
<i>Subjective evaluation of mood</i>			
Alertness	4.76 $\pm$ 0.5	4.98 $\pm$ 0.5	5.41 $\pm$ 0.4
Contentedness	3.75 $\pm$ 0.5	4.51 $\pm$ 0.4	4.28 $\pm$ 0.4
Calmness	3.59 $\pm$ 0.4	4.22 $\pm$ 0.4	4.19 $\pm$ 0.4
<i>Sleep questionnaire</i>			
Sleep complaints (#)	1.22 $\pm$ 0.6	1.72 $\pm$ 0.5	1.44 $\pm$ 0.5
Sleep (h)	8.39 $\pm$ 0.2	8.22 $\pm$ 0.2	8.28 $\pm$ 0.2
Awakenings (#)	0.56 $\pm$ 0.2	1.00 $\pm$ 0.2	0.94 $\pm$ 0.3
Sleep latency (min)	10.5 $\pm$ 2.5	17.5 $\pm$ 4.3	12.4 $\pm$ 3.8
<i>Subjective driving quality</i>			
Pre-test (mm)	82.2 $\pm$ 4.3	84.1 $\pm$ 4.3	71.9 $\pm$ 5.7
Post-test (mm)	64.8 $\pm$ 5.2	67.4 $\pm$ 4.8	58.5 $\pm$ 5.9

Table 2. Summary of results of the subjective measures. Treatments as described in table 1. ^a drug- placebo differences after sequential Bonferroni correction with $p < .01$; NS: not significant.

Standard Deviation of Speed, Break RT and Time to Speed Adaptation were elevated in women as compared to men ($F_{1,91}=12.05$; $p=.001$; $F_{1,91}=8.80$; $p=.004$; $F_{1,91}=11.96$; $p=.001$), but there was no interaction between Gender and Treatment on any driving variable.

Cognitive and Psychomotor Tests

A summary of descriptive and quantitative statistical analysis of cognitive and psychomotor parameters is given in Table 1. Reaction time in the Divided Attention Task was affected by Treatment ($F_{5,80}=3.13$; $p=.013$) and Period ($F_{5,80}=2.92$; $p=.021$). Drug-placebo contrasts showed that mequitazine 15 mg produces significantly longer RTs ($F_{1,80}=15.04$; $p<.001$). On average subjects responded fastest in the sixth period (1.73 sec), while being slowest (1.92 sec) in the fifth period. A polynomial contrast demonstrated that there was no linear trend over the different periods. No interaction was found between Treatment and Period. Mean reaction times of the Divided Attention Task are presented in Figure 2. The polynomial contrast showed a linear effect of mequitazine on the RT ($F_{3,46}=11.7$; $p=.001$), indicating that RT rose linearly with increasing dose. No other variable of the cognitive and psychomotor tests was affected by Treatment.

Subjective measures

A summary of descriptive and quantitative statistical analysis of subjective measures is given in Table 2. Sleep complaints, hours of sleep, number of awakenings and sleep latency of the night before testing, as well as subjective driving quality did not significantly differ between treatments as expected.

Treatment effect on alertness was significant ($F_{5,80}=2.36$; $p=.048$), subjects rated their alertness after dexchlorpheniramine as significantly lower than after placebo ($F_{1,80}=9.63$; $p=.003$). Calmness and contentedness were not affected by Treatment.

There was no overall effect of Treatment on subjective driving ability rated before and

Mean $\pm$ SEM per treatment			Treatment effect		
Meq15	Cet	Dex	F	df	p
5.42 $\pm$ 0.5	5.10 $\pm$ 0.4	6.15 $\pm$ 0.4	2.36	5,80	.05
4.41 $\pm$ 0.4	4.29 $\pm$ 0.5	4.71 $\pm$ 0.4	2.26	5,80	NS
3.91 $\pm$ 0.4	4.50 $\pm$ 0.4	4.55 $\pm$ 0.4	1.32	5,80	NS
			χ^2	df	p
2.33 $\pm$ 0.8	1.94 $\pm$ 0.6	2.67 $\pm$ 0.8	5.35	5	NS
8.11 $\pm$ 0.3	8.17 $\pm$ 0.3	7.78 $\pm$ 0.4	4.27	5	NS
0.94 $\pm$ 0.2	1.17 $\pm$ 0.4	1.83 $\pm$ 0.6	3.65	5	NS
14.2 $\pm$ 4.5	11.6 $\pm$ 3.2	16.5 $\pm$ 5.7	7.93	5	NS
71.0 $\pm$ 6.9	72.5 $\pm$ 5.2	65.7 $\pm$ 5.8	7.43	5	NS
54.9 $\pm$ 6.2	61.1 $\pm$ 5.1	50.0 $\pm$ 6.0	5.57	5	NS

Figure 1. Mean (+SEM) SDLP for each treatment. Treatments are cetirizine (CET), placebo (PLA), mequitazine 5 mg (MEQ5), mequitazine 10 mg (MEQ10), mequitazine 15 mg (MEQ15) and dexchlorpheniramine (DEX). * drug-placebo differences after sequential Bonferroni correction with $p < .01$; ** polynomial contrast with $p < .05$

after driving. Drug-placebo contrasts showed that subjects expected their driving as going to be more impaired after dexchlorpheniramine than after placebo. However, using sequential Bonferroni correction, this effect was no longer significant ($z = -2.5$; $p = .013$; $\alpha = .01$). Contrasts with Bonferroni correction demonstrated that dexchlorpheniramine also did not differ significantly from placebo when driving quality was rated after the test ($z = -2.0$; $p = .045$; $\alpha = .01$).

Figure 2. Mean (+SEM) RT of the Divided Attention Task for each treatment. Treatments are cetirizine (CET), placebo (PLA), mequitazine 5 mg (MEQ5), mequitazine 10 mg (MEQ10), mequitazine 15 mg (MEQ15) and dexchlorpheniramine (DEX). * drug- placebo differences after sequential Bonferroni correction with $p < .01$; ** polynomial contrast $p < .05$

DISCUSSION

Only few studies had examined the sedative effects of mequitazine prior to the present study. Most of them indicated that mequitazine was non-sedating on the basis of questionnaires (Gervais et al., 1975; Blamoutier, 1978; Muler & Blum, 1978). Studies employing objective laboratory tests reported that mequitazine 5 mg produced no impairment of psychomotor and cognitive functions (Caille, 1979; Hindmarch & Easton, 1986). Only one group of researchers reported performance impairment in tests of visuo-motor coordination and information processing in female volunteers after treatment with a single dose of mequitazine 10 mg (Nicholson & Stone, 1983). Results from the present study confirmed the latter finding in a mixed population. Mequitazine significantly increased SDLP or "weaving" in the highway driving tests in a dose related manner even though the separate dose effects failed to reach statistical significance. Divided attention performance was also affected by mequitazine. Reaction time in the visual search task increased in a dose related manner and significantly differed from placebo at the highest dose. Together these data indicate that mequitazine can produce performance impairment, particularly at higher doses.

Impairment after higher doses of mequitazine was limited to performance during highway driving and in the divided attention task. Performance in memory, syntactic reasoning, critical flicker fusion frequency and critical tracking test remained unaffected by mequitazine at any dose. The selectivity of this drug effect may indicate that some psychological domains or functions are particularly susceptible to H1-antagonism. Both affected tasks involve

attention, the performance in the highway driving task mainly depends on sustained attention, while the capacity to perform two tasks simultaneously involves divided attention. The sensitivity of these tasks for H1-antagonism may be related to the central role of brain histamine in arousal and sleep-wake regulation. Task performance drawing primarily on attentional resources may be more vulnerable to fluctuations in sleep-wake levels as compared to tasks drawing primarily on sensorimotor control (e.g. critical tracking) or memory (e.g. word learning and syntactic reasoning). Curran et al. (1998) confirmed this notion by showing that certain antihistamines, i.e. diphenhydramine, selectively impaired arousal while leaving memory intact, whereas benzodiazepines and cholinergic antagonists affected both (Curran, Pooviboonsuk, Dalton, & Lader, 1998).

Driving impairment after mequitazine doses was relatively mild when compared to the effects of 1st generation antihistamines in the highway driving test. The effect of mequitazine on SDLP was small when compared with dexchlorpheniramine in this study, and much smaller when compared with other 1st generation antihistamines tested in previous studies, e.g. clemastine 2 mg, triprolidine 5 mg and diphenhydramine 50 mg (Robbe & O' Hanlon, 1990; Ramaekers & O' Hanlon, 1994; Vuurman, Uiterwijk, Rosenzweig, & O' Hanlon, 1994; O' Hanlon & Ramaekers, 1995). Mequitazine 15 mg increased SDLP by 1.1 cm, whereas increments in SDLP observed after single administration of 1st generation antihistamines were at least twice that size. Triprolidine 10 mg and diphenhydramine 50 mg produced an increase in SDLP of 3.4 cm and 4.5 cm respectively compared to placebo (Riedel, Ramaekers, Uiterwijk, & O' Hanlon, 1990; Ramaekers & O' Hanlon, 1994), while in the present study dexchlorpheniramine caused an increase of 2.4 cm. The clinical relevance of changes in SDLP has previously been determined by establishing the relationship between blood alcohol concentration and SDLP in the highway driving tests (Louwerens, Gloerich, de Vries, Brookhuis, & O' Hanlon, 1987). Their findings indicate that a blood alcohol concentration (BAC) of 0.5 mg/ml produces an increase in SDLP of 2.2 cm compared to placebo. That change is considered clinically relevant since a BAC > 0.5 mg/ml is associated with an increase in the risk of a fatal traffic accident (Borkenstein, Crowther, Shumate, Ziel, & Zylman, 1974). The increase in SDLP after treatment with dexchlorpheniramine should thus be considered as practically relevant, whereas the mean change in SDLP after all mequitazine doses was well below the criterion value of clinical relevance. In fact, the effects of mequitazine were not very different from other "non-sedating" second generation antihistamines given in multiple or higher than normal doses in healthy volunteers (O' Hanlon & Ramaekers, 1995).

Dexchlorpheniramine's reduction of alertness and driving capacity of healthy volunteers in the present study confirmed the general notion that 1st generation antihistamines can impair performance to significant levels. However, dexchlorpheniramine's effects on the highway driving performance were also less pronounced than those observed for other related compounds. The reason is that dexchlorpheniramine was given as a sustained release formulation. Basically this means that during time of testing only half of the substance (i.e. 3 mg) had been liberated and absorbed for systemic use, whereas the remaining 3 mg was gradually released 3 to 6 hours post administration. Dexchlorpheniramine's effects would have been twice as big if it had been released all at once. Similar findings have been reported with triprolidine. A single dose of triprolidine 5 mg produced more driving impairment as compared to a controlled release formulation of triprolidine 10 mg (Riedel, Schoenmakers, & O' Hanlon, 1989; Riedel et al., 1990).

Cetirizine 10 mg did not affect any performance measure in the present study. This seems somewhat surprising given that clinical studies have shown elevated levels of drowsiness in patients treated with cetirizine (Monroe, 1988; Meltzer, Weiler, & Widlitz, 1996; Mann, Pearce, Dunn, & Shakir, 2000). Still, previous studies assessing cetirizine's effects on psychomotor behaviour and driving have provided mixed results. Several studies demonstrated sedative effects of cetirizine (5–15 mg) using psychomotor tasks e.g. reaction speed, tracking behaviour, divided attention, and subjective measures of sleep (Ramaekers et al., 1992; Nicholson & Turner, 1998), whereas others did not show this effect in doses up to 20 mg (Gengo, Gabos, & Mechtler, 1990; Hindmarch, Johnson, Meadows, Kirkpatrick, & Shamsi, 2001). Using the same highway driving test as the present study, Ramaekers et al. (1992) showed a significantly impairing single dose effect of cetirizine 10 mg on driving, whereas Volkerts et al. (1992) were unable to assess any impairment after the single and repeated administration of the same dose. It was suggested that the discrepancy in results was related to differences in subject population and time of testing in both studies (O'Hanlon & Ramaekers, 1995). The study showing an effect employed a mixed-gender population, while the one showing no effect used a male population. In the latter study the acute effects of cetirizine were assessed at T_{max} , i.e. 1–2 hours post-drug, whereas in the former study performance was assessed between 3–4 hours post-drug. The hypothesis that males and females differed in their sensitivity to cetirizine, or antihistamines in general, was investigated in two subsequent studies (Vuurman et al., 1994; Vermeeren et al., 2002). They demonstrated that antihistamine induced impairment is generally more pronounced in female subjects. The study by Vermeeren et al. (2002) employed cetirizine 10 mg as one of the comparative drugs. It showed that single and repeated doses of cetirizine produced mild driving impairment between 3–4 hours post-dosing, and that women were more impaired. The hypothesis that cetirizine's effect also depends on time of testing was basically confirmed by the failure in the present study to establish any effect of cetirizine on driving performance of males and females between 1–2 hours post-drug. The absence of a cetirizine effect between 1–2 hours post-drug in this study and that by Volkerts et al. (1992) indicates that there is a possible time shift between peak plasma concentrations and maximal drug effect. This time lag has been found using wheal and flare tests and electroencephalographic measures of sedation (Shall, Barkley, & Millard, 1989; Sannita, Crimi, Riela, Rosadini, & Brusasco, 1996; Urien, Tillement, Ganem, & Kuch, 1999). The likelihood of detecting an impairing effect of cetirizine may therefore increase when testing is conducted between 3–4 hours post-drug, i.e. closer to the time when cetirizine's pharmacodynamic effect is maximal.

Although it is clear that SDLP reflects a fundamental aspect of driving performance, i.e. road tracking control, it should not be taken as an overall measure of driving. Driving is a complex task comprising decision making, risk evaluation, interaction with other road user and a range of other higher-level skills. Drug induced changes in any of these task parameters will not automatically be reflected in SDLP. Nonetheless, performance in the highway driving test seems highly relevant because it has been shown to strongly correlate ($r=.95$) with the incidence of somnolence in patients treated with antidepressants, most of which are also strong H1-receptor antagonists (Ramaekers, 2003). In addition, it has been shown that drug effects measured in a range of conventional psychomotor tests, e.g. tracking, reaction time, critical flicker fusion were only moderately related to performance in the highway driving test. The lack of correlation between performance in conventional laboratory test and in the actual driving test suggests the former are less sensitive to drug effects or possess less construct validity (Ramaekers, 2003).

In conclusion, mequitazine caused mild, dose related impairment of driving and attention. Mequitazine's effect on performance is comparable to other "non-sedative" second generation antihistamines in that impairment is virtually absent at lower doses but apparent at higher doses.

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Repeated-dose effects of mequitazine, cetirizine and dexchlorpheniramine on driving and psychomotor performance

CHAPTER 3

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ABSTRACT

Aims: Previous studies demonstrated that the antihistamines mequitazine, cetirizine and dexchlorpheniramine produce mild sedation after single doses. It is unknown, however, whether acute sedation persists after repeated dosing. Therefore, the present study assessed the effects of repeated dosing of these antihistamines on driving and psychomotor performance.

Methods: Sixteen healthy volunteers were treated with mequitazine 10 mg q.a.m., cetirizine 10 mg q.a.m., dexchlorpheniramine Repetab 6 mg b.i.d. and placebo for four separate 8-day periods. Drug effects were assessed on day 1 and day 8 using two on-the-road driving tests (highway driving and car following), psychomotor tests (tracking and divided attention) and subjective questionnaires.

Results: Both dexchlorpheniramine and mequitazine significantly impaired driving performance on the highway driving test on the first day; dexchlorpheniramine increased SDLP-scores by 2 cm (95% confidence interval (CI): 0.5 to 3.8) and mequitazine by 2.5 cm (CI: 1.0 to 4.3). These effects on driving performance disappeared after 8 days of treatment. No effect of treatment was found on car following, tracking and divided attention. Although subjective ratings confirmed that subjects knew their driving had been impaired in the mequitazine and dexchlorpheniramine condition after completion of the highway driving test on day 1, they did not expect their driving to be affected before the start of the test. Cetirizine did not impair performance on any of the tests.

Conclusions: Single doses of mequitazine 10 mg and dexchlorpheniramine Repetab 6 mg cause mild driving impairment. However, when taken over several days, the impairing effect wears off, possibly as a result of tolerance.

INTRODUCTION

Antihistamines (H1-antagonists) are widely used to treat allergies and do so by blocking peripheral H1-receptors. However, these drugs also cross the blood-brain barrier and block neuronal histamine transmission as well as other neurotransmitter systems (e.g. serotonin, acetylcholine, noradrenaline) in the central nervous system (Simons & Simons, 1994). As a consequence they produce sleepiness, fatigue and sedation (Passalacqua et al., 1996). The sedative effects of antihistamines can lead to diminished concentration or productivity and an increased risk for occupational injuries and traffic accidents (Gilmore, Alexander, Mueller, & Rivara, 1996; Nolen, 1997; Burton, Conti, Chen, Schultz, & Edington, 2001). Therefore it is necessary to study and compare the sedative and potentially impairing effects of all antihistamines.

First generation antihistamines have been shown to produce significant performance impairment in psychomotor and in driving tests (Moskowitz & Burns, 1988; O'Hanlon & Ramaekers, 1995; Hindmarch & Shamsi, 2001). More recent antihistamines, such as cetirizine, loratadine, ebastine and terfenadine were developed to overcome the sedative side effects of the first generation antihistamines. These second generation antihistamines cross the blood-brain barrier less readily, and consequently are less sedating than their predecessors when given in the recommended dose (Hindmarch & Shamsi, 1999). Experimental studies have shown that single therapeutic doses of second generation antihistamines produce little or no impairment of attention, memory, vigilance, psychomotor performance or driving (Moskowitz & Burns, 1988; O'Hanlon & Ramaekers, 1995; Kay et al., 1997; Hindmarch & Shamsi, 2001). Higher doses, however, were occasionally found to produce significant sedative effects, although less pronounced than those of first generation antihistamines (Riedel, Ramaekers, Uiterwijk, & O' Hanlon, 1990; Brookhuis, De Vries, & De Waard, 1993; Ramaekers & O'Hanlon, 1994; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994).

Since antihistamines are usually taken for periods longer than one day in the treatment of allergic rhinitis or urticaria, it is not only relevant to assess their effects after single doses, but also after repeated doses, when blood levels are at steady state. Studies have shown that their impairing effects can either diminish or increase over time (Seppala, Nuotto, & Korttila, 1981; Riedel et al., 1990; Robbe & O' Hanlon, 1990; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992; O'Hanlon & Ramaekers, 1995; Vermeeren & O'Hanlon, 1998; Hindmarch & Shamsi, 2001; Richardson, Roehrs, Rosenthal, Koshorek, & Roth, 2002; Verster, de Weert et al., 2003; Verster, Volkerts et al., 2003). On the one hand, the effects of triprolidine (5 and 10 mg), diphenhydramine (50 mg) and clemastine (2 mg), on driving and psychomotor performance were found to diminish, although not disappear with repeated dosing (Seppala et al., 1981; Robbe & O' Hanlon, 1990; Volkerts et al., 1992; Vermeeren & O'Hanlon, 1998; Richardson et al., 2002; Verster, de Weert et al., 2003; Verster, Volkerts et al., 2003). On the other hand, high doses of ebastine (30 mg) and terfenadine (120 mg), were found to produce sedation only after repeated doses (Riedel et al., 1990; O'Hanlon & Ramaekers, 1995; Hindmarch & Shamsi, 2001). It seems therefore that effects can diminish over time as a result of tolerance, or increase as a result of accumulation, depending on the drug and dose.

The objective of the present study was to assess the effects of repeated doses of mequitazine 10 mg, dexchlorpheniramine Repetab 6 mg and cetirizine 10 mg that were previously shown to produce performance impairment after single doses (Muler & Blum, 1978; Caille, 1979; Nicholson & Stone, 1983; Ramaekers, Uiterwijk, & O'Hanlon, 1992; Nicholson & Turner,

1998; Vermeeren, Ramaekers, & O'Hanlon, 2002; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004). Impairing effects were assessed using two validated driving tests and psychomotor tests previously shown to be sensitive to antihistamine induced sedation (Ramaekers et al., 1992; Verster, Volkerts et al., 2003; Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004).

METHODS

Subjects

Sixteen healthy volunteers (8 males and 8 females), aged between 22 and 45 years, were recruited by means of newspaper advertisements. Subjects were healthy according to medical history, physical examination, electrocardiogram, blood and urine analysis. All participants possessed a valid driver's license for at least 3 years and had driving experience of at least 5000 km per year. Subjects with a history of major medical or psychiatric disorders were excluded from the study, as were subjects with unusual sensitivity to antihistamines, drug abuse and chronic use of medication (except contraceptives). Women who were not using an approved contraception or women who were pregnant or lactating were excluded. Written informed consent was acquired from each subject prior to participation. The study was approved by the Ethics Committee of Maastricht University and conducted in accordance with the World Medical Associations Declaration of Helsinki (Edinburgh modification, 2000).

One male subject dropped out for reasons unrelated to the treatment. Mean $\pm$ SD age of the remaining 15 participants was 32 ± 9.1 years and mean weight $\pm$ SD was 73.7 ± 15.1 kg (women, 64.5 ± 10.8 kg; men 84.3 ± 12.4 kg). All subjects were non-smokers and used an average of 2.7 ± 2.2 caffeine containing beverages per day.

Drug Administration

This study was conducted according to a 4-way, double blind, cross-over design. Treatments consisted of a regular therapeutic dose: mequitazine 10 mg once daily in the morning (q.a.m.), cetirizine 10 mg q.a.m.; dexchlorpheniramine 6 mg (Repetab) twice daily (b.i.d.), and placebo (b.i.d.). Treatment duration was 8 days starting on the morning of day 1. Tests were conducted on day 1 and 8 of each treatment period. The washout period between treatment periods was at least 7 days.

On test days, drugs and placebo were administered using a double dummy technique, since cetirizine is more rapidly absorbed than mequitazine and dexchlorpheniramine; cetirizine reaches peak plasma concentrations ($T_{\max}$) approximately 1 hour after oral dosing, whereas mequitazine and dexchlorpheniramine reach $T_{\max}$ between 3 and 4 hours after administration. Therefore, mequitazine and dexchlorpheniramine were administered at 09.00 hours, i.e. three hours before driving, with a placebo capsule at 11.00 hours to maintain blinding. Cetirizine was administered at 11.00 hours, i.e. 1 hour before driving, with a placebo capsule at 09.00 hours to ensure blinding. In the placebo condition, placebo capsules were administered at both times. Between test days, subjects continued treatments at home, taking one capsule in the morning and one in the evening. In the mequitazine and cetirizine conditions, the active drug was taken in the morning while a placebo was taken at night.

Dexchlorpheniramine and placebo were both taken in the morning and in the evening in the dexchlorpheniramine and placebo condition, respectively. Subjects noted the times of drug administration in a diary, as well as the use of any concomitant medication.

Procedure

Subjects were individually trained in all tests in the two weeks prior to their first treatment period. Subjects had to abstain from alcohol the day before testing and agreed to have a good night's rest of at least 7 hours. On test days consumption of caffeine was not allowed and smoking was prohibited 30 minutes prior and during testing. On test days, subjects were transported to the laboratory where drugs were administered at 09.00 and 11.00 hours. At arrival, sleep quality of the previous night was measured using the Groningen Sleep Quality Scale. At 10.00 hours they received a standardized light meal. The highway-driving test started at 12.00 hours and the car-following test at 13.00 or 13.30 hours. Laboratory tests were started at 14.30 hours.

Performance measures

Tests used in this study have been described in more detail in previous papers (Vermeeren & O'Hanlon, 1998; Theunissen et al., 2004).

• *Driving tests*

In the highway-driving test, the subject drives a specially instrumented vehicle over a 100 km (61 miles) distance on a primary highway. The subject has to maintain a steady lateral position between the delineated boundaries of the right (slower) traffic lane and to maintain a constant speed of 95 km (58 miles) per hour. The primary dependent measure is the Standard Deviation of Lateral Position (SDLP), which is an index of the continuous road tracking error.

In the car-following test subjects drive a specially instrumented car and follow a vehicle controlled by an experimenter. The latter or "leading" car occasionally changes speed and briefly lights up its brake lights. Subjects are required to keep driving at the same speed as the leading vehicle and to maintain a 15-30 meter distance between the cars. In addition, subjects have to react as quickly as possible to the brake lights of the leading car. The primary dependent measures are time to speed adaptation (in ms), and reaction time (in ms) to the brake lights. Deviation in distance to the leading car (in m) is a secondary parameter.

During both driving tests a licensed driving instructor accompanies the subject, and can intervene when necessary by using dual controls.

• *Psychomotor tests*

The Critical Tracking Test measures the subjects' ability to control a displayed error signal in a first-order compensatory tracking task. The frequency at which control is lost is called the 'critical frequency' or ' λ_c ' (rad/sec). The test includes five trails; the average score is calculated after removing the highest and the lowest scores, and is the primary variable in this test.

The Divided Attention Task is used to measure the subject's ability to divide attention between two tasks performed simultaneously. The primary task consists of a tracking task in the central visual field and the secondary task is a monitoring task in the peripheral visual field. Subjects react to peripheral targets using a foot pedal. Dependent variables are the absolute mean tracking error over the entire test and mean reaction time to peripheral targets.

• Subjective measures

Sleep quality of the previous night was assessed by means of the Groningen Sleep Quality Scale (Mulder-Hajonides van der Meulen, 1981). This questionnaire scores the number of sleep complaints, ranging from 0 (good sleep) to 14 (bad sleep), and specific questions about the total amount of sleep, number of awakenings and the estimated time needed to fall asleep.

Subjective driving questionnaires were used in order to evaluate whether patients' subjective experience of their driving ability corresponds with their objective performance on the driving tests. Prior to the highway driving test, subjects estimated their driving ability and after completion of the test they rated driving performance, using 100mm visual analogue scales ranging from 0 (very bad driving) to 100 (very good driving).

Statistical analysis

Driving and psychomotor parameters were analyzed separately for days 1 and 8, using an ANOVA with Subject, Treatment and Period as factors. Subsequently, analyses for comparing treatments with placebo were conducted, using three simple contrasts with sequential Bonferroni correction. In case of a significant effect, one tailed, 95% confidence intervals (CI) of drug-placebo differences were calculated. The effects of gender on driving performance were analyzed, using a model including Treatment, Period, Gender and Gender by Treatment. All statistical tests were conducted using SPSS (version 10.0).

RESULTS

Missing data

Due to technical problems, the car-following test could not be performed by two subjects on two separate occasions. Distance measures between the cars was lost for another two subjects on two separate occasions also as a result of technical problems.

Driving Performance

Four highway driving tests of a single subject were terminated before scheduled completion, because the driving instructor (on day 1 and 8 of the placebo condition and day 1 of the dexchlorpheniramine condition) or the subject (day 8 of cetirizine treatment) judged it would be unsafe to continue. The respective rides were 91%, 90%, 68% and 50% complete when the test was stopped. SDLP scores calculated over the completed parts of these rides were 23.8, 24.6, 32.7 and 24.6cm, respectively. Statistical analysis of datasets including or excluding scores of incomplete rides revealed comparable results, therefore incomplete rides were included in the analysis.

A summary of descriptives and quantitative statistical analyses of all performance parameters is presented in Table 1. Mean (SEM) SDLP in each condition and for both days is shown in Figure 1.

The overall effect of Treatment on SDLP was significant on day 1 ($F_{3,39}=8.16$; $p<.001$) but not on day 8 ($F_{3,39}=0.99$). Contrasting each drug with placebo showed that on day 1, SDLP was significantly increased after treatment with mequitazine (mean 2.5; CI: 1.03 to 4.25; $F_{1,39}=11.03$; $p=.002$) and dexchlorpheniramine (mean 2.0; CI: 0.46 to 3.68; $F_{1,39}=6.75$; $p=.013$), but not after cetirizine (mean 0.8; $F_{1,39}=.79$). The overall effect of Period on SDLP was significant on day 1 and 8 ($F_{3,39}=4.15$; $p=.012$; $F_{3,39}=4.69$; $p=.007$). Contrasting driving performance in

	Mean $\pm$ SEM per treatment				Treatment effect		
	PLA	MEQ	CET	DEX	F	df	p
DAY 1							
<i>Driving tests</i>							
SDLP (cm)	19.2 $\pm$ 1.0	21.7 $\pm$ 1.1 ^a	18.4 $\pm$ 0.8	21.2 $\pm$ 1.3 ^a	8.16	3,39	<.001
Time to speed adaptation (sec)	1.9 $\pm$ 0.2	2.3 $\pm$ 0.3	2.1 $\pm$ 0.3	2.0 $\pm$ 0.4	1.02	3,38	NS
Brake reaction time (msec)	476 $\pm$ 19	528 $\pm$ 29	537 $\pm$ 24	492 $\pm$ 26	2.36	3,38	NS
SD headway (m)	5.2 $\pm$ 1.1	4.3 $\pm$ 0.7	5.3 $\pm$ 0.7	4.0 $\pm$ 0.5	0.74	3,38	NS
<i>Critical tracking task</i>							
Critical frequency (rad/sec)	3.9 $\pm$ 0.2	3.8 $\pm$ 0.2	4.0 $\pm$ 0.2	3.9 $\pm$ 0.2	1.21	3,39	NS
<i>Divided attention task</i>							
Tracking error (mm)	21.2 $\pm$ 1.5	21.1 $\pm$ 1.2	20.4 $\pm$ 1.4	22.9 $\pm$ 1.4	2.83	3,39	.05
Reaction time (msec)	1747 $\pm$ 64	1799 $\pm$ 54	1807 $\pm$ 69	1809 $\pm$ 70	0.76	3,39	NS
DAY 8							
	PLA	MEQ	CET	DEX	F	df	p
<i>Driving tests</i>							
SDLP (cm)	19.9 $\pm$ 1.0	21.0 $\pm$ 1.2	19.6 $\pm$ 1.0	19.9 $\pm$ 1.0	0.99	3,39	NS
Time to speed adaptation (sec)	2.2 $\pm$ 0.2	2.2 $\pm$ 0.3	2.0 $\pm$ 0.2	2.0 $\pm$ 0.2	0.80	3,38	NS
Brake reaction time (msec)	506 $\pm$ 23	521 $\pm$ 33	510 $\pm$ 27	484 $\pm$ 14	0.60	3,38	NS
SD headway (m)	5.5 $\pm$ 1.2	5.0 $\pm$ 0.7	5.1 $\pm$ 0.8	4.5 $\pm$ 0.8	0.41	3,36	NS
<i>Critical tracking task</i>							
Critical frequency (rad/sec)	4.0 $\pm$ 0.2	4.0 $\pm$ 0.2	3.9 $\pm$ 0.2	4.0 $\pm$ 0.2	0.32	3,39	NS
<i>Divided attention task</i>							
Tracking error (mm)	20.0 $\pm$ 1.3	20.6 $\pm$ 1.3	20.4 $\pm$ 1.3	20.9 $\pm$ 1.6	0.39	3,39	NS
Reaction time (msec)	1787 $\pm$ 98	1692 $\pm$ 59	1832 $\pm$ 69	1721 $\pm$ 77	1.53	3,39	NS

Table 1. Summary of results from the driving and psychomotor tests on day 1 and day 8. Treatments are placebo (PLA), mequitazine 10 mg q.a.m. (MEQ), cetirizine 10 mg q.a.m (CET) and dexchlorpheniramine 6 mg Reperab b.i.d (DEX). Significant drug-placebo differences are indicated by ^a $p < .017$. NS, not significant; df, degrees of freedom.

period 1 with performance in subsequent periods revealed no systematic change over time, however, and more importantly, no interactions were found between Treatment and Period. There were no significant main effects of Gender or Gender by Treatment interactions on day 1 or day 8.

Performance in the car-following test was not significantly affected by Treatments, Periods or Gender on days 1 or day 8. However, it should be mentioned that the incompleteness of the car-following data might be related to the absence of an effect.

Psychomotor tests

A summary of descriptives and statistical analyses of the psychomotor tests is also presented in Table 1. Tracking performance in the critical tracking test was not significantly affected on day 1 or 8, and there was only a nearly significant overall effect of Treatment on tracking in the divided attention task ($F_{1,39}=2.83$; $p=.051$) on the first day of treatment. Subjects achieved the smallest tracking error in the cetirizine condition and the largest in the dexchlorpheniramine condition. Yet, drug-placebo contrasts showed no significant differences.

Figure 1. Mean (+SEM) SDLP for each treatment on day 1 and day 8. Treatments are cetirizine 10 mg q.a.m (CET), placebo (PLA), mequitazine 10 mg q.a.m. (MEQ), and dexchlorpheniramine 6 mg Repetab b.i.d. (DEX). Asterisks indicated significant differences from placebo after sequential Bonferroni correction, i.e. $p < .017$.

	Mean $\pm$ SEM per treatment				Treatment effect		
	DAY 1				F	df	p
	PLA	MEQ	CET	DEX			
<i>Subjective driving quality</i>							
Pre-test (mm)	73.7 $\pm$ 6.3	79.1 $\pm$ 6.5	78.5 $\pm$ 4.6	68.7 $\pm$ 6.3	1.06	3,39	NS
Post-test (mm)	67.9 $\pm$ 6.6	55.1 $\pm$ 7.5 ^b	64.7 $\pm$ 6.9	51.5 $\pm$ 8.0 ^a	4.55	3,39	.008
<i>Sleep Questionnaire</i>							
Sleep latency (min)	12.4 $\pm$ 2.2	18.8 $\pm$ 4.5	18.9 $\pm$ 4.6	22.6 $\pm$ 5.0	1.06	3,39	NS
Number of awakenings	1.1 $\pm$ 0.3	1.0 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.4	0.00	3,39	NS
Sleep (h)	7.6 $\pm$ 0.2	7.2 $\pm$ 0.2	6.7 $\pm$ 0.3	7.1 $\pm$ 0.3	2.05	3,39	NS
Number of complaints	1.0 $\pm$ 0.4	1.7 $\pm$ 0.9	2.6 $\pm$ 0.9	2.7 $\pm$ 0.9	1.23	3,39	NS
	DAY 8				F	df	p
	PLA	MEQ	CET	DEX			
<i>Subjective driving quality</i>							
Pre-test (mm)	77.5 $\pm$ 5.8	73.0 $\pm$ 4.2	86.7 $\pm$ 3.0	72.2 $\pm$ 6.4	2.66	3,39	NS
Post-test (mm)	64.3 $\pm$ 5.7	59.5 $\pm$ 6.5	62.7 $\pm$ 7.8	62.3 $\pm$ 6.5	0.23	3,39	NS
<i>Sleep Questionnaire</i>							
Sleep latency (min)	22.3 $\pm$ 6.8	14.6 $\pm$ 3.1	22.9 $\pm$ 7.1	14.4 $\pm$ 2.1	1.14	3,39	NS
Number of awakenings	0.7 $\pm$ 0.3	0.7 $\pm$ 0.2	0.8 $\pm$ 0.3	1.3 $\pm$ 0.4	1.46	3,39	NS
Sleep (h)	7.4 $\pm$ 0.2	7.5 $\pm$ 0.2	7.2 $\pm$ 0.2	7.3 $\pm$ 0.3	0.36	3,39	NS
Number of complaints	2.6 $\pm$ 1.0	1.5 $\pm$ 0.4	1.9 $\pm$ 0.7	1.8 $\pm$ 0.6	0.60	3,39	NS

Table 2. Summary of results of the subjective measures on day 1 and day 8. Abbreviations are as indicated in Table 1. Significant drug-placebo differences are indicated by ^a $p < .017$; ^b $p < .025$. High scores on the subjective driving quality indicating better driving performance.

Subjective measures

A summary of descriptives and quantitative statistical analyses of the subjective measures is presented in Table 2.

On day 1 and day 8 sleep quality of the night before testing was comparable in all conditions.

Prior to the driving tests, subjects did not estimate their driving ability to be affected by any of the treatments on day 1 or day 8. At the end of the tests on day 1 however, subjects did notice that their driving performance had been impaired ($F_{3,39}=4.55$; $p=.008$). In line with objective measures of driving performance, subjects rated their driving quality in the mequitazine and dexchlorpheniramine conditions as worse than after placebo (mean -12.8 ; CI: -24.2 to -2.7 ; $F_{1,39}=6.4$; $p<.025$ and mean -16.4 ; CI: -27.8 to -6.3 ; $F_{1,39}=10.2$; $p<.017$, respectively).

DISCUSSION

Results of this study show that mequitazine 10 mg and dexchlorpheniramine Repetab 6 mg produced mild driving impairment on the first day of treatment. These results were expected and support our previous findings that single doses of these drugs can have impairing effects on actual driving (Theunissen et al., 2004). The magnitude of the driving impairment found after single doses of mequitazine 10 mg and dexchlorpheniramine Repetab 6 mg is comparable to what has been found for second generation antihistamines such as acrivastine 8 mg and mizolastine 10 and 20 mg (Ramaekers & O'Hanlon, 1994; Vuurman et al., 1994). The present study also showed, however, that these effects disappear within 8 days of treatment.

Although the effects on driving found for mequitazine confirm our previous results, they are not supported by two earlier studies. Blamoutier (1978) and Hindmarch and Easton (1986) concluded that mequitazine 5 and 10 mg do not produce acute daytime drowsiness. Yet, these investigators used subjective measures and cognitive tests. So their results are in fact in line with those of our present and previous study, showing no significant impairment of mequitazine on performance in psychomotor and cognitive tests or on subjective measures of sedation. This might indicate that these tests are not good predictors for driving ability (Verster, Volkerts, & Verbaten, 2002; Ramaekers, 2003), or that the effects of these antihistamines were too subtle to be picked up by these tests.

Although dexchlorpheniramine in immediate release formulations (2 and 4 mg) has considerable sedative effects (Okamura et al., 2000; Kamei et al., 2003), results from this study suggests that these effects can be reduced by a controlled release formulation. Similarly it has been shown that controlled release formulations of triprolidine also reduce maximal levels of impairment (Brookhuis et al., 1993; O'Hanlon & Ramaekers, 1995). Therefore it seems that controlled release formulations are a good way to diminish the sedative effects of antihistamines.

Cetirizine 10 mg had no effects on driving in the present study. Previous studies using the same driving test, however, demonstrated small but significant acute impairing effects after single doses of cetirizine 10 mg (Ramaekers et al., 1992; Vermeeren et al., 2002). The main difference between the latter studies and the present one is the time of testing with respect to drug administration. Ramaekers et al.,

(1992) and Vermeeren et al., (2002) assessed the effects between 2 and 3 hours after ingestion, whereas in the present study the effects of cetirizine on driving performance were tested between 1 and 2 hours after ingestion (i.e. at T_{max}). A previous study (Volkerts et al., 1992) using the same test also failed to find significant effects of cetirizine between 1 and 2 hours after dosing. Together these results suggest that there might be a delay between peak plasma concentrations and maximal effect on performance in the highway driving test. However, because of the impairment demonstrated in two previous driving studies and on psychomotor and subjective measures in other studies, it can not be concluded that cetirizine is always free of sedating effects (Ramaekers et al., 1992; Nicholson & Turner, 1998; Vermeeren et al., 2002; Tashiro et al., 2004).

The clinical relevance of performance changes in the highway driving test has previously been determined by establishing the relationship between blood alcohol concentration (BAC) and SDLP (Louwerens, Gloerich, de Vries, Brookhuis, & O'Hanlon, 1987). Results showed that a BAC of 0.5 mg/ml is associated with an average increase in SDLP of 2.2 cm. Since a BAC of 0.5 mg/ml is associated with a significantly higher risk in traffic accidents (Borkenstein, Crowther, Shumate, Ziel, & Zylman, 1974), an SDLP increase of about 2.2 cm is considered clinically relevant. On the first day of treatment mequitazine and dexchlorpheniramine increased SDLP with 2.5 and 2.0 cm respectively. In a previous study, however, mequitazine 10 mg caused an acute SDLP increase of 1.0 cm and dexchlorpheniramine an increase of 2.4 cm (Theunissen et al., 2004). Although these results seem inconclusive about the degree of impairment caused by mequitazine and dexchlorpheniramine, it shows that some individuals are prone to the sedating effects of these antihistamines and will show signs of impaired driving.

After 8 days of treatment, no treatment caused impairment in driving performance. The fact that the acute impairing effect of these antihistamines disappear after repeated doses has been found previously for other antihistamines and is probably due to tolerance (O'Hanlon & Ramaekers, 1995; Kay et al., 1997; Richardson et al., 2002). Interestingly, a similar tolerance for the effects of H1-antagonism has been shown with tricyclic antidepressants, whose sedative effects are also mainly caused by H1-receptor blockade (Ramaekers, 2003). The mechanism whereby tolerance for the impairing effects of antihistamines develops, however, is still unclear.

As reported before (Vermeeren et al., 2002), subjects were not aware of the performance impairment caused by antihistamines. On the first day of mequitazine and dexchlorpheniramine treatment subjects were aware of their impaired driving only after the test was completed, but were unable to predict the impairment beforehand. In practice this means that patients treated with antihistamines may be confident about their driving ability, whereas in fact they pose a considerable risk to traffic safety. Therefore, drug labels should warn explicitly for the impairing effects of sedating antihistamines and advice patients to be particularly careful at the beginning of treatment even if they feel capable of driving.

In conclusion, this study showed that mequitazine 10 mg and dexchlorpheniramine Repetab 6 mg can produce mild but clinically relevant effects on driving performance on the first day of treatment but no longer after 8 days of treatment. After 8 days of treatment, the impairing effect of mequitazine and dexchlorpheniramine had disappeared.

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Stimulating effects of H1-antagonists

CHAPTER 4

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ABSTRACT

Whereas antihistamines are generally known for their sedative side effects, this review shows that several studies also found mild stimulating effects on performance for the H1-antagonists terfenadine, ebastine, fexofenadine and desloratadine. These stimulating effects were mostly demonstrated in tasks involving high levels of attention, e.g. divided attention tasks, vigilance tasks and driving tasks. The stimulating effects of these antihistamines were often dependent of the given dose; however the relation was not always linear. The mechanism responsible for the stimulating effects of these four antihistamines is still unclear, though it is hypothesized that it involves other neurotransmitters like dopamine and GABA, or that it acts through the H3 histamine receptor. Further research is needed to clarify the ambiguous role of histamine in processes of arousal. In addition, it would be useful to determine whether terfenadine, ebastine, fexofenadine and desloratadine can return allergic patient's performance back to their preclinical level.

INTRODUCTION

Histamine is an endogenous substance which affects both the central and peripheral nervous system, and acts through activation of three receptor subtypes; H1, H2 and H3 (Steinbusch, 1991; Brown, Stevens, & Haas, 2001). In allergic persons, peripheral release of histamine by allergens causes symptoms of allergy such as itching and sneezing. H1-receptor antagonists or antihistamines relieve symptoms of allergic rhinitis and urticaria by blocking peripheral H1-receptors. In addition, H1-antagonists are able to cross the blood brain barrier and enter the CNS where they affect central histaminergic neurotransmission. Histamine in the brain is involved in the regulation of arousal (Lin, 2000). During the active phase of animals, the activity of the central histaminergic system increases while it decreases when the animals are asleep (Yamatodani et al., 1991; Onoe et al., 1992; Vanni Mercier, Gigout, Debilly, & Lin, 2003).

By blocking central H1-receptors, antihistamines cause side effects such as sedation, sleepiness and drowsiness. These side effects can have serious consequences for daily activities. In response to this problem, a second generation of H1-antagonists was developed. Studies investigating the effects of these new antihistamines have indeed demonstrated that when given in their therapeutic dose they produce less subjective sedation and have less impairing effects on performance (Ramaekers, Uiterwijk, & O'Hanlon, 1992; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994; Mann, Pearce, Dunn, & Shakir, 2000). The lack of sedative effects of second generation antihistamines is often said to be the result of their inability to pass the blood brain barrier and consequent lack of central H1-receptor blockade. Several studies, however, did demonstrate different levels of occupancy of central H1-receptors after administration of second generation antihistamines. Using PET scans, Tashiro et al., (2002 and 2004), for example, showed that cetirizine occupied about 30% of the central H1-receptors. Furthermore, receptor occupancy was found to correlate with the degree of sedation and performance impairment caused by antihistamines (Yanai, Okamura, Tagawa, Itoh, & Watanabe, 1999). For example, the sedating antihistamine dexchlorpheniramine was found to produce larger H1-receptor occupancy ($\pm 50\%$) than the less sedating antihistamine ebastine ($\pm 10\%$) (Tagawa et al., 2001).

Surprisingly, a few studies, designed to measure potentially sedating effects of antihistamines, found that some of the second generation antihistamines (e.g. fexofenadine and terfenadine) seemed to improve performance suggesting that these compounds somehow increased wakefulness rather than causing sedation (Clarke & Nicholson, 1978a; Vermeeren & O'Hanlon, 1998). Initially, such results were spurious and not given further attention. However, over the years more researchers sporadically reported similar effects (Moskowitz & Burns, 1988; Mattila, Kuitunen, & Pletan, 1992; Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004), which warranted the initiation of studies specifically designed to test the hypothesis that certain antihistamines may have slightly stimulating effects and thereby improve performance (Theunissen, Jonkman, Kuypers, & Ramaekers, *In press*).

The present paper intends to review the existing evidence that some antihistamines may have stimulating effects and improve performance. First of all, experimental studies showing stimulant effects of terfenadine, ebastine, fexofenadine and desloratadine on objective and subjective performance measures will be described. Subsequently, the possible mechanisms whereby H1-antagonists cause stimulating effects will be explored, discussing the involvement of dopamine, GABA and H3-receptors.

ANTI-HISTAMINES WITH STIMULATING EFFECTS

The antihistamine for which most indications of stimulation are found is terfenadine, but similar indications have been found for ebastine, desloratadine and fexofenadine (for an overview see Table 1).

Terfenadine

Terfenadine was developed in the 1980's as one of the first second generation antihistamines (Emanuel, 1999), and its effect on performance and cognitive function have been tested repeatedly ever since. A few of those studies found significantly stimulating effects of terfenadine in objective performance tests compared with placebo.

The first investigators reporting significant performance improvement in healthy volunteers following the administration of terfenadine were Moskowitz and Burns (1988). These investigators had conducted a study comparing the effects of single doses of terfenadine (60 mg), diphenhydramine (50 mg) and placebo on a critical tracking task, a visual search task, a divided attention task (a combination of critical tracking and visual search) and a vigilance task in 18 healthy males. Performance was measured at 1, 3, and 5 hours after drug or placebo administration. Surprisingly, results showed that subjects demonstrated significantly better performance in the critical tracking task three hours after treatment with terfenadine than after placebo. Similarly, average performance in the visual search task was better although not significantly after treatment with terfenadine at one and three hours after treatment. In the divided attention task, tracking was also slightly better than placebo at one and three hours after terfenadine treatment, while response time of the visual search subtask was consistently better. Furthermore, the ability to sustain attention over an extended period, as measured by the vigilance task, was shown to improve after terfenadine treatment. In contrast, diphenhydramine treatment resulted in impaired performance on all tasks. Consequently the researchers concluded that in all tasks the subjects demonstrated improved performance after terfenadine treatment compared to placebo treatment.

The second report of significant performance improvement following administration of terfenadine was by Betts, Kenwood, Dalby, Hull and Wild (1989). Betts et al., (1989) demonstrated improved driving performance after a high dose of terfenadine in a study comparing the effects of two doses of terfenadine (60 and 120 mg) with two doses of cetirizine (10 and 20 mg) and placebo. Tests used were a driving manoeuvre test, a reaction time test and subjective measures of mood, tension and arousal. In the driving test subjects performed significantly better on the gap estimation test after being treated with terfenadine 120 mg as compared to placebo and cetirizine (10 mg). Terfenadine 60 mg did not improve performance in the driving test and neither dose had an effect on any of the other measures of performance and sedation.

Several other studies found evidence for stimulating effects of terfenadine using objective performance measures, such as driving tasks and EEG's, however the difference from placebo failed to reach significance. The first study showing non-significant stimulating effects of terfenadine was by Betts, Markman, Debenham, Mortiboy and McKevitt (1984). In this study the effects of repeated doses of terfenadine (60 mg) on driving manoeuvres and subjective mood, tension, arousal and fitness to drive were compared with those of triprolidine (10 mg). Treatment with terfenadine (60mg) caused healthy subjects to complete the driving test faster than when treated with placebo. Subjects also indicated that

they felt more alert and fit to drive after terfenadine (60 mg) than after triprolidine treatment. However none of the results of terfenadine in this study differed significantly from placebo.

Three out of four studies using a standardized highway driving test to assess the possible effects of terfenadine on driving, found non-significant improving effects (Riedel, Schoenmakers, & O' Hanlon, 1989; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992; Ramaekers & O'Hanlon, 1994). The highway driving test is a 1-hour on the road driving test conducted during normal traffic, which has been used repeatedly to demonstrate the effects of psychoactive drugs on driving performance (O'Hanlon, Haak, Blaauw, & Riemersma, 1982; Ramaekers, 2003; Vermeeren, 2004). In this test, subjects drive a car over a 100-km circuit, while attempting to maintain a constant speed and a steady lateral position in the traffic lane. During the ride, the car's position relative to the white lane boundary is measured with a frequency of 4 Hz and converted off-line into the standard deviation of lateral position (SDLP), an index of weaving.

The first two studies using this test to assess the effects of terfenadine on driving were conducted by Riedel et al., (1989). They conducted a single dose and repeated dose study in healthy volunteers. No improving effects were found in the single dose study. In the repeated dose study, subjects' performance on day 1 and day 4 of treatment with terfenadine 60 mg b.i.d. was compared with that of placebo. In addition, the combination of each treatment with a dose of alcohol was studied on both days. The results showed that on the first day of treatment with terfenadine subjects performed better on the driving test compared to placebo. Also, terfenadine in combination with alcohol resulted on average in better driving performance than the placebo-alcohol combination on the first day of treatment. However, both performance improvements found after terfenadine treatment (with and without alcohol) were not significantly different from placebo. After 4 days of treatment with terfenadine, the performance ameliorating effects of terfenadine seemed to have disappeared.

In a subsequent study assessing the effects of terfenadine on performance in the highway driving test, a high dose of terfenadine tended to improve performance of healthy subjects (Volkerts et al., 1992). Volkerts et al., (1992) conducted a study to compare the effects of terfenadine 60 (b.i.d.) and 120 mg (q.d.) on driving and psychomotor performance with cetirizine (10 mg), triprolidine (5 mg) and placebo after 1 and 4 days of treatment. On the first day of treatment, subjects in this study demonstrated improved performance on the highway driving test after treatment with terfenadine 120 mg, but not after the 60 mg dose. Similar to the findings by Riedel et al., (1989) after 4 days of treatment the effects of driving had disappeared. On the other hand, terfenadine 60 mg was found to increase sleep latency compared to placebo after 4 days of treatment in the study by Volkerts et al., (1992). The improved driving and increased sleep latency caused by terfenadine treatment, however, were not significantly different from placebo.

Finally, Ramaekers and O'Hanlon (1994) demonstrated dose dependent improving effects of terfenadine on performance in the highway driving test. Ramaekers and O'Hanlon (1994) compared the effects of three doses of terfenadine (60, 120 and 180 mg) on driving performance with those of acrivastine (8, 16 and 24 mg), diphenhydramine (50 mg) and placebo in healthy volunteers. While performance on the highway driving task was significantly impaired after treatment with diphenhydramine and acrivastine, subjects treated with terfenadine were better able to drive with a steady lateral position, although not significantly better than placebo.

Other methods, besides performance measures, to assess the effects of psychoactive drugs on arousal are psychophysiological measures, such as EEG, or subjective measures such as questionnaires or visual analogue scales. Simons et al., (1994 and 1996) used event related potentials, in particular the P300 component, to assess the potential sedative effects of terfenadine (60 mg) in healthy children (Simons, Reggin, Roberts, & Simons, 1994) and adults (Simons, Fraser, Reggin, & Simons, 1996). P300 is a measure of sustained attention and processing speed and drugs that adversely affect the central nervous system have the potential to slow P300 latency. As expected, the children's frontal and parietal P300 latency was not increased in the auditory oddball task compared to baseline, after terfenadine treatment, whereas placebo and chlorpheniramine (4 mg) caused an increase in P300 latency. In adults however, contrary to expectations, a slight stimulating effect was found on the event related potential 2,5 hours after drug administration, since terfenadine decreased P300 latency in the auditory oddball task. In the same study, diphenhydramine (50 mg) increased P300 latency. Thus whereas chlorpheniramine and diphenhydramine impaired the cognitive processes underlying the P300 component, terfenadine did not delay P300 latency but rather had the tendency to accelerate these cognitive processes.

Finally, even studies examining the effects of antihistamines on subjective measures of sedation, have sometimes indicated that terfenadine did not produce more sleepiness than placebo but rather the opposite. Reinberg, Levi, Guillet, Burke and Nicolai (1978) studied the effects of two doses of terfenadine (20 and 60 mg) and clemastine (1 and 3 mg) in healthy volunteers, in a morning or evening dose. When given in an evening dose, terfenadine 60 mg caused less subjective sleepiness, although not significantly less than placebo. Other measures like eye-hand coordination and mathematical skills were not affected by terfenadine in this study. Clarke and Nicholson (1978b) compared the effects of a morning dose of terfenadine 60 mg with chlorpheniramine, clemastine, promethazine and placebo on visuo-motor coordination and subjective measures of performance and well-being in healthy females. Measurements were conducted at 5 different times after drug intake. Visual analogue scales measuring subjective feelings of sedation showed that subjects reported significantly improved wakefulness and alertness at 0,5 and 3,5 h after ingestion of terfenadine, although performance in the visuo-motor test was not affected by terfenadine.

Three of the studies described above demonstrated significant improvements after terfenadine treatment (60 and 120 mg). Significant improvements were found on subjective measures of sleepiness (Clarke & Nicholson, 1978a), driving (Betts et al., 1989) and driving related skills such as divided attention and tracking behaviour (Moskowitz & Burns, 1988). These results are supported by several other studies finding on average better, but statistically not significantly better, performance after terfenadine treatment (60 and 120 mg) (Reinberg et al., 1978; Betts et al., 1984; Riedel et al., 1989; Volkerts et al., 1992; Ramaekers & O'Hanlon, 1994; Simons et al., 1994; Simons et al., 1996).

In sum, the above studies all indicate that terfenadine has stimulating properties. The effects seem to be dependent of dose, however high doses do not always cause significant stimulating effects. Therefore it remains unclear which dose is optimal for detecting stimulant effects. On the other hand, the fact that no study was designed to detect stimulant effects makes the findings of these effects even stronger. And although terfenadine was the first antihistamine to demonstrate stimulant effects, it could be elucidating to investigate whether the effect is specific for terfenadine or whether it has been demonstrated in other antihistamines.

Ebastine

One antihistamine for which performance improving effects have also been reported is ebastine. Stimulating properties of ebastine were first measured in a study conducted by de Vries, de Waard and Brookhuis (1989), but not analyzed and reported as such in their paper. O'Hanlon and Ramaekers (1995) performed additional post-hoc analyses on these data, which clearly revealed ebastine's potential of ameliorating driving performance. In the study by de Vries et al., (1989), ebastine's (10, 20 and 30 mg) effect on the highway driving test was compared with triprolidine (10 mg) and placebo after acute and subchronic treatment. The results indicated that subjects were better able to keep a steady position (SDLP) in the traffic lane after an acute dose of ebastine 10 mg and 20 mg compared to placebo. Only the 10 mg dose significantly improved driving performance in the highway driving test (in O'Hanlon & Ramaekers, 1995). After 5 days of treatment with ebastine, the improving effect of the 20 mg dose disappeared and the 30 mg dose was shown to significantly impair driving performance on the highway driving test (O'Hanlon & Ramaekers, 1995).

Further evidence for stimulating effects of ebastine was found in a repeated dose study by Mattila et al., (1992). They assessed the effects of ebastine (20 mg) and placebo on objective as well as subjective measures of performance after 6 days of treatment and on day 7 in combination with alcohol. Testing was done at baseline and at 2, 4 and 6 hours after treatment. When subjects were treated with ebastine, they demonstrated a slightly but significantly improved body balance at 2 h post-drug compared to baseline. Ebastine treatment also caused a significant improvement in simple tracking in a simulated driving task at 4 h compared to baseline. Furthermore, ebastine did not enhance the effects of alcohol and even tended to counteract these effects on the reaction time in the simulated driving task.

It seems that like terfenadine, ebastine was found to improve performance significantly (De Vries et al., 1989; Mattila et al., 1992) and these improving effects appeared to be dependent of the given dose.

Fexofenadine

A third antihistamine for which stimulating effects have been reported is fexofenadine. Fexofenadine is the active metabolite of terfenadine and therefore structurally also related to it. Therapeutic doses of fexofenadine range from 60 to 180 mg.

The first suggestion of stimulating effects of fexofenadine resulted from a study using the standardized highway driving test described above. Vermeeren and O'Hanlon (1998) studied the effects of fexofenadine (120 and 240 mg) after single and repeated doses on driving and psychomotor tests and compared it with clemastine (2 mg) and placebo. After a single dose of fexofenadine, none of the measures significantly differed from placebo. After four days of treatment, fexofenadine 120 mg b.i.d. was found to significantly improve driving performance on the highway driving task compared to placebo. On the fifth day of fexofenadine treatment, subjects were also given a dose of alcohol. Results showed that fexofenadine 120 mg b.i.d. significantly counteracted the impairing effects of alcohol on driving performance. In addition, this effect was almost significant for the fexofenadine 240 mg o.d. regimen.

There are indications from more recent studies that support the conclusion that fexofenadine may have slightly stimulating effects. Ridout, Shamsi, Meadows, Johnson and Hindmarch (2003) investigated the effects of fexofenadine, alone and in combination with alcohol, on

Chapter 4

Reference	N	Subjects	Dose (mg)	Regimen	Measure	Statistical difference from placebo
Terfenadine						
(Moskowitz & Burnis, 1988)	18	M	60 o.d.	S	Visual search	NS
					Critical tracking	Sign
					Divided attention	Sign
					Vigilance	Sign
(Betts et al., 1989)	10	F	120 o.d.	S	Gap estimation	Sign
(Betts et al., 1984)	12	F	60 b.i.d.	R	Driving	NS
					Subjective alertness	NS
					Fit to drive	NS
(Riedel et al., 1989)	16	M	60 b.i.d.	S	Highway driving test	NS
			60 b.i.d. + alcohol	S	Highway driving test	NS
(Volkerts et al., 1992)	27	M	120 o.d.	S	Highway driving test	NS
					Sleep latency	NS
			60 b.i.d.	R	Sleep latency	NS
(Ramaekers & O'Hanlon, 1994)	18	F	60 o.d.	S	Highway driving test	NS
			120 o.d.	S	Highway driving test	NS
			180 o.d.	S	Highway driving test	NS
(Simons et al., 1994)	15	M&F	60 o.d.	S	P300	NS
(Simons et al., 1996)	15	M	60 o.d.	S	P300	NS
(Reinberg et al., 1978)	10	M&F	60 o.d.	S (evening dose)	Subjective sleepiness	NS
(Clarke & Nicholson, 1978b)	6	F	60 o.d.	S	Subjective alertness	Sign
					Subjective wakefulness	Sign
Ebastine						
(O'Hanlon & Ramaekers, 1995)	15	M	10 o.d.	S&R	Highway driving test	Sign
			20 o.d.	S	Highway driving test	NS
			30 o.d.	S	Highway driving test	NS
(Mattila et al., 1992)	12	M&F	20 o.d.	R	Tracking in simulated driving	Sign
					Body balance	Sign
			20 o.d. + alcohol	R	RT in simulated driving	Sign
Fexofenadine						
(Vermeeren & O'Hanlon, 1998)	24	M&F	120 b.i.d.	R	Highway driving test	Sign
			120 b.i.d. + alcohol	R	Highway driving test	Sign
			240 o.d. + alcohol	R	Highway driving test	NS
(Ridout et al., 2003)	18	M	180 o.d.	S	Subjective sedation	NS
					CRT	NS
(Theunissen et al., In press)	16	M&F	180 o.d.	S	Movement time RT	Sign
					P1-latency	Sign
			360 o.d.	S	Tracking error	Sign
					P3-latency	Sign
Desloratadine						
(Valk et al., 2004)	21	M	5 o.d.	S	Vigilance in divided attention task	NS
(Vuurman et al., 2004)	18	M&F	5 o.d.	S	Brake reaction time	Sign
					Reaction time divided attention task	NS

Table 1. Summary of studies showing stimulant effects for terfenadine, ebastine, fexofenadine or desloratadine. N: number of subjects, F: female subjects, M: male subjects, o.d.: once daily, b.i.d.: twice daily, S: single dose, R: repeated dose, NS: not significant, Sign: significant with p-value $\leq .05$.

subjective and objective measures of sedation, such as a critical flicker fusion test, choice reaction time test and brake reaction test. Scores for subjective sedation showed a significant treatment effect; fexofenadine with and without alcohol resulted in a reduction in sedation from baseline at 1, 3 and 5 hours post-drug. However, at no point in time did the subjective sedation score for fexofenadine differ significantly from placebo. In line with this, performance on the choice reaction tests seemed improved though not significantly by fexofenadine as compared to placebo.

Theunissen et al., (In press) conducted an event related potential study that was specifically designed to detect stimulant effects of fexofenadine. Fexofenadine was administered in relatively high single doses of 180 and 360 mg and the effects were assessed under increasing workload conditions. Event related potentials showed that fexofenadine in general shortened latencies of the P100 and P300 components measured during the divided attention task, indicating faster early attentional processing and faster stimulus evaluation processes. This was supported by results from performance tests showing a significant interaction between effects of the drugs and workload. Workload increased tracking error, yet less so when subjects were treated with fexofenadine 360 mg relative to placebo. In addition, the number of control losses increased less with increasing workload after treatment with fexofenadine 360 mg. Fexofenadine 180 mg was also found to improve performance on the movement component of a reaction time task.

It is clear from the above studies that fexofenadine like terfenadine and ebastine has the potential to improve performance especially in tasks that require a high level of attention, such as driving and divided attention skills.

Desloratadine

Recently, evidence for stimulating effects has been found for desloratadine, a relatively new antihistamine. Desloratadine is an active metabolite of loratadine and is given in therapeutic doses of 5 mg.

Valk, Van Roon, Simons and Rikken (2004) studied the effect single doses of desloratadine 5 mg on performance in a simulated flight cabin and compared it with diphenhydramine (50 mg) and placebo in healthy volunteers. Performance measures included objective tests, such as a divided attention task measuring vigilance and tracking, and subjective questionnaires for assessing sleepiness. At 2 and 3 hours post-drug, desloratadine seemed to improve performance on the vigilance task compared to placebo. The difference between desloratadine and placebo did however not reach significance.

Vuurman et al., (2004) also compared single doses of desloratadine 5 mg with diphenhydramine (50 mg) and placebo in healthy volunteers. The drugs' effects were measured on two driving tests and several objective (memory, tracking, reasoning, divided attention, critical flicker fusion,...) and subjective performance tasks. Driving tests were the standardized highway driving test described before and a car-following test measuring the ability to adapt to changes in speed and react to brake lights of a preceding vehicle. Results showed that subjects had significantly faster brake reaction times following desloratadine treatment compared to placebo and diphenhydramine. Similarly, desloratadine had a positive effect on driving performance in the highway driving test and response speed in the divided attention task, although these effects did not reach significance for these measures.

The above studies demonstrate that desloratadine, like terfenadine, ebastine and fexofenadine, also may have stimulating properties. Although the effects seem dose dependent for different drugs, the relationship is not consistent. It is interesting that all four antihistamines belong to the piperidine group. This suggests that the mechanism underlying these stimulating effects might be related to the chemical structure of these compounds.

In conclusion, the experimental studies described above were almost all designed to examine the safety of second generation antihistamines on cognitive and psychomotor performance. Unexpectedly however, they showed that terfenadine, ebastine, fexofenadine and desloratadine have the potential to improve cognitive and psychomotor performances, suggesting that they had stimulant rather than sedative effects. The fact that the performance improving effects of these antihistamines reached significance in only a few studies indicates that if they do have stimulating effects, these effects are very mild compared to known stimulants like caffeine or amphetamines. In addition, some drugs' stimulating effects have only been demonstrated after higher than therapeutic doses or after repeated doses e.g. fexofenadine, whereas others, e.g. ebastine, no longer stimulated performance but rather caused impairing effects when doses were increased or given over longer periods. Interestingly, the stimulating effects were in many cases demonstrated in tests which rely heavily on divided and/or sustained attention, e.g. the standardized highway driving test was shown to be sensitive for the stimulating effects of all four antihistamines (see figure 1).

Figure 1. Effects of terfenadine, ebastine, fexofenadine and desloratadine on performance in the standardized highway driving test. Shown are mean changes from placebo in Standard Deviation of Lateral Position (SDLP), a negative score indicates better performance. In the study of Ramaekers & O'Hanlon (1994), the driving test was performed twice; once between 1 and 2 hours, and once between 3 and 4 hours after drug intake. * indicate significant improvement compared to placebo ($p < .05$)

POSSIBLE MECHANISMS UNDERLYING STIMULATING EFFECTS OF H1-ANTAGONISTS

Assuming that the seemingly stimulating effects found for some H1-antagonists are real, what could be the explanation? What could be the underlying neural mechanism and how does it explain the differences between antihistamines? A few suggestions, based on animal research, have been put forward which might explain the mild stimulating effects that were found for terfenadine, ebastine, fexofenadine and desloratadine.

Inhibition of dopamine reuptake

One suggested mechanism is that antihistamines, besides blocking H1-receptors, also inhibit dopamine reuptake. This blockade causes an increase in the dopamine availability (Dringenberg, de Souza-Silva, Schwarting, & Huston, 1998), which is known to increase arousal and attention (Robbins, 1997). Psychostimulants, like cocaine and amphetamine, increase levels of dopamine and noradrenaline by blocking their reuptake and increasing their release, thereby improving psychomotor functions, such as attention, vigilance and reaction times (Fleming, Bigelow, Weinberger, & Goldberg, 1995; Johnson et al., 1998). So, if H1-antagonists also block dopamine reuptake they could produce effects similar to psychostimulants (Vermeeren, 2003), yet they must do so in a more limited way in the doses tested, since their effects are very mild as compared to cocaine or amphetamines.

The inhibition of dopamine reuptake by some antihistamines has been demonstrated in rats and mice (Oishi, Shishido, Yamori, & Saeki, 1994; Matsunaga et al., 1998). Oishi et al., (1994) studied in vivo effects of several antihistamines on monoamine turnover in mice. Seven antihistamines (diphenhydramine, tripeleennamine, promethazine, chlorpheniramine, mepyramine, clemizole and homochlorcyclizine) were found to significantly decrease dopamine turnover. The effect was suggested to be caused by inhibition of dopamine reuptake. This hypothesis is supported by a study by Matsunaga et al., (1998). These investigators specifically examined the inhibiting effects of antihistamines on neuronal dopamine uptake into striatal synaptosomes. Results showed that four of the antihistamines studied inhibited neuronal dopamine reuptake. Interestingly, ebastine and terfenadine were found to be the most potent inhibitors of dopamine reuptake.

Behavioural studies in animals also provide additional evidence that some antihistamines have the ability to stimulate dopamine transmission. Several studies reported antihistamines to have rewarding and reinforcing effects, which for most drugs are related to dopamine increases in mesolimbic areas (Bergman & Spealman, 1988; Sato et al., 1996; Suzuki et al., 1999). Bergman & Spealman (1988) studied the reinforcing effects of chlorpheniramine, diphenhydramine, loratadine and astemizole, using rate of self-administration in squirrel monkeys. Chlorpheniramine and diphenhydramine produced increases in response rate to the same extent as dopamine reuptake inhibitors, bupropion and cocaine. In addition, Bergman & Spealman (1988) demonstrated that some of the behavioural effects caused by dopamine reuptake inhibitors (bupropion and cocaine) and an H1-antagonist (diphenhydramine) could be attenuated by a dopamine receptor antagonist. Therefore, the authors suggested that the behavioural effects caused by H1-antagonists and dopamine reuptake inhibitors are mediated by the same neurochemical mechanism, namely dopamine reuptake inhibition.

Suzuki et al., (1999) studied the rewarding effects of antihistamines in rats using a place preference paradigm. In this test, the animals are first place conditioned, i.e. rats were given

an injection with an antihistamine in one compartment, while they received a saline injection in another compartment. After the conditioning phase, rats demonstrated a preference for the compartment where they were given tripeleennamine or the optical isomers of chlorpheniramine, indicating a rewarding effect which is thought to be related to an enhanced dopaminergic transmission (Leshner & Koob, 1999). The behavioural effects caused by tripeleennamine and dl-chlorpheniramine disappeared after treatment with a dopamine antagonist. Together these results suggest that some, but not all, H1-antagonists increase dopamine transmission. The researchers added that the rewarding effects are not mediated by histamine blockade, since the rewarding effects caused by the optical isomers of chlorpheniramine did not correlate with their H1-antagonistic potency.

Sato et al., (1996) investigated the effects of antihistamines on L-dopa-induced behavioural excitement in mice. Their study indicated that several antihistamines (e.g. d-chlorpheniramine and diphenhydramine) enhanced the behavioural excitement caused by a combination of L-dopa and the MAO-inhibitor pargyline. A selective dopamine antagonist, on the other hand, inhibited the excitement induced by L-dopa and pargyline. The results of this study are again an indication for dopamine reuptake inhibition by H1-antagonists.

Disinhibition of dopaminergic activity through GABA

A second mechanism suggested to underlie the stimulating effects of H1-antagonists, involves GABA-neurons. Korotkova, Haas and Brown (2002) examined the effects of histamine on spontaneous firing of GABA and dopamine neurons in vitro. Their study demonstrated that histamine increased the firing frequency of GABA neurons. Histamine did not affect the firing of dopamine neurons, suggesting that histamine has no direct effect on dopamine neurons. In vivo, however, stimulation of GABA-ergic neurons causes inhibition of dopaminergic activity. Therefore, Korotkova et al., (2002) suggest that histamine inhibits dopaminergic neurons indirectly through histamine induced excitation of GABA-ergic neurons. In addition, their study demonstrated that mepyramine, an H1-antagonist, blocked the histamine induced excitation of GABA neurons. As a consequence, it is likely that H1-antagonists might also stimulate dopaminergic neurotransmission by decreasing the tonic GABA-ergic inhibition of dopamine pathways, i.e. disinhibition of dopaminergic activity (Vermeeren, 2003).

H3-antagonism

A final explanation for the stimulating effects of some H1-antagonists might be found in their interaction with other histamine receptors, in particular the H3-receptor. The histamine H3-receptor, discovered in the 1980's, is located presynaptically acting as an autoreceptor, but also as a heteroreceptor. As an autoreceptor it regulates the synthesis and release of histamine; and as a heteroreceptor the release of other neurotransmitters (Arrang, Garbarg, & Schwartz, 1983; Blandina, Bacciottini, Giovannini, & Mannaioni, 1998).

Evidence that antihistamines do not bind solely on H1-receptors comes from a study by Sharif, Su and Yanni (1994). They showed that the several H1-antagonists also bind to central H2- and H3-receptors in rodents, although with different affinities. It was shown that various antihistamines have different ratios in binding affinity for H1- and H3-receptors (e.g. the receptor affinity ratio H3:H1 was 9,562 for emedastine while 82 for levocabastine).

Since blockade of the H1- and H3-receptors has opposing effects on histamine transmission, it is possible that some antihistamines with relatively high affinity for the H3-receptors stimulate rather than block histaminergic transmission depending on the dose. Stimulation of histaminergic transmission by H3-antagonists increases arousal. For example, Monti et al., (1991) and Monti, Jantos, Ponzoni and Monti (1996) showed that the H3-antagonists thioperamide and carboperamide increased wakefulness and decreased slow wave sleep and REM sleep in rats, whereas an H3-agonists increased slow wave sleep.

Although the increased wakefulness following administration of an H3-antagonist can be the result of increased histamine levels, Monti et al., (1996) already noted that the noradrenaline, dopamine, serotonin and acetylcholine neurotransmitter systems might also be involved, since H3-receptors are also heteroreceptors. These receptors have indeed been shown to regulate release of dopamine, noradrenaline, serotonin and acetylcholine (Schlicker & Kathmann, 1998; Witkin & Nelson, 2004).

Nevertheless, two studies suggest that the effect of H3-antagonists on wakefulness mainly results from the enhancement of histamine release. In one study, ciproxifan, an H3-antagonist, was also shown to have a waking effect in cats and an attention enhancing effect in rats (Ligneau et al., 1998). When ciproxifan was given in combination with a H1-antagonist (mepyramine), the enhancement of wakefulness did not appear, indicating that the effect of ciproxifan was probably caused by increased release of histamine through H3-blockade (Ligneau et al., 1998). Parmentier et al., (2002) also demonstrated increased wakefulness (delayed sleep latency, suppression of slow wave sleep and paradoxical sleep) in mice after ciproxifan treatment. Knockout mice lacking the enzyme histidine decarboxylase responsible for histamine synthesis, however, did not show evidence of changes in wakefulness. This finding also suggests that the increase in arousal and wakefulness after H3-antagonism is mediated through the increased synthesis and release of histamine.

CONCLUSIONS

In this review we have demonstrated that there is evidence suggesting that at least four H1-antagonists have the potential to stimulate psychomotor performance. First of all, this finding implicates that these 'non-sedating' H1-antagonists also have central effects, suggesting that they are able to cross the blood brain barrier. So even though it is often stated that second generation antihistamines do not cause sedation because they do not act centrally, the stimulating effects found for some second generation antihistamines bears evidence that they do enter the central nervous system.

In treatment of allergies, sedation is one of the most reported side effects of antihistamines. In choosing the right treatment, less sedating second generation antihistamines are recommended over the older, highly sedating first generation antihistamines. It can now even be proposed that antihistamines with small stimulating properties should even be more beneficial for patients with allergies, since they may also experience disease-related impairments (Blaiss, 2000; Burton, Conti, Chen, Schultz, & Edington, 2001). The studies described above, however, were all done in healthy populations. One previous study, examining the effect of the second generation antihistamine, loratadine, found that it improved allergic children's learning performance compared to symptomatic children without treatment, but that their performance was still impaired compared to that of healthy children (Vuurman, van Veggel, Uiterwijk, Leutner, & O'Hanlon, 1993). It would therefore be enlightening to see whether

any of the four mildly stimulating antihistamines is able to bring patients' performance back to its baseline level.

A few hypotheses for the stimulating effects of H1-antagonists have been outlined, suggesting a role for dopamine, GABA and H3-receptors. It is possible that different mechanisms are responsible for the stimulating effects of the different antihistamines, or that combinations of these factors sometimes add up to a measurable effect. As Matsunaga et al., (1998) demonstrated, ebastine and terfenadine were found to be the most potent dopamine reuptake inhibitors. However, there are no studies available testing the dopamine reuptake inhibiting potential of fexofenadine and desloratadine. In addition no study has tested any of the four antihistamines on their GABA-inhibiting potential or H3 binding potency. So the exact mechanism whereby each antihistamine produces its stimulating effects remains uncertain.

Recently, more research is dedicated to H3-antagonists and their effect on cognitive functioning (Esbenshade et al., 2004; Vohora, 2004). Several H3-antagonists are being developed and have been reported to effect wakefulness and cognition in rodents (Monti et al., 1996; Prast, Argyriou, & Philippu, 1996; Bernaerts, Lamberty, & Tirelli, 2004). In addition, enhanced performance was demonstrated in animal models for ADHD (Fox et al., 2002; Fox et al., 2003). Since H3-antagonists are so far not approved for clinical use, the therapeutic benefits in humans have not been studied yet. However, if the stimulant effects of the antihistamines described in this review are a result of H3-antagonism, it is a first indication that H3-antagonists are not only able to improve cognitive performance in animals but also in humans.

This review showed that there is extensive evidence indicating that the non-sedating antihistamines, terfenadine, ebastine, fexofenadine and desloratadine have the potential to stimulate performance in healthy volunteers, especially in attention demanding tasks. Although the mechanism whereby these antihistamines cause stimulant effects remains unclear, the finding could mean an important improvement in the quality of life of allergic patients.

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Stimulating effects of fexofenadine under high workload conditions. A combined neurophysiological and behavioral approach

CHAPTER 5

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ABSTRACT

Antihistamines are known for their sedative effects. However, some studies suggested mild stimulant effects in case of fexofenadine. The goals of this study are to examine whether fexofenadine possesses stimulating properties and to determine whether such stimulating effects are related to workload. 16 healthy volunteers received a single dose of 180 and 360 mg fexofenadine and placebo on separate test days. Drug effects were assessed using a divided attention task (DAT), continuous performance task (CPT) and motor choice reaction time test (MCRT). Sensitivity of the tasks was increased by manipulating the workload during task performance. Event Related brain Potentials (ERP's) were measured in the DAT and CPT to study the underlying neurophysiological processes. An interaction effect of Treatment and Workload was found on tracking performance in the DAT and on movement time in the MCRT. Performance on the DAT was less affected by increments in workload after fexofenadine as compared to placebo. P1 and P3 latency were affected by Treatment x Workload and Treatment respectively and indicated faster attentional and information processing latencies following fexofenadine treatment. Treatment did not influence performance in the CPT task or in the ERP's measured during this task. The MCRT demonstrated faster movement times following fexofenadine treatment. These results suggest that although the neurophysiological data indicate central nervous system (CNS) activation after fexofenadine treatment, the magnitude of the centrally activating effects is too small to produce relevant performance improvement at the behavioral level.

INTRODUCTION

Allergies such as allergic rhinitis, conjunctivitis and urticaria are caused by hypersensitivity for peripheral histamine. Relief of symptoms is accomplished by antihistamines which reach their therapeutic effect by blocking peripheral histamine receptors (H₁). The first antihistamines developed were lipophilic and therefore entered the brain easily where they also blocked central histamine neurotransmission. Central histamine neurotransmission is involved in the maintenance of arousal (Onoe et al., 1992; Onodera, Yamatodani, Watanabe, & Wada, 1994). Blocking central H₁-receptors by antihistamines has been shown to induce somnolence and to seriously diminish cognitive, psychomotor and driving performance in healthy volunteers (Rombaut & Hindmarch, 1994; Simons, 1994; O'Hanlon & Ramaekers, 1995). Other side effects of first generation antihistamines, such as diphenhydramine, triprolidine, clemastine or chlorpheniramine, are blurred vision and dry mouth as a result of muscarinic antagonism (Snyder & Snowman, 1987; Gengo, 1996; Passalacqua et al., 1996).

Second generation antihistamines (also called non-sedating antihistamines) were developed to overcome the problem of sedation. These antihistamines are less lipophilic and cross the blood-brain barrier more slowly than their predecessors. However, recent studies have shown that also 2nd generation antihistamines have the potential to cause sedation (O'Hanlon & Ramaekers, 1995). Several 2nd generation antihistamines (acrivastine, cetirizine, mizolastine and emedastine) mildly impaired driving when given in therapeutic doses (Ramaekers & O'Hanlon, 1994; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994; Vermeeren, Ramaekers, & O'Hanlon, 2002). Other 2nd generation antihistamines (loratadine, mequitazine and terfenadine) did not have significant effects on driving performance when taken in recommended doses but had at least measurable effects after doubling the dose (Riedel, Ramaekers, Uiterwijk, & O'Hanlon, 1990; Theunissen, Vermeeren, van Oers, van Maris, & Ramaekers, 2004). These results indicate that not all second-generation antihistamines share the same low tendency to produce sedation.

Recently some 2nd generation antihistamines were even found to possess stimulating effects. Fexofenadine, for instance, did not impair psychomotor and driving performance when given in single doses ranging from 60 to 240 mg (Vermeeren & O'Hanlon, 1998; Hindmarch & Shamsi, 1999; Nicholson, Stone, Turner, & Mills, 2000; Weiler et al., 2000; Bower et al., 2003) but rather improved driving performance (Vermeeren & O'Hanlon, 1998), an effect which was previously also demonstrated for ebastine 10 mg (O'Hanlon & Ramaekers, 1995). Single doses of desloratadine 5 mg also did not cause impairing effects on actual driving and psychomotor performance but did improve brake reaction time in the driving test (Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004). Terfenadine is yet another antihistamine which has shown not to impair performance but rather improve performance on psychomotor tasks (Moskowitz & Burns, 1988) and subjective alertness and wakefulness (Clarke & Nicholson, 1978; Reinberg, Levi, Guillet, Burke, & Nicolai, 1978). Improved psychomotor performance and body balance were also found after single doses of ebastine (Mattila, Kuitunen, & Pletan, 1992). The clinical significance of these findings is unclear, but they indicate that these antihistamines do enter the brain and can cause stimulating effects.

The goals of this study are to examine whether fexofenadine possesses stimulating properties and to assess whether its stimulating effects are related to workload. It is expected that tasks with a high workload are more sensitive for a stimulating drug effect. Dependent variables include behavioral measures as well as Event Related brain Potentials (ERP's).

ERPs are particularly useful for measuring temporal and cognitive information processes that precede an overt, behavioral response.

MATERIALS AND METHODS

Subjects

Sixteen healthy volunteers (8 males and 8 females), aged between 21 and 35 years were recruited by means of newspaper advertisements. Subjects were first screened using a medical history questionnaire. Each qualified subject underwent a physical examination in which an electrocardiogram was made and a blood sample was taken. Mean (SD) age of the participants was 23.3 (3.19) years.

Exclusion criteria were: history of major medical or psychiatric disorder, any non-corrected visual or psychomotor defect, unusual sensitivity to antihistamines, drug abuse and chronic use of medication. Female subjects could not participate when pregnant or lactating, and were required to use an effective contraceptive during the study. After having received all necessary information, every participant gave their written consent. The study was approved by the medical Ethical committee of Maastricht University and subsequently carried out in accordance with the World Medical Associations Declaration of Helsinki (Edinburgh modification, 2000).

Procedure

Drugs and placebo were administered according to a 3-way, double-blind, cross-over design. A wash-out period of at least 7 days proceeded in between treatments. Treatments consisted of single doses of placebo, fexofenadine 180 mg and fexofenadine 360 mg (therapeutic dose of fexofenadine is 120 to 180 mg). Drugs and placebo were administered in orally identically appearing formulations to ensure blinding.

All subjects were trained on all tests a few days prior to their first treatment period. Subjects were prohibited from consuming alcohol for 24h before testing. Half an hour before drug intake all subjects received a standard meal. Consumption of caffeine containing beverages was not allowed on test days. Smoking was prohibited 30 minutes prior and during testing. Behavioral and ERP testing were performed between 2-3 hours after drug intake.

Assessments

• *Critical Tracking Task (CTT)*

In the critical tracking task, the subject controls an unstable cursor on a computer screen using a joystick (Jex, McDonnell, & Phatak, 1966). An error signal causes the cursor to become increasingly unstable on a horizontal axis, causing it to diverge from the centre of the axis. The subject's task is to try to keep the cursor in the center of the axis by continuously making compensatory joystick movements. The frequency of cursor deviations increases as a stochastic, linear function of time, therefore the subject is required to make compensatory movements with a progressively higher frequency. Eventually, the subject's response adds to, rather than subtracts from, the error and consequently control is lost. The frequency at which the subject loses the control is the critical frequency (λ_c). The test is performed five times; the average critical frequency is calculated without the lowest and highest score and is the dependent variable of this test. Depending on the competence of the subject, this task takes 3 to 8 minutes.

• *Divided Attention task (DAT)*

The Divided Attention Task measures the ability to divide attention between two simultaneous tasks (Moskowitz, 1973). As a primary task, the subject performs the same tracking task as described above but at a constant level of difficulty. The task is repeated 3 times, each with the primary task set at a different level of difficulty in order to assess the interaction between mental workload and drug treatment. Task difficulties (λ_c) are set at 50, 60 and 70% of each subjects' maximal performance as measured during training sessions of critical tracking task. As a secondary task, the subject monitors a central display upon which single digits (0 to 9) are presented for 17 milliseconds with a variable inter stimulus interval between 1.03 and 1.23 seconds. The occurrence of the digit "2" is a signal for the subject to remove his/her foot from a pedal as rapidly as possible. In total, 75 targets and 375 distractors are presented. Mean absolute tracking error (mm) is the dependent variable in the primary task; number of correct responses and mean reaction time (ms) of these responses are the performance measures in the secondary task. Depending on the competence of the subject, this task takes about 10 minutes.

It is hypothesized that performance in the primary task will decline as a result of the increased workload and in addition performance on the secondary task will be negatively influenced by the increased workload of the primary task.

• *Continuous Performance Task (CPT)*

Continuous Performance Tasks (Conners, 1992) have been used repeatedly to study vigilance and attention, and several variants of this test have been developed. The version used in the present experiment is the CPT-ax task. In this task, letters are presented to the subject one by one on a computer screen for 150 msec with an Inter Stimulus Interval (ISI) of 600 msec. The subjects' task is to press a button as fast as possible when the target letter X appears, but only when it is preceded by an A (Go condition). In situations in which the cue letter A is not followed by the target X, subjects have to inhibit their prepared responses (NoGo condition). Thus, the task measures attention associated with Go responses as well as inhibition processes (evoked by NoGo trials). The task included 48 Go stimuli (A-X), 96 NoGo trials (A-nontarget) and 240 randomly presented letters. Nontarget letters were E, H, L and K. The task was divided in four blocks and lasted in total approximately 10 minutes.

In order to differentiate workload conditions in the CPT-ax task a high load version was developed. In this version, the target letter is an X with a small dot on top of it. The letter X with a small dot underneath was added as a nontarget, and had to be ignored. In total this task included 48 Go trials (A-X-dot on top), 144 NoGo trials (48 A-X-dot below and 96 A-nontarget) and 288 randomly presented letters. Except for the changed target letter and the added nontarget, the task is identical to the easy version. The variables measured in both tasks are number of correct responses, number of false alarms and reaction time of these responses.

• *Motor Choice Reaction Time (MCRT)*

The Motor Choice Reaction Test is a test in which reaction time is studied as a function of task difficulty (Houx & Jolles, 1993). The subject is presented with a computerized panel with one central red and 5 white buttons. The subject is asked to hold the central red button until one of the white buttons lights up. As soon as a white button illuminates, the participant has to release the red button and press the illuminated button and return to the red central button as fast as possible. Three task conditions with increasing difficulty were used: simple reaction time, in which only the upper button illuminates; choice reaction

time, in which one of a defined set of three buttons illuminates; and incompatible reaction time, which is the same as the previous condition but the task is to press the button located to the right of the illuminated button. Reaction time was divided into an initiation phase, i.e. time from stimulus onset until release of the red button, and a movement phase, i.e. time between release of the red button and pressing the response button. Initiation time represents the time needed for perception, decision and motor planning while movement time represents the time needed for actual movement execution. Dependent measures are median initiation and movement time in the three workload conditions (simple, choice and incompatible condition). Task duration is approximately three minutes.

• *Event Related Potentials*

Recording - EEG-activity was recorded by means of an electro-cap from an array of 30 electrodes from the standard 10-20 system (Fz, Cz, Pz, Oz, F3, F4, F7, F8, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2, Fp1, Fp2, Ft7, Ft8, Fc3, Fc4, Tp7, Tp8, Cp3, Cp4, FCz, CPz). Electrodes were filled with electro-gel. All electrodes were referenced to the left mastoid; FPz was used as ground electrode. Horizontal EOG was recorded using electrodes attached to the outer canthi of the eyes, while vertical EOG were recorded from infraorbital and supraorbital electrodes placed in line with the pupil of the left eye. All electrode impedances were kept below 5 K Ω . ERP's were collected using the Neuroscan 4.1 software, and SynAmps amplifiers were used. All signals were continuously sampled at a rate of 250 Hz and digitally filtered online with a high-pass filter of 0.05 Hz and a low-pass filter of 50 Hz. Continuous signals were epoched into 1200 msec sweeps for the divided attention task and into 950 msec sweeps in the CPT-ax tasks, both including a 200 msec pre-stimulus baseline.

Signal Analysis - All of the sampled EEG and EOG epochs were baseline corrected and filtered off-line using a 30-Hz, 24-dB/oct digital low-pass filter. EEG's were corrected for vertical eye movements according to a procedure by Semlitsch, Anderer, Schuster, and Presslich (1986). Sweeps containing an artifact exceeding +75 or -75 μ V were rejected.

ERP-components - The ERP-components of interest in the tasks used are the occipital P1, the frontal N2 and parietal P3 (or P3b). P1 is a positive peak which appears around 100 msec, above visual cortex and reflects early attentional processes (Mangun & Hillyard, 1990; Mangun, 1995), and is specifically sensitive to spatial attributes of the stimulus (Rugg, Milner, Lines, & Phalp, 1987), task load and salience (Taylor, 2002). In go-nogo tasks, the N2 wave (a negative wave occurring around 200 msec post-stimulus) is reported to be related to response inhibition (Jodo & Kayama, 1992; Falkenstein, Hoormann, & Hohnsbein, 1999). The parietal P3, a positive wave between 300-800 msec, has mostly been demonstrated in so-called oddball tasks (Picton, 1992; Polich & Kok, 1995). In these kinds of tasks, subjects are presented with frequent and rare stimuli in a random order. P3 amplitude is shown to be affected by the probability of the rare stimulus (Duncan-Johnson & Donchin, 1977), in both passive and active tasks (Mertens & Polich, 1997). Other factors like attention, stimulus quality and task relevance also appear to affect P3 amplitude (Smulders, Kok, Kenemans, & Bashore, 1995). The P3 component has also previously shown to be an indicator for processing capacity in dual tasks. P3 elicited by a secondary test, has been found to decrease in amplitude with increases in the perceptual or cognitive difficulty of the primary task (Isreal, Chesney, Wickens, & Donchin, 1980; Wickens, Kramer, Vanasse, & Donchin, 1983; Brocke, Tasche, & Beauducel, 1996; Kok, 2001). On the other hand, P3 latency of the secondary task is

affected mainly by stimulus evaluation time of the primary task (Duncan-Johnson, 1981; Smulders et al., 1995).

In the dual-task (divided attention task), ERP's were measured in relation to the secondary task. ERP-averages for individual subjects were calculated for targets and distractors. Artifact-free epochs ranged between 60 and 75 for targets and between 300 and 375 for distractors. Parietal (Pz) P3 peak amplitude and latency was determined in a window between 350 and 650 msec as a measure of the amount of invested capacity in the secondary task under different workload conditions. It is expected that the P3 amplitude will decrease as a function of workload because of the diminished capacity available for the secondary task. Furthermore, the maximum P1 amplitude and latency at Oz was scored between 80 and 200 msec to examine effects of primary task load on early attentional processing of stimuli in the secondary task.

For the easy CPT-ax version, individual ERP averages were calculated for correctly detected targets, for correctly rejected nontargets following A that shared no features with the target letter (E, H, L), and for the correctly rejected nontarget letter K following A, which has similarities with the target letter. For the harder CPT-ax task, averages were calculated for correctly detected targets (X-dot on top following A) and 3 types of correctly rejected distractors (random letters (E, H, L), K's and X's-dot below, all following the cue letter A). All ERP's were calculated based on at least 23 and maximum 48 artifact-free epochs. In both tasks the maximum amplitude and peak latency of the frontal N2 (Fz) was measured between 150 and 350 msec following onset of the stimulus as an indicator of response inhibition which is expected to be larger in distractor than target conditions. The maximum parietal P3 peak and its latency were measured at Pz between 250 and 600 msec after stimulus onset and was taken as a measure of attention invested in the processing of targets (compared to nontargets). All time windows were defined after inspection of the grand averages.

Analysis

All parameters that were normally distributed were subjected to repeated measures analysis of variance (ANOVA). Performance data from the DAT were tested for the main effects of Treatment (3 levels), Workload (3 levels) and Treatment by Workload. ERP data were tested for an additional factor Stimulus-type (2 levels). Performance and ERP data from the CPT tasks were tested for the main effect of Treatment in the easy and high load conditions separately. ERP-analysis also included the additional factor Stimulus-type (3 levels in the easy version and 4 levels in the difficult version). Performance data from the MCRT task were tested for the effects of Treatment (3 levels) and Workload (3 levels). Type I errors associated with inhomogeneity of variance were controlled by decreasing the degrees of freedom using Greenhouse-Geisser corrections, and the probability estimates were based on these reduced degrees of freedom. Separate drug-placebo comparisons were conducted only in case of a significant main effect of Treatment or Treatment x Workload by means of simple contrasts with Bonferroni correction. The main variables of the divided attention task (RT, tracking error and P3) were tested 1-tailed because of the one-sided nature of the prediction. All other evaluations were carried out in a similar fashion, but were tested 2-tailed and significance level was $p < .05$ in all cases. Variables that were not normally distributed were analyzed using the non-parametric Friedman test. All statistical tests were conducted using SPSS (version 10.0).

Chapter 5

RESULTS

A summary of descriptive and quantitative statistical analyses of the behavioral results in each treatment condition are shown in Table 1 and of ERP-measures in each treatment are shown in Table 2.

Critical Tracking Task

There was no effect of Treatment on CTT.

Divided Attention Task

In the primary task of the DAT, tracking error was significantly affected by Workload level ($F_{2,30}=128.1$ $p<.01$, one sided), i.e. tracking error increased when workload increased. There was no main effects of Treatment, but the interaction between Treatment and Workload

	Mean $\pm$ SEM per treatment			Treatment effect				Treatment x Workload		
	Placebo	Fexo 180	Fexo 360	F	X ²	df	p	F	df	p
CTT										
Lambda-C (rad/sec)	4.31 $\pm$ 0.16	4.34 $\pm$ 0.15	4.35 $\pm$ 0.14	.48	-	2.30	NS	-	-	-
DAT										
Tracking error (mm)	14.0 $\pm$ 0.8	13.0 $\pm$ 0.8	13.2 $\pm$ 0.7	.87	-	2.60	NS	4.47	1.15	.026
Workload 50	10.7 $\pm$ 0.9	10.1 $\pm$ 1.1	10.7 $\pm$ 1.0							
Workload 60	13.6 $\pm$ 1.1	13.1 $\pm$ 1.3	12.7 $\pm$ 0.9							
Workload 70	17.6 $\pm$ 1.3	15.9 $\pm$ 1.3	16.2 $\pm$ 1.1							
Reaction Time (msec)	557 $\pm$ 11	561 $\pm$ 12	562 $\pm$ 11	-	.13	2	NS	-	-	-
Workload 50	560 $\pm$ 20	559 $\pm$ 20	572 $\pm$ 17							
Workload 60	550 $\pm$ 22	563 $\pm$ 22	551 $\pm$ 18							
Workload 70	561 $\pm$ 18	562 $\pm$ 20	565 $\pm$ 21							
Hits (#)	72.1 $\pm$ 0.6	71.6 $\pm$ 0.7	71.8 $\pm$ 0.6	-	.90	2	NS	-	-	-
Workload 50	72.4 $\pm$ 0.9	71.6 $\pm$ 1.0	72.1 $\pm$ 0.7							
Workload 60	72.3 $\pm$ 1.2	72.5 $\pm$ 0.9	72.2 $\pm$ 1.0							
Workload 70	71.4 $\pm$ 1.0	70.6 $\pm$ 1.7	70.9 $\pm$ 1.4							
CPT										
<i>Easy load</i>										
Hits (#)	45.9 $\pm$ 0.7	46.9 $\pm$ 0.6	46.9 $\pm$ 0.6	-	4.78	2	NS	-	-	-
Reaction time (msec)	380 $\pm$ 15	371 $\pm$ 13	382 $\pm$ 12	1.90	-	2.30	NS	-	-	-
<i>High load</i>										
Hits (#)	46.9 $\pm$ 0.4	46.1 $\pm$ 0.8	46.7 $\pm$ 0.5	-	1.59	2	NS	-	-	-
Reaction time (msec)	398 $\pm$ 13	392 $\pm$ 14	411 $\pm$ 13	3.28	-	2.30	.051	-	-	-
MCRT										
Initiation time (msec)	344 $\pm$ 8	341 $\pm$ 8	342 $\pm$ 11	0.61	-	2.56	NS	2.52	26.366	NS
Simple	298 $\pm$ 7	292 $\pm$ 6	303 $\pm$ 13							
Choice	336 $\pm$ 7	334 $\pm$ 9	337 $\pm$ 10							
Incompatible	399 $\pm$ 11	398 $\pm$ 12	389 $\pm$ 12							
Movement time (msec)	102 $\pm$ 6	97 $\pm$ 6	101 $\pm$ 5	2.08	-	2.56	NS	2.58	4.56	.047
Simple	104 $\pm$ 6	97 $\pm$ 6	98 $\pm$ 6							
Choice	98 $\pm$ 6	97 $\pm$ 6	101 $\pm$ 5							
Incompatible	105 $\pm$ 6	99 $\pm$ 6	104 $\pm$ 5							

Table 1. Summary of the results on the critical tracking task, divided attention task, continuous performance task and motor choice reaction task. Treatments are placebo, fexofenadine 180 mg (fexo 180) and fexofenadine 360 mg (fexo 360). NS: not significant; df: degrees of freedom.

	Mean $\pm$ SEM per treatment			Treatment effect			Treatment $\times$ Workload		
	Placebo	Fexo 180	Fexo 360	F	df	p	F	df	p
DAT									
P1-latency (msec)	137.7 $\pm$ 2.8	137.7 $\pm$ 2.7	135.9 $\pm$ 2.6	.57	2,30	NS	3.03	4,60	.024
Targets	138.2 $\pm$ 0.3	136.0 $\pm$ 2.9	133.3 $\pm$ 2.8						
Nontargets	137.3 $\pm$ 3.1	139.4 $\pm$ 3.0	138.4 $\pm$ 2.9						
P1-amplitude (μ V)	4.5 $\pm$ 0.3	4.3 $\pm$ 0.2	4.4 $\pm$ 0.3	.54	2,30	NS	.81	4,60	NS
Targets	4.8 $\pm$ 0.3	4.4 $\pm$ 0.3	4.7 $\pm$ 0.4						
Nontargets	4.1 $\pm$ 0.3	4.2 $\pm$ 0.2	4.1 $\pm$ 0.3						
P3-latency (msec)	511.7 $\pm$ 6.6	504.5 $\pm$ 7.1	493.0 $\pm$ 6.4	4.492	2,30	.02	1.33	4,60	NS
Targets	484.3 $\pm$ 6.7	477.1 $\pm$ 7.8	471.3 $\pm$ 6.7						
Nontargets	539.1 $\pm$ 9.0	532.0 $\pm$ 9.2	514.7 $\pm$ 9.6						
P3-amplitude (μ V)	8.7 $\pm$ 0.5	8.2 $\pm$ 0.5	8.4 $\pm$ 0.5	0.87	2,30	NS	0.46	4,60	NS
Targets	14.6 $\pm$ 0.8	13.7 $\pm$ 0.9	13.9 $\pm$ 0.8						
Nontargets	2.8 $\pm$ 0.2	2.7 $\pm$ 0.2	2.8 $\pm$ 0.3						
CPT									
<i>Easy load</i>									
N2-latency (msec)	263.9 $\pm$ 5.0	267.8 $\pm$ 4.6	265.2 $\pm$ 5.4	1.044	2,30	NS			
N2-amplitude (μ V)	-2.2 $\pm$ 0.6	-2.4 $\pm$ 0.8	-2.6 $\pm$ 0.8	0.444	2,30	NS			
P3-latency (msec)	376.5 $\pm$ 4.3	376.4 $\pm$ 4.7	380.9 $\pm$ 4.5	0.51	2,30	NS			
P3-amplitude (μ V)	13.0 $\pm$ 1.0	14.4 $\pm$ 1.0	12.7 $\pm$ 1.0	3.14	2,30	.058			
<i>High load</i>									
N2-latency (msec)	272.8 $\pm$ 3.6	274.5 $\pm$ 3.5	274.1 $\pm$ 3.6	0.286	2,30	NS			
N2-amplitude (μ V)	-1.2 $\pm$ 0.5	-1.9 $\pm$ 0.5	-2.0 $\pm$ 0.6	1.041	2,30	NS			
P3-latency (msec)	406.8 $\pm$ 5.7	404.8 $\pm$ 5.8	405.6 $\pm$ 4.9	0.133	2,30	NS			
P3-amplitude (μ V)	13.2 $\pm$ 0.9	13.8 $\pm$ 0.9	13.3 $\pm$ 0.9	0.463	2,30	NS			

Table 2. Summary of ERP latencies and amplitudes in the divided attention task and continuous performance tasks. Treatments are placebo, fexofenadine 180 mg (fexo 180) and fexofenadine 360 mg (fexo 360). NS: not significant; df: degrees of freedom.

Figure 1. Δ tracking error (mm) in the divided attention task for workload 60 and 70 condition and for each treatment; placebo, fexofenadine 180 mg (fexo 180) and fexofenadine 360 mg (fexo 360). * indicate significant ($p < .05$) drug-placebo differences pooled over workload.

Figure 2. Grand average ERP's showing P1 at Oz for targets and for workload 50, 60 and 70 of the divided attention task. Abbreviations as in figure 1.

Figure 3. Grand average ERP's showing P3 at Pz for targets and for workload 50, 60 and 70 of the divided attention task. Abbreviations as in figure 1.

reached significance ($F_{1,15}=4.47$; $p=.026$). As can be seen in table 1, the increase in tracking error in the two hardest workload conditions was less during fexofenadine treatment as compared to placebo. Additional analyses employing difference scores from the 2 highest workload conditions versus the easiest workload condition provided further support for this notion as indicated by an overall effect of Treatment ($F_{2,30}=2.948$; $p=.034$). Separate drug-placebo contrasts furthermore revealed that increments in tracking error were less after fexofenadine 360 mg as compared to placebo ($F_{1,15}=4.793$; $p=.023$). Mean increments of tracking error in the highest workload conditions for each treatment are shown in Figure 1. Reaction time and the number of hits were not significantly affected by Treatment.

ERP P1 latency demonstrated significant effects of Treatment $\times$ Workload ($F_{4,60}=3.03$; $p=.024$) and Stimulus-type ($F_{1,15}=20.0$; $p<.01$). The Treatment $\times$ Workload interaction indicated that that while workload augmented, P1 amplitude increased in the placebo

Figure 4. P1-latency (msec) on the secondary task of the DAT (a) and P3-latency (msec) for the targets in the secondary task of the DAT (b). Latencies are given for each workload condition (50, 60, 70) and for each dose of fexofenadine. Abbreviations as in figure 1.

condition, but decreased in the fexofenadine conditions (see figure 4). P1 amplitude was only affected by Stimulus-type ($F_{1,15}=4.55; p=.05$).

P3 latency revealed significant main effects of Treatment ($F_{2,30}=4.5; p=.02$), Stimulus-type ($F_{1,15}=17.2; p<.01$) and Workload ($F_{2,30}=5.6; p<.01$). P3 latency occurred earlier after fexofenadine 360 mg as compared to placebo ($F_{1,15}=8.8; p=.01$). However, there were no interactions between Treatment x Workload or Treatment x Stimulus-type on P3 latency. For P3 amplitude there was only an effect of Stimulus ($F_{1,15}=96.0; p<.001$), with amplitudes being larger for targets. P1 and P3 grand averages recorded in each treatment and workload condition are given in figures 2 and 3 respectively. P1 and P3 latencies as a function of workload and dose are shown in figure 4.

Continuous Performance Task

There was no significant effect of Treatment on the percentage of correctly detected targets or hit reaction time in the easy CPT-ax. In the difficult version there was an almost significant overall effect of Fexofenadine on hit reaction time ($F_{2,30}=3.28; p=.051$). Mean scores demonstrated that subjects in the fexofenadine 180 mg condition responded fastest, followed by placebo and then by fexofenadine 360 mg. However, further testing with simple contrasts did not yield significant differences between drug conditions. Other parameters of the CPT-tasks showed no significant effects of the factor Treatment.

As mentioned earlier, parietal P3 and frontal N2 ERP components were determined in Go (target) and NoGo (distractor) conditions. No Treatment effects were found for P3 or N2 components. A main effect of Stimulus-type was found for parietal P3 latency in the easy version ($F_{2,30}=4.9; p=.015$) and the difficult version ($F_{3,45}=6.4; p=.001$). In both versions of the CPT-ax task, an effect of Stimulus-type on latency ($F_{1,5,22.1}=28.2; p<.001$) and amplitude ($F_{2,30}=44.0; p<.001$) of the frontal N2 was found.

Motor Choice Reaction Time

There was no main effect of Treatment on initiation time or movement time. However the interaction between Treatment x Workload (task difficulty) did significantly affect movement time ($F_{4,56}=2.58; p=.047$). The interaction indicated that fexofenadine produces faster movement times in the Simple and the Incompatible conditions, relative to placebo. Drug-placebo contrasts showed that fexofenadine 180mg produced a significantly faster movement time than placebo ($F_{1,14}=6.53; p<.025$).

DISCUSSION

Previous studies found that in contrast to most second generation antihistamines, fexofenadine does not produce sedative effects (Hindmarch, Shamsi, Stanley, & Fairweather, 1999; Bower et al., 2003; Ridout, Shamsi, Meadows, Johnson, & Hindmarch, 2003) and one study even suggested small stimulating effects after fexofenadine treatment (Vermeeren & O'Hanlon, 1998). In the present study the stimulating effects of fexofenadine were investigated using behavioral and electrophysiological measures.

The behavioral results of the divided attention task in this study showed that the primary tracking task was affected by workload. Increasing the workload caused the subjects to have more trouble keeping the cursor stable, resulting in an increase in tracking error. In addition, after treatment with fexofenadine tracking error increased less as a function of workload. There was no effect of fexofenadine on the behavioral results of the secondary task of the DAT.

Due to the nature of the task, ERP's could only be measured in relation to the secondary task of the divided attention task. The ERP-data showed that brain activity in the secondary task of the divided attention task was significantly affected by fexofenadine and workload. Spatial attention studies have earlier demonstrated that P1-latency reflects the timing of early attentional processes (Mangun & Hillyard, 1990, 1995). In the present study, P1 amplitude was larger for targets than distractors, indicating an attention effect in a non-spatial attention test. P1-latency increased as a function of workload when subjects were treated with placebo but the opposite happened in the fexofenadine condition. It appears that especially the timing of early attentional processing is affected by the task difficulty by being delayed when the task gets harder. However, when treated with fexofenadine, this early processing occurred faster in the harder task conditions, thus fexofenadine appeared

to have a facilitating effect on early attentional processing when primary task requirements are higher.

Fexofenadine caused faster P3 latencies in the secondary task of the DAT, while higher workload conditions caused a delayed P3 response. As P3 latency has been linked with stimulus evaluation processes (Duncan-Johnson, 1981; Willard, Johnson, & Rosenfeld, 1994; Smulders et al., 1995; Kok, 1997), these results indicate that when workload is increased, stimulus evaluation time increases, demonstrated by the later P3 peak. Fexofenadine on the other hand causes the stimulus evaluation process to be completed faster. P3 amplitude in response to secondary task stimuli was not affected by fexofenadine or workload. Previous studies have demonstrated that P3 amplitude is a measure of the amount of mental capacity that is invested in a task (Kok, 1997). The lack of an effect of workload or fexofenadine on P3 amplitude would therefore indicate that these factors did not affect the amount of mental capacity available for the secondary task. Using an auditory oddball task as primary task and a tracking task as secondary, Wickens, Isreal and Donchin (1977) and Isreal et al., (1980) did find a decrease in P3 amplitude in the primary task when introducing this concurrent task, but found no further decrement in P3 when the secondary task became more difficult. It was interpreted that tracking difficulty and oddball task performance are mainly dependent on different processes; with the tracking task relying mostly on response-related resources, while the oddball task is thought to mainly address perceptual resources (Kok, 1997).

Fexofenadine did not influence performance in the CPT-ax tasks. Only in the difficult version an effect of drug was found on the reaction time, it was however unclear which drug condition caused this effect. The event related potentials measured during the CPT-ax tasks were unaffected by drug treatment. Task manipulations, however, had an effect on event related potentials involved in target processing and target inhibition of the CPT-ax tasks. These effects confirm that stimuli that must be attended to generate larger P3 peaks than stimuli that are to be ignored (Picton, 1992; Coull, 1998). The frontal N2 peak, thought to represent an inhibition process in Go/NoGo tasks, was later and larger when NoGo stimuli did share features with the target letter (e.g. K and X-dot below). This finding points to increased inhibitory effort in conditions in which NoGo stimuli resemble Go stimuli in at least some stimulus features and supports an inhibition hypothesis of the frontal N2 (Jodo & Kayama, 1992).

A stimulant effect of fexofenadine was also demonstrated in the motor choice reaction task. Fexofenadine interacted with task difficulty of the motor choice reaction time and fexofenadine 180 mg caused faster movement times. As there was no effect on initiation or reaction time, this suggests that fexofenadine only affected the purely motor component and not the cognitive aspect of this task.

On the basis of the effects found in the motor choice reaction task and the divided attention task, behaviorally as well as physiologically, it can be concluded that fexofenadine has slightly stimulating properties. Consequently it is evident that fexofenadine has the capability of crossing the blood brain barrier and act centrally. However, it is still unclear by which mechanism fexofenadine stimulates cognitive processes. One hypothesis is that fexofenadine has an effect on the dopamine system, where it blocks the reuptake of dopamine presynaptically, causing an increase in the dopamine availability. This increased dopamine availability could produce effects similar to psychomotor stimulants. The inhibitory effect of antihistamines on the neuronal uptake of dopamine has already been demonstrated in rats and mice (Oishi, Shishido, Yamori, & Saeki, 1994; Matsunaga et al.,

1998) e.g. in the neostriatum and nucleus accumbens (Dringenberg, de Souza-Silva, Schwarting, & Huston, 1998). Evidence for the dopamine reuptake hypothesis is also found in behavioral animal studies reporting antihistamines to increase the rate of fixed interval responding (Bergman & Spealman, 1988) and potentiate conditioned place preference (Suzuki et al., 1999). These effects were probably mediated by dopamine uptake inhibition since the effects attenuated after treatment with dopamine antagonists (Bergman & Spealman, 1988; Suzuki et al., 1999).

In conclusion, the neurophysiological data indicated CNS activation after fexofenadine treatment. However, the stimulant effects of fexofenadine at the behavioral level were minor and only demonstrated in high workload conditions. Together, these results suggest that fexofenadine's centrally activating effects are generally too small in magnitude to produce clinically relevant performance improvement at the behavioral level.

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Chapter 5

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Effects of a high dose of fexofenadine on cognitive function and motor impulsivity

CHAPTER 6

Based on:

Theunissen, E. L., van Kroonenburg, M. J., van Deursen, J.A., Blom-Coenjaerts, C., & Ramaekers, J.G. Stimulating effects of fexofenadine: testing the dopamine transporter hypothesis. (*Submitted*).

ABSTRACT

Background: First and second generation antihistamines are known to produce different degrees of sedation. However, a few studies have shown that the H1-antagonist fexofenadine produces mild stimulant effects. These stimulant effects might be caused by fexofenadine's interaction with the dopamine system.

Aim: In the present study, the effect of a high dose of fexofenadine on cognitive performance and motor impulsivity was investigated in a between subject study.

Methods: Forty healthy subjects received either fexofenadine 360 mg or placebo. Cognitive performance was measured with the digit symbol substitution test (DSST) and motor impulsivity with a stop signal task (SST). In addition, subjective and physiological effects of fexofenadine were observed.

Results: The results demonstrate that fexofenadine improved performance on the DSST at $T_{\max}$ of the drug. Fexofenadine did not affect motor impulsivity, subjective experience or physiological measures.

Conclusion: From these results it is concluded that fexofenadine has mild stimulant effects which are short-lived and not comparable to the effects of psychostimulants.

INTRODUCTION

Histamine is an endogenous substance involved in allergic reactions. It is stored and released by mast cells in the periphery and its actions are mediated by three receptors; H1, H2 and H3. In order to relief allergic symptoms, antihistamines or H1-antagonists block peripheral H1-receptors to prevent histamine from binding at these sites. However, histamine has also been found to act in the central nervous system. As a neurotransmitter it is involved in the maintenance of arousal and the regulation of the sleep-wake cycle (Tashiro et al., 2002). Since antihistamines also block the central histamine receptors, they interfere with these processes of arousal and as a consequence produce sedation. First generation antihistamines in particular, have been demonstrated to seriously diminish cognitive, psychomotor and driving performance in healthy volunteers (Rombaut & Hindmarch, 1994; Simons, 1994; O'Hanlon & Ramaekers, 1995; Kay, 2000).

Besides binding at H1-receptors, antihistamines have also been reported to inhibit the neuronal uptake of dopamine in the neostriatum and nucleus accumbens of rats and mice (Oishi, Shishido, Yamori, & Saeki, 1994; Matsunaga et al., 1998), resulting in increased dopamine levels (Dringenberg, de Souza-Silva, Schwarting, & Huston, 1998). The dopaminergic system plays a major role in the processing of reward and reinforcement (Wise & Rompre, 1989; Leshner & Koob, 1999). At a behavioral level, dopamine stimulation can be expected to resemble the effects of psychostimulants like improved psychomotor function and attentional processes during task performance (Higgins et al., 1993; Lamers et al., 2003). Therefore, antihistamines which interact with the dopamine system and augment the dopamine levels can be expected to produce stimulant effects or at least counteract the sedative effect caused by the histamine blockade. Indeed, previous studies have indicated that stimulant effects can be found for certain antihistamines; i.e. terfenadine, ebastine desloratadine and fexofenadine (Theunissen, Vermeeren, Vuurman, & Ramaekers, In Press). Acute doses of terfenadine (60 mg) were found to improve tracking and vigilance (Moskowitz & Burns, 1988). Ebastine (10 and 20 mg) improved performance in an actual and simulated driving test (Mattila, Kuitunen, & Pletan, 1992; O'Hanlon & Ramaekers, 1995) while desloratadine 5 mg decreased brake reaction time in a driving test (Vuurman, Rikken, Muntjewerff, de Halleux, & Ramaekers, 2004). Fexofenadine (120 mg) treatment also resulted in improved performance in an actual driving test (Vermeeren & O'Hanlon, 1998) and improved primary task performance in a divided attention task (Theunissen, Jonkman, Kuypers, & Ramaekers, In press). In addition, neurophysiological ERP measurements also showed that fexofenadine decreased P300 latency, indicating improvement of information processing. Several other studies demonstrated a tendency of improved performance after treatment with these antihistamines, although the effect did not reach significance. Therefore, in combination with the few significant effects that were demonstrated, it can be concluded that the stimulant effect caused by these antihistamines is marginal, and not comparable to the effects of psychostimulants such as amphetamines.

Although stimulants can improve psychomotor and cognitive performance, they might also result in impulsivity and have negative effects on functions like inhibition behavior. Obviously in a lot of daily situations the ability to respond fast is essential, but in some instances the ability to inhibit responses is just as crucial. We were therefore also interested in the effect of fexofenadine on a motor impulsivity task.

The goal of the present study was to investigate whether a high dose of fexofenadine has stimulant properties. First of all, we expect to demonstrate an improved performance in a cognitive task after treatment with fexofenadine, as shown in previous studies. Secondly, we are interested to see how fexofenadine influences motor impulsivity in a stop task. And finally, we were interested to see how subjects experience the effects of fexofenadine subjectively and how it affects physiological measures like heart rate and blood pressure.

MATERIAL AND METHODS

Subjects

Forty healthy volunteers (20 males and 20 females) aged between 19 and 47 were recruited through local newspaper advertisements. Volunteers were screened using a medical history questionnaire and subjects with a history of major medical or psychiatric disorder, any non-corrected visual or psychomotor defect, unusual sensitivity to antihistamines, drug abuse and chronic use of medication or cigarettes, were excluded. Female subjects could not participate when pregnant or lactating, and were required to use an effective contraceptive during the study. Subjects were randomly assigned to a fexofenadine or placebo group. The groups were matched for age and sex. Mean (SD) age of the participants was 28.8 (8.3); the mean age of the placebo group was 28.95 (8.6) and 28.65 (8.2) for the fexofenadine group. Written informed consent was acquired from all participants prior to participation. The study was approved by the Ethics Committee of Maastricht University and conducted in accordance with the World Medical Associations Declaration of Helsinki (Edinburgh modification 2000).

Drug treatment

The study was conducted according to a double blind, placebo-controlled between subjects design. Treatments consisted of a single dose of fexofenadine 360 mg or placebo. Fexofenadine is a potent and selective histamine H1-antagonist. Absorption of fexofenadine occurs rapidly, with peak plasma levels reached in 1 to 2 hours. Elimination half-life of fexofenadine is 9 to 14 hours (Product Monograph). Treatments were given in the morning after arrival at our facilities and were administered as identical appearing capsules to ensure blinding.

Procedure

Subjects were individually trained in all tests in the week prior to their test day. The use of alcohol was prohibited from 24 hours prior to the test day and consumption of caffeine was not allowed on the test day. A baseline test battery was obtained when subjects arrived at our facilities. Subsequently they received their treatment. A second and third test battery was administrated 1h15min and 3h15min after drug intake. Subjects received a standard lunch 2h45min post drug.

Performance measures

• Digit symbol substitution task (DSST)

A computerized version of the original DSST from the Wechsler Adult Intelligence Scale was used to measure information processing and psychomotor performance (Wechsler, 1981).

The subject is shown an encoding scheme at the top of a computer screen consisting of a row of nine digits (0-9) which are randomly associated with nine symbols. A row of nine response buttons, representing the same symbols, is presented at the bottom of the screen. A randomization procedure makes sure that the symbols never appear at the same ordinal position within both rows. Single digits (0-9) are presented one by one in the centre of the screen. The subjects' task is to match each appearing digit with the corresponding symbol from the encoding list by clicking the correct response buttons. The number of digits correctly encoded within 3 minutes is the performance measure.

• *Stop Signal Task (SST)*

The stop signal task used in this study was an adapted version of the one described by Fillmore, Rush & Hays (2002). The test was made up of 176 trials in which one letter (A, B, C or D) was presented in the center of a computer screen. All four letters were presented equally often and were presented for 500 msec with an inter stimulus interval of 2500 msec. Subjects were required to react to these letters by pressing one of two buttons (one for A and C, another for B and D). Occasionally however, the presentation of a stimulus was followed by the presentation of a stop signal. The stop signal consisted of an asterisk which appeared in one of the corners of the screen for 500 msec. The delay between the appearance of the stimulus and the stop signal varied; i.e. 50, 150, 250 or 350 msec. A total of 48 stop signals were presented; equally divided over the different delay categories and different stimuli. Whenever a stop signal was presented, subjects had to withhold their response. Dependent variables in this test are the number of correct responses to the go signals (hits), the number of successfully inhibited responses (correct inhibitions) per delay, mean reaction time of the hits (Go-RT) and an estimated time required to inhibit responses (stop signal reaction time, SSRT). The SSRT was calculated based on the probability of inhibiting responses to stop-signals and the distribution of RT's to go-signals after excluding outliers (Logan, 1994).

• *Addiction research center inventory (ARCI)*

The Addiction Research Center Inventory is designed to be sensitive to the subjective effects of different classes of psychoactive drugs (Martin, Sloan, Sapia, & Jasinski, 1971). It consists of 49 true/false questions and yields five different scales: the Benzedrine Group (BG) and Amphetamine (A) scales, sensitive to amphetamine-like stimulating effects; the Pentobarbital, Chlorpromazine, Alcohol Group (PCAG), sensitive for sedation; the Lysergic Acid Diethylamide (LSD) scale, a measure of dysphoria; and the Morphine-Benzedrine Group (MBG), sensitive to euphoric effects. The ARCI is administered at baseline and in the third test battery.

Physiological measures

Heart rate and blood pressure (systolic and diastolic pressure) were measured twice; once at baseline and once 3h45 minutes after drug intake. At both times, subjects had to lie down for approximately 5 minutes before physiological measures were determined.

ANALYSIS

To correct for baseline differences between groups, difference scores were calculated and analyzed. A repeated measure analysis of ANOVA with Treatment (2 levels) as a between factor and Time

Performance test	Placebo			Fexofenadine		
	Baseline	1h15min	3h15min	Baseline	1h15min	3h15min
DSST						
Hits (n)	89.4±2.3	89.7±2.7	92.3±2.9	84.2±2.3	86.9±2.3	86.6±2.5
Stop Signal Task						
Hits (n)	125.7±0.4	125.9±0.4	125.4±0.6	124.8±0.8	125.5±0.6	124.4±0.8
Go-RT (msec)	547±17	550±17	548±20	584±22	588±23	572±22
SSRT (msec)	273±8	265±6	273±8	261±10	266±10	272±8
Correct inhibitions (n)	8.8±0.5	8.9±0.5	8.6±0.6	9.7±0.4	9.6±0.4	9.1±0.1
ARCI	<i>Baseline</i>		<i>3h15min</i>	<i>Baseline</i>		<i>3h15min</i>
Mbg	4.5±0.7		4.6±0.7	5.1±0.6		5.2±0.7
Lsd	-2.0±0.2		-2.2±0.2	-2.1±0.2		-1.7±0.4
Pcag	-8.5±0.5		-5.5±0.6	-1.2±0.4		-0.7±0.5
Bg	2.1±0.4		1.7±0.5	2.0±0.3		1.4±0.4
Ag	2.3±0.4		2.2±0.5	1.9±0.3		2.1±0.3
Physiological measures	<i>Baseline</i>		<i>3h45min</i>	<i>Baseline</i>		<i>3h45min</i>
Diastolic pressure (mmHG)	75.2±2.0		74.3±2.1	75.2±1.3		74.0±1.3
Systolic pressure (mmHG)	123.1±2.7		122.5±3.1	120.4±3.0		122.5±3.1
Heart rate (bpm)	68.8±2.1		64.0±2.0	74.6±2.6		66.4±1.7

Table 1. Mean ($\pm$ SEM) absolute values for both groups on the DSST, SST, ARCI and physiological measures at the different testing times.

Figure 1. Digit symbol substitution test: change from baseline in mean hits at 1h15minutes and 3h15minutes after drug-intake.

(2 levels) as a within factor was applied on all variables from the SST and DSST. Variables of the ARCI and physiological measures were tested using a *t*-test for independent samples. All variables were tested 2-tailed, except for the DSST because of the one-sided nature of the prediction. A significance level of $p < .05$ was used to detect differences between the treatment responses in the statistical tests. All statistical tests were conducted using SPSS (version 10.0).

RESULTS

A summary of the results of the psychometric tasks and the physiological measures of both treatment groups is shown in Table 1. There was no significant overall effect of Treatment or Time on the number of hits in the DSST, however the interaction between Treatment and Time was significant ($F_{1,38}=3.74$; $p=.03$). Whereas the number of hits after fexofenadine treatment was increased in test battery 2 and 3 compared to baseline, after placebo treatment only the third test battery showed increased hits compared to baseline (fig. 1).

In the stop signal task there were no significant overall effects of Treatment or Time on the number of hits, correct inhibitions, Go-RT or SSRT. A significant Treatment $\times$ Time effect was found on the number of correct inhibitions after a 350 msec delay ($F_{1,38}=9.11$; $p<.025$). Mean scores show that fexofenadine resulted in a decrease in correct inhibitions as compared to baseline in the third test battery, whereas placebo resulted in a slight increase in the 350 msec delay condition (fig. 2).

Analysis of the ARCI indicated that there was no significant difference between the two treatment groups, on any of the scales. Also analysis of the physiological measures showed no significant difference between the two treatment groups at any measure.

Figure 2. Stop signal test: Mean proportion of correct rejections at the four stimulus-stop signal delays, for each treatment and at both measurement times.

DISCUSSION

Previous studies have demonstrated that unlike other antihistamines, fexofenadine does not cause sedation, but might even slightly improve performance, especially after high doses (Vermeeren & O'Hanlon, 1998; Theunissen et al., *In press*). In this study we investigated the stimulant effect of a high dose of fexofenadine on cognitive function and motor impulsivity.

Mild stimulant effects of high doses of fexofenadine have been demonstrated earlier on driving related performance, psychomotor performance and attention (Theunissen et al., *In Press*). In the present study, a high dose of fexofenadine resulted in a significant interaction between fexofenadine and time of measurement for the number of correct responses on the digit symbol substitution task. In the fexofenadine group, subjects produced more correct responses at both measurement times compared to baseline. However, only around one hour after drug intake did fexofenadine cause better performance than placebo. Around three hours after drug administration, both placebo and fexofenadine caused an increase in the number of correct responses compared to baseline, but the difference between the groups was no longer significant. It seems that fexofenadine mildly stimulated performance on a cognitive, psychomotor task, but only when peak plasma concentrations of the drug were maximal.

In this study, the effect of fexofenadine on a stop task was also investigated, in order to assess fexofenadine's effect on motor impulsivity. In previous studies, the effects of psychostimulants like cocaine and d-amphetamine on motor impulsivity have yielded contradictory results. De Wit, Enggasser and Richards (2002) found that d-amphetamine caused faster Stop RT but had no effect on Go RT in a stop signal task. D-amphetamine also decreased the number of commission errors in a Go-NoGo task. Fillmore, Rush, and Marcinski (2003), found a decrease in inhibitions in a cued Go-NoGo test in subjects with a history of substance abuse who were given d-amphetamine (5, 10 and 20 mg). Also acute cocaine treatment resulted in a decreased inhibitory control in subjects with a history of cocaine abuse (Fillmore et al., 2002). Thus whereas the results of de Wit et al., (2002) indicated improved motor impulsivity, Fillmore et al., (2002 and 2003) showed impaired response control after psychostimulant treatment. This difference might be explained by differences in prior stimulant use by the subjects (Fillmore, Kelly, & Martin, 2005). Results in the present study showed that fexofenadine had no effect on the reaction time of the go or stop process in the stop signal task. Only one effect was found around three hours post drug; subjects treated with fexofenadine made less correct inhibitions when the delay between stimulus and stop signal was the longest. At the other intervals such an effect was not apparent. Since fexofenadine had no effect on the go and stop reaction times, it can not be suggested that the decrease in inhibitions is due to a slowing of the stop process or acceleration of the go response. Therefore it is possible that this effect of fexofenadine on correct rejections is in fact a random result due to a type I error and consequently it is concluded that fexofenadine had no effect on motor impulsivity.

The ARCI questionnaire was administered to see how subjects subjectively experience the effect of fexofenadine. Previous studies using the ARCI have demonstrated that the A-scale in particular, is sensitive for the stimulant effects of d-amphetamine, MDMA and cocaine (Cami et al., 2000; Holdstock & de Wit, 2001; de Wit et al., 2002; Haga, Baker, & Rush, 2003). The present study showed that the stimulant effect of fexofenadine is probably too mild for subjects to be subjectively aware of the effect, since none of the scales

demonstrated a significant effect of fexofenadine. In addition, fexofenadine did not produce differences in the physiological measures. This is in contrast with psychostimulant drugs like amphetamine or MDMA which have been demonstrated to increase both blood pressure and heart rate (Liechti & Vollenweider, 2000; Makris, Rush, Frederick, & Kelly, 2004). Together, this indicates that the stimulant effect of fexofenadine is not of the same magnitude as the stimulating effects of amphetamine-like drugs.

It should be mentioned, though, that the ARCI and physiological measures were only determined at baseline and 3 hours post-drug, and not at the time when stimulant effects were demonstrated in this study. Other studies were able however to demonstrate stimulant effects of fexofenadine after its T_{max} (Vermeeren & O'Hanlon, 1998; Theunissen et al., In press). Nevertheless, from the present study it appears that the stimulant effects of fexofenadine are not long-lasting.

In conclusion, the results indicate that fexofenadine improved performance on a cognitive task. However, the stimulant effect is short-lived and not comparable to the degree of the stimulation found in psychostimulants, like amphetamine, MDMA or cocaine. This conclusion was also supported by the absence of an effect of fexofenadine on the motor impulsivity task, the drug experience questionnaire and the physiological measures.

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Fexofenadine's potential to inhibit dopamine reuptake in healthy volunteers: a SPECT study

CHAPTER 7

Based on:

Theunissen, E. L., van Kroonenburg, M. J., van Deursen, J.A., Blom-Coenjaerts, C., & Ramaekers, J.G. Stimulating effects of fexofenadine: testing the dopamine transporter hypothesis. (*Submitted*).

ABSTRACT

Background: The H1-antagonist, fexofenadine, has repeatedly been shown to possess mild stimulating properties. However, the pharmacological mechanism underlying this stimulating effect is unknown. One hypothesis suggests that fexofenadine produces an increase in the dopamine levels by blocking the dopamine transporter.

Aim: In the present study, it was assessed whether fexofenadine blocks the dopamine transporter in the striatum.

Methods: Sixteen healthy volunteers were included in a between subject study. Half of the subjects received 360 mg of fexofenadine while the other half received placebo. Subjects were subsequently injected with the radiotracer [123 I]FP-CIT, which has a high affinity for the dopamine transporter. The binding potential of FP-CIT was measured using single-photon emission computed tomography (SPECT).

Results: The results of this study demonstrated that there was no difference in binding potential of FP-CIT at the dopamine transporter between the placebo and fexofenadine treated subjects in the striatum.

Conclusion: The present results do not provide evidence for the hypothesis that fexofenadine stimulates performance by blocking the dopamine transporter.

INTRODUCTION

The most reported side effect of patients who use antihistamines is sedation. Antihistamines are classically divided into first and second generation antihistamines, with the first generation causing serious sedative effects, and second generation producing less, but still measurable sedative effects (O'Hanlon & Ramaekers, 1995; Hindmarch & Shamsi, 1999).

In contrast to other antihistamines, fexofenadine was previously found not to cause sedation but to mildly stimulate performance on several performance and attention measures (Vermeeren & O'Hanlon, 1998; Theunissen, Jonkman, Kuypers, & Ramaekers, *In press*; Theunissen, Vermeeren, Vuurman, & Ramaekers, *In Press*). However, the pharmacological mechanism responsible for the stimulating effects is still unclear.

Several studies have demonstrated that antihistamines influence endogenous dopamine levels in animals. Oishi, Shishido, Yamori, and Saeki (1994) studied monoamine levels after administration of a catecholamine synthesis inhibitor (α -MT) and antihistamines in mice. Administration of α -MT resulted in a decrease in the dopamine level. Seven antihistamines (e.g. diphenhydramine, tripeleminamine, promethazine and chlorpheniramine) were found to significantly increase extracellular levels of dopamine after α -MT dopamine depletion. Therefore, Oishi et al., (1994) concluded that dopamine reuptake is inhibited by most antihistamines. Matsunaga et al., (1998) examined the effects of 10 antihistamines (astemizole, azelastine, ebastine, emadastine, ketotifen, oxatomide, terfenadine, pemirolast and tranilast) on neuronal dopamine reuptake in the rat striatum (Matsunaga et al., 1998). The results showed that the degree of affinity for dopamine transporters varied considerably, and ebastine and terfenadine (i.e. the parent drug of fexofenadine) possessed the strongest inhibitory potencies for dopamine reuptake transporters. Chlorpheniramine and pyrilamine were also found to increase extracellular dopamine levels in the neostriatum and nucleus accumbens of rats (Dringenberg, de Souza-Silva, Schwarting, & Huston, 1998). Recently, Lapa, Mathews, Harp, Budygin, and Jones (2005) demonstrated a dose-related increase in locomotor activity in mice after treatment with the H1-antagonist diphenylpyraline. In addition, diphenylpyraline was found to inhibit dopamine reuptake and to increase extracellular dopamine levels in the nucleus accumbens.

The evidence from animal studies above, suggests that changes in dopamine availability might mediate the mild stimulating effects of the H1-antagonists such as fexofenadine (Vermeeren, 2003). The increased level of endogenous dopamine is thought to be a consequence of a blocking of the dopamine transporter (DAT). This suggested mechanism still needs to be tested in humans and in order to do so ligand binding assessment by PET or SPECT appears to be the best method. The current study therefore investigates the affinity of fexofenadine for the dopamine transporter in humans, using SPECT. As far as we know, this is the first attempt to explore the binding potential of an antihistamine on the dopamine transporter in humans.

METHODS

Subjects

Sixteen volunteers (8 males and 8 females) aged between 32 and 47 were recruited through local newspaper advertisements. Volunteers were screened using a medical history questionnaire and subjects with a history of major medical or psychiatric disorder, any non-corrected visual or

psychomotor defect, unusual sensitivity to antihistamines, drug abuse and chronic use of medication, were excluded. Female subjects could not participate when pregnant or lactating, and were required to use an effective contraceptive during the study. All participants were non-smokers. Subjects were randomly assigned to an experimental and control group. The groups were matched for age and sex. Mean (SD) age of the participants was 37.6 (4.3); the mean age of the placebo group was 37.9 (5.0) and 37.4 (3.9) for the fexofenadine group. Written informed consent was acquired from all participants prior to participation. The study was approved by the Ethics Committee of Maastricht University Hospital and conducted in accordance with the World Medical Associations Declaration of Helsinki (Edinburgh modification 2000).

Design and drug treatment

The study was conducted according to a double blind, placebo-controlled between group design. Treatments consisted of a single dose of fexofenadine 360 mg or placebo. Treatments were administered as identical appearing capsules to ensure blinding.

Procedure

Subjects were not allowed to use alcohol from 24 hours prior to the test day and consumption of caffeine was not allowed on the test day. After arrival at our facilities, subjects' physiological measures (heart rate and blood pressure) were determined after a five minute horizontal rest. Subsequently they received the treatment (fexofenadine 360 mg or placebo). One hour after drug intake, subjects were injected with the [123 I] FP-CIT tracer. Two hours and forty-five minutes post-drug, subjects received a standard lunch and physiological measures were determined a second time three hours and forty-five minutes post-drug. Four hours after drug intake the SPECT scan was taken.

• Radioligand

[123 I]FP-CIT (N-w-fluoropropyl-2 β -carbomethoxy-3 β -[4-iodophenyl] nortropane) is a tracer for SPECT imaging the dopamine transporter (DaTSCAN, Nycomed, Amersham, UK). An average dose of 185 MBq of the radioligand was injected as a slow bolus, followed by 10 ml saline to flush the i.v. line.

• SPECT procedure

SPECT imaging was performed at the department of Nuclear Medicine (University Hospital Maastricht) using a Siemens Multispect triple-headed gamma camera, equipped with parallel-hole low energy collimators. SPECT acquisition was performed 3 hours after the injection of the tracer (4 hours post drug). Data was collected from 64 angular values over 360° in a 128x128 matrix, with a total acquisition time of 32 minutes (30s/projection).

• Data Processing

Filtered back-projection was performed using a Butterworth filter with a cut-off value of 0.5 and an order of 0.4. For analysing the striatal [123 I]FP-CIT binding, a semi-automatic template model programme was used to calculate the ratios between left and right striatal and occipital regions, respectively (figure 1). Also a separation was made between the caudate nucleus and putamen. The ratios were corrected using Alderson's brain phantom (putamen/occipital cortex and caudate nucleus/occipital cortex).

Figure 1. [123 I]FP-CIT SPECT images of one subject. On the left, a transverse slice with the striatum showing a high level of radioactivity is shown. On the right, the template is put on the caudate nucleus, putamen and on the occipital regions, in order to calculate the binding ratio of FP-CIT.

Another method to compare [123 I]FP-CIT binding in the two groups involved SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK). To obtain consonant orientation between the data sets, realignment of the data was performed. The realigned data were co-registered and normalized to a standard, NMI SPECT template, of normal dopamine uptake. As regions of interest, the basal ganglia, were used to study between group differences. Between group differences were tested using one way ANOVA for independent samples. The results were analyzed using a threshold of $p < 0.01$ uncorrected. Results were reported when a cluster was significant at $p < 0.05$ corrected.

STATISTICS

Physiological measures were first corrected for baseline differences by calculating the difference score. The difference in physiological measures and binding potential between the groups was tested with a t-test for independent samples. A significance level of $p < 0.05$ was used. All analyses were carried out with SPSS 10.0 for Windows.

RESULTS

Physiological measures

Mean scores on the heart rate and blood pressure difference scores are shown in table 1. No difference on the physiological measures appeared to be significantly different between the two groups.

[123 I]FP-CIT SPECT imaging

Mean differences scores in the binding potential of FP-CIT in the caudate nucleus and putamen for both groups are shown in table 2. There were no significant differences in

	Placebo	Fexofenadine	Df	t	Sig
Systolic pressure (mmHG)	-4.13±5.2	-2.13±3.8	14	-3.09	NS
Diastolic pressure (mmHG)	-1.63±2.9	-1.38±2.9	14	-0.61	NS
Heart rate (bpm)	-5.0±2.4	-7.63±3.7	14	0.597	NS

Table 1. Mean change from baseline ($\pm$ SEM) in the physiological measures in the placebo and fexofenadine group. Bpm: beats per minute; NS: not significant; df: degrees of freedom.

	Placebo	Fexofenadine	Df	t	Sig
Caudate nucleus left	11.80±0.9	10.89±1.4	14	0.562	NS
Caudate nucleus right	10.38±0.6	10.45±0.8	14	-0.071	NS
Putamen left	11.53±0.6	10.75±1.2	14	0.567	NS
Putamen right	10.32±0.6	10.53±0.6	14	-0.257	NS

Table 2. Mean [123]FP-CIT SPECT binding ratios ($\pm$ SEM) in the placebo and fexofenadine group. NS: not significant; df: degrees of freedom.

binding potential between the two groups. Also the SPM analysis did not result in significant differences between the two treatment groups.

DISCUSSION

The dopamine transporter is an important presynaptic receptor, which recollects dopamine when released into the synaptic cleft. Subsequently when the dopamine transporter is blocked, the availability of dopamine in the synaptic cleft increases (Chen & Reith, 2000).

Animal studies have previously demonstrated that several antihistamines inhibit dopamine reuptake and thereby affect the level of dopamine (Oishi et al., 1994; Matsunaga et al., 1998; Lapa et al., 2005). The present study was set up to test whether fexofenadine blocks the DAT. This was done in order to find support for the hypothesis that this DAT blockage is responsible for the stimulating effects that were previously demonstrated after fexofenadine treatment. Therefore, the binding competition between 360 mg of fexofenadine and the radiotracer FP-CIT for the dopamine transporter was studied in the striatum. The results showed, however, that there was no difference in binding potential of FP-CIT between the placebo and fexofenadine group.

Previous studies which demonstrated inhibition of dopamine reuptake by antihistamines have been performed in animals in vitro (Oishi et al., 1994; Matsunaga et al., 1998; Lapa et al., 2005) and in vivo (Dringenberg et al., 1998). Although these studies investigated several antihistamines, fexofenadine was not among these. Studies to determine the binding affinity of fexofenadine for the DAT in humans are currently nonexistent. In this study we presumed that the binding affinity of FP-CIT and fexofenadine would be about equal and that the co-administration of these ligands would lead to a competition for the DAT. It cannot be excluded, however, that the binding affinity of FP-CIT is much higher compared to fexofenadine. In such a scenario, it is thinkable that fexofenadine would be fully displaced from the transporter in the presence of FP-CIT.

The results from the present study do however not allow us to draw any firm conclusion on this notion.

The timing of the SPECT-scan is probably not a reason why a decreased binding of FP-CIT after fexofenadine treatment could not be found. Since we demonstrated a stimulating effect of fexofenadine around T_{max} (i.e. 1 hour after treatment) but not three hours after drug intake in the previous chapter of this dissertation, one could suggest that the blocking of the DAT by fexofenadine had already disappeared at the time of scanning (i.e. 4 hours post-drug). However, in other recent studies, the stimulating effects of fexofenadine were shown to persist for 2-4 hours (Vermeeren & O'Hanlon, 1998; Theunissen et al., In press). Therefore, it can safely be concluded that the SPECT measurement was conducted within a relevant time window.

The present study was set up to find evidence for the hypothesis that fexofenadine's stimulating properties come about by its potential to block the dopamine transporter and subsequently increase dopamine levels. The results of the [123]FP-CIT SPECT binding ratio's, demonstrated no difference between the placebo and fexofenadine group. Thus so far, there is no evidence for the suggestion that the stimulating effect of fexofenadine in humans is caused by a blocking of the dopamine transporter. There are two other hypotheses which try to explain how fexofenadine causes stimulating effects (Vermeeren, 2003; Theunissen et al., In Press). One assumption is based on the finding of Korotkova, Haas and Brown (2002), who demonstrated that histamine stimulates GABA-neurons and that this excitation was blocked by the antihistamine mepyramine. GABA has an inhibiting effect on dopamine release, so when GABA is inhibited this leads to excitation of the dopamine cells due to disinhibition. Another suggestion is that the histamine autoreceptor (H3) is blocked by fexofenadine, leading to an increase in histamine, which causes an increased level of arousal. Several H1-antagonists have been demonstrated to bind with different affinities to the central H3-receptors in rodents (Sharif, Su, & Yanni, 1994). Further research is needed to investigate whether any of these hypotheses can explain the pharmacological mechanism responsible for the stimulating effect of fexofenadine.

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General discussion

CHAPTER 8

In this thesis, old problems and new insights about antihistamines were assessed and discussed. Old problems refer to the well established fact that many antihistamines produce drowsiness which may in turn cause severe performance impairment. Over the years, antihistamine research has produced an extensive classification of the sedative potential of almost every 1st and 2nd generation antihistamine (O'Hanlon & Ramaekers, 1995; Simons, Fraser, Reggin, & Simons, 1996; Hindmarch & Shamsi, 1999; Shamsi & Hindmarch, 2000). This line of research has had a positive influence on the prescription routines of physicians who have started to select drugs not only on the basis of their therapeutic potential but also on the presence or absence of side effects. The first part of the present thesis builds on this traditional line of research by investigating the sedative potential of one of the few 2nd generation antihistamines of which the sedative potential has not yet been fully determined, i.e. mequitazine.

New insights refer to the phenomenon that some antihistamines were shown to slightly improve performance in certain laboratory tasks. These activating effects cannot be explained by blockade of the H1-receptor in the brain which is the main cause of the sedating effect of antihistamines. There's a growing body of evidence that the activating effects of certain antihistamines are not anomalous findings but represent a real pharmacodynamic effect. The second part of this thesis further explored the true nature of these so called stimulating effects. Event related brain potentials were used to investigate the subtle stimulating effects of the drug on cognitive processes. In addition, receptor binding after antihistamine treatment was studied using ligand binding SPECT-scans, in order to discover the mechanism leading to the stimulating effect.

In this final chapter, the findings which emerged from the previous chapters are discussed in a broader perspective, in addition to some general issues.

OBJECTIVE VERSUS SUBJECTIVE MEASUREMENT OF SEDATION

In order to be able to advice patients about the safety of drugs, methods for measuring the sedating effects are needed. A reliable way to determine the sedating potential of psychoactive drugs is to measure the drowsiness caused by these drugs, using objective performance tests and/or subjective questionnaires. By using subjective measures of drowsiness, sedation caused by second generation antihistamines often goes unnoticed (Seidel, Cohen, Bliwise, & Dement, 1987; Simons, Fraser, Reggin, & Simons, 1995). Using objective tests of impairment, it was found that differences exist in sedation between the first and second generation antihistamines, but also within the group of second generation antihistamines (O'Hanlon & Ramaekers, 1995; Hindmarch & Shamsi, 1999). In addition, many researchers found that although subjects do experience drowsiness, they are often not aware of the amount of performance impairment a drug is causing. In *chapter 2 and 3* of this dissertation, it was again demonstrated that although the objective tests indicated impairment, it did not show from subjective measures of sedation. This unawareness of the impairment could put the patients in considerable danger, since they may take part in high risk activities, such as controlling machines or driving. It can thus be concluded that objective tests are essential to assess the antihistamine-related impairment.

EFFECT OF PSYCHOACTIVE DRUGS ON DRIVING PERFORMANCE

Driving is a skill which incorporates many different functions such as cognitive processes, sensory perceptions and motor skills. In today's society, driving has almost become indispensable and the roads have become crowded with cars and other road users. So, when someone's driving skills are impaired, this does not only affect the driver's safety, but also endangers the safety of others. For these reasons, governments apply strict laws to driving under the influence of alcohol which is known to impair driving performance (Zador, Krawchuk, & Voas, 2000). Applying such laws for medicinal drugs is however not that simple, because of various reasons. This would mean, for example, that a large proportion of the population would be excluded from taking part in traffic. In addition, relatively simple and reliable breath analyzer tests are available for estimating the amount of alcohol in the blood circulation, but such easy tests do not exist for measuring circulating levels of psychoactive substances. Therefore, it is essential that drugs are screened thoroughly on their potential to affect patients' driving performance and that research into the development of safe medicines continues.

Over the years, many studies have confirmed that the standard highway driving test is highly sensitive to impairment caused by psychoactive drugs. This test was developed in the 1980's in The Netherlands, and this method has since been used to test the effects of several psychoactive substances on driving performance (O'Hanlon, Haak, Blaauw, & Riemersma, 1982). The primary outcome is the standard deviation of lateral position (SDLP), which is an index of road tracking or weaving. The SDLP is a reliable measure, with test-retest reliability coefficients higher than $r=0.85$ (Ramaekers, Anseau, Muntjewerff, Sweens, & O'Hanlon, 1997).

In *chapter 2 and 3*, the sedative effects of mequitazine, cetirizine and dexchlorpheniramine were compared using objective tests as well as subjective questionnaires. Results from the experimental studies described in *chapter 2 and 3* demonstrated the acute sedating effect of a first generation antihistamine, dexchlorpheniramine, and of a second generation antihistamine, mequitazine. These antihistamines only had an effect on the highway driving test and not on the cognitive tests or subjective measures, though. *Chapter 3* demonstrated that this sedation diminished when treatment was continued over several days. In neither study did cetirizine demonstrate sedating effects on driving or cognitive performance, probably because cetirizine's sedative effects are limited to a certain time window and to highly sensitive persons.

Drugs which have typically shown large effects on the highway driving tests include tricyclic antidepressants, anxiolytics and hypnotics (O'Hanlon, Vermeeren, Uiterwijk, van Veggel, & Swijgman, 1995; Vermeeren et al., 2002; Verster, Volkerts, & Verbaten, 2002; Ramaekers, 2003). The level of impairment differs for different drugs, depending on the drug, dose and time of measurement, but some drugs reach SDLP increases up to 10 cm. Therefore, the effects of antihistamines on driving performance that were demonstrated in this thesis, seem rather minor. However, when compared with the effects of alcohol, it appeared that the impairing effect of dexchlorpheniramine and mequitazine are clinically significant. A previous study demonstrated that a blood alcohol concentration (BAC) of 0.5 mg/ml (the legal limit in most European countries) produced an increase of about 2.2 cm on the SDLP, the primary variable of the highway driving test (Louwerens, Gloerich, de Vries, Brookhuis, & O'Hanlon, 1987). Since a BAC of 0.5 mg/ml is associated with a significantly

higher risk in traffic accidents (Zador et al., 2000), an SDLP increase of about 2.2 cm is considered clinically relevant. In *chapter 2*, it was shown that mequitazine 10 mg caused an SDLP increase of 1.0 cm and dexchlorpheniramine an increase of 2.4 cm, while in *chapter 3* mequitazine 10 mg increased SDLP with 2.5 cm and dexchlorpheniramine with 2.0 cm on the first day of treatment. While these results seem conflicting about the level of impairment caused by mequitazine and dexchlorpheniramine, it indicates that some individuals are sensitive for the sedating effects of these antihistamines and will show clinically significant impairment in driving, comparable to that of an alcohol-intoxicated driver with an approximate BAC of 0.5 mg/ml.

When compared with other antihistamines, it seems that the driving impairment caused by mequitazine and dexchlorpheniramine is smaller than that produced by first generation antihistamines, which demonstrated increases in SDLP between 2 and 5 cm (Riedel, Ramaekers, Uiterwijk, & O' Hanlon, 1990; Volkerts, Van Willigenburg, Van Laar, & Maes, 1992; Ramaekers & O'Hanlon, 1994; Vuurman, Uiterwijk, Rosenzweig, & O'Hanlon, 1994; Verster et al., 2003). The effect of dexchlorpheniramine, a first generation antihistamine, on SDLP was unexpectedly low. This finding can be explained by the formulation of the drug; i.e. dexchlorpheniramine was administered as a slow release formulation, so that the substance is gradually and slowly released. Consequently, it appears that a slow release formulation seems a good way to overcome the strong sedating effect of first generation antihistamines. Other studies, with the first generation antihistamine triprolidine, also support this suggestion (Riedel, Schoenmakers, & O' Hanlon, 1989; Riedel et al., 1990).

Together with many others studies, the driving studies described in this thesis demonstrated that second generation antihistamines can impair performance because of the sedating effects they produce. It should therefore be clear that the term "non-sedating" antihistamines which is also often used to discriminate this class of drugs, is an inappropriate term. The distinction with the first generation is that those antihistamines clearly produce sedation after the recommended dose, while nearly all second generation antihistamines only produce sedation after higher than therapeutic doses.

STIMULATING EFFECTS OF ANTIHISTAMINES

The product marketing of fexofenadine focuses on the claim that this antihistamine does not enter the CNS and therefore does not cause sedative effects. Several clinical trials have indeed demonstrated that the use of fexofenadine is not associated with feelings of drowsiness and sleepiness (Bernstein et al., 1997; Howarth, Stern, Roi, Reynolds, & Bousquet, 1999; Mann, Pearce, Dunn, & Shakir, 2000). In *chapter 5 and 6* it was even demonstrated that fexofenadine mildly stimulates performance of healthy subjects in tasks with a high workload. From *chapter 4* it became evident that this stimulating effect is not only specific for fexofenadine, but that other studies have also sporadically reported stimulating effects of terfenadine, desloratadine and ebastine. As most subjects were not aware of the stimulating effect, the clinical significance of these findings is unclear, and it is unlikely that these drugs will be abused as stimulants. In *chapter 6* it was concluded that the effects of fexofenadine on psychomotor tasks is not comparable to the effect of stimulant drugs such as amphetamines that was found in previous studies. In addition, if we compare the results of fexofenadine and psychostimulants on performance in the standard highway driving test, we see that

Chapter 8

psychostimulants like MDMA and methylphenidate produce a decrease in SDLP of about 2 cm (Ramaekers & Kuypers, 2004b, 2004a) whereas fexofenadine (120 mg) produced a decrease of around 1.5 cm after repeated doses. It would be interesting to compare the effects of fexofenadine with a stimulant directly in a future experimental study.

The mild stimulating effects of fexofenadine and some other antihistamines indicate that these drugs do cross the blood brain barrier and interact with central arousal processes. Thus it can not be claimed that fexofenadine does not enter the central nervous system. Several ideas about the mechanism leading to the increased arousal have been postulated in *chapter 4*. It is suggested that fexofenadine causes an increase in dopamine by blocking the dopamine transporter or by blocking GABA. Another suggestion is that an increase in histamine due to a blocking of the histamine autoreceptor is the cause of the increased arousal. For all hypotheses, some indirect evidence is available mainly from animal studies (Oishi, Shishido, Yamori, & Saeki, 1994; Monti, Jantos, Ponzoni, & Monti, 1996; Korotkova, Haas, & Brown, 2002). In *chapter 7*, the dopamine transporter blocking hypothesis was directly tested in healthy humans, but could not be confirmed. Future research is needed to find the process responsible for the heightened arousal in humans, e.g. the involvement of dopamine in this process could be tested by assessing the extracellular dopamine levels after fexofenadine treatment in humans.

By causing mild stimulating effects instead of sedative effects, fexofenadine and a few other antihistamines clearly discriminate from the first and second generation antihistamines. Although the exact mechanism whereby these drugs induce stimulation rather than sedation, remains unclear, it is advisable to group these antihistamines in a different drug class. Previous researchers have already suggested that these antihistamines should be called the third generation, and probably this term is more appropriate than stimulating antihistamines, since the stimulating effects seem somewhat minor.

HISTAMINE AND AROUSAL

The knowledge that histamine plays an important role in arousal is mainly based on the observation that blocking histamine neurotransmission by H1-antagonists causes a decrease in arousal levels. Many first generation antihistamines were also found to affect other neurotransmitter systems involved in arousal, including acetylcholine, serotonin, noradrenaline, dopamine and GABA (Speeg, Wang, Avant, Parker, & Schenker, 1981; Oishi et al., 1994; Sangalli, 1997; Dringenberg, De Souza Silva, Rossmuller, Huston, & Schwarting, 1998). Binding at these receptors seems to be dependent of the given antihistamine and the given dose. A complicating factor is that these neurotransmitter systems do not act independently but rather interact with each other (Saper, Chou, & Scammell, 2001). Therefore the sedating effects of these antihistamines can not be completely explained by blockade of the histamine neurotransmission.

Findings that second generation antihistamines bind to a much lesser extent at the central H1-receptors, has often led to the conclusion that they do not enter the central nervous system. However these studies do not exclude that second generation antihistamines bind at other neurotransmitter receptors. In addition, several studies have since demonstrated that most second generation antihistamines, especially in high doses, bind at central H1-receptors, although to a lesser extent than first generation antihistamines (Tashiro et al., 2004). The variation in binding at H1-receptors and other neurotransmitter

receptors might account for the variation in sedating potential of these second generation antihistamines.

The studies with fexofenadine described in this thesis, clearly demonstrate that this antihistamine also has psychoactive effects, and thus acts centrally. In *chapter 7*, it could not be demonstrated that fexofenadine binds at the dopamine transporter, however. Future studies with stimulating antihistamines should include receptor binding studies, so that it can be elucidated which neurotransmitter system(s) is/are responsible for the arousal-promoting effects in these drugs. A particularly interesting target for further research is the histamine H₃-receptor, since H₃-antagonists have repeatedly demonstrated to enhance cognition and wakefulness in animals (Leurs, Blandina, Tedford, & Timmerman, 1998; Vohora, 2004).

CONSEQUENCE FOR PATIENTS

Although the studies described in this dissertation were performed in healthy subjects, some generalization for the patient population is possible. It is well documented that the allergic condition in itself has impairing effects on the functioning of the patient. Patients report diminished quality of life and experience difficulties in their working situation (Meltzer, Nathan, Selner, & Storms, 1997; Blaiss, 2000). Studies have also demonstrated a diminished working productivity in allergic patients (Burton, Conti, Chen, Schultz, & Edington, 2001). Therefore, the ideal antihistamine should also result in improved daily functioning. First generation antihistamines were effective in relieving the allergic symptoms, and thereby do affect the patients' quality of life. But because these drugs caused sedative effects, patients were again limited in their daily functions. So depending on the severity of the complaints and on the drugs taken, the patient had to choose between the lesser of two evils, and treatment was often discontinued. Second generation antihistamines are as effective as the first generation and in clinical trials, these antihistamines are mostly preferred over first generation antihistamines, because they produce less sedation (Harvey et al., 1996; Nolen, 1997). A few antihistamines were even found to improve patients' quality of life compared to placebo (Meltzer & Grant, 1999). Fexofenadine treatment, for example, was found to improve patient's quality of life and to reduce the performance impairment due to the allergic condition (Meltzer, Casale, Nathan, & Thompson, 1999).

Physicians should provide correct information to patients about the different antihistamines available, and although there are still inexpensive first generation antihistamines on the market, the first choice of treatment should be a second generation or preferably a third generation antihistamine.

CONCLUSION

For quite some time antihistamines have been divided into first and second generation antihistamines. Numerous studies have however demonstrated that the distinction between these two categories is small. The previous chapters have contributed to the notion that there is a considerable amount of variation in sedation among the second generation antihistamines, and that although they bind less to central H₁-receptors, they are not free of impairing effects. Probably other neurotransmitter systems are also involved in generating the sedation in these antihistamines. Therefore, the most appropriate way to determine the

sedating effect of antihistamines is to test them extensively using objective tests, including the highway driving test. Subsequently these results should be used to inform patients reliably about the safety of the drug and the risk they are taking when participating in traffic.

Only a few recently developed antihistamines were found to be free of sedative effects, and were even reported to mildly stimulate performance. It might be a good idea to group these antihistamines in a different class, in order to clearly discriminate them from the sedating first and second generation antihistamines. At present, it remains unclear how these antihistamines cause their stimulating effect.

Taken together, the information provided in this dissertation has contributed to the knowledge about the sedating and stimulating effects of antihistamines. This information should be taken into account when choosing the appropriate treatment for an allergic condition, so that the choice of treatment is not only based on efficacy and costs, but also on safety and effect on quality of life. In addition, further research should concentrate on possible other neurotransmitter systems involved in arousal which might further explain the sedating and stimulating effects of antihistamines.

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Summary

A large proportion of the population suffers from allergies, and consequently use antihistamines to relieve the symptoms. It is relatively well known that psychoactive drugs like hypnotics, antidepressants and illicit drugs can influence people's performance, however fewer people are aware of the effects antihistamines have on daily functions such as driving.

The first antihistamines developed to treat allergic patients produced considerable sedation, which forced the pharmaceutical industry to develop better drugs with fewer side effects. In the eighties, new antihistamines were introduced, hence called the second generation antihistamines. The assumption that all second generation antihistamines are non-sedating, however, does not hold. Previous studies have demonstrated that almost all second generation antihistamines have the potential to produce sedation, although generally to a lesser extent than the first generation. The sedating effects are largely dependent on the given dose and in most cases disappear when treatment is continued over a longer period. When compared with the effects of alcohol on the standard highway driving test, the impairing effect of first generation antihistamines is larger than that of the legal limit of alcohol (BAC 0.5mg/ml). The driving impairment caused by second generation antihistamines, is of a comparable magnitude as that of the legal limit of alcohol. It is however disturbing that most patients are not aware of the influence these drugs have on their daily functioning. In questionnaires measuring subjective sedation or subjective performance, the effects of second antihistamines are most often not found. Therefore it should be advised that all antihistamines are tested using objective tests, sensitive for small sedating effects.

Sporadically, some antihistamines have shown to be able to stimulate performance in some tests. However, it is not clear how these H1-antagonist are able to stimulate performance. Nevertheless, it is obvious that stimulating antihistamines will be preferred by patients over the sedating ones. At present, the stimulating effects of these antihistamines appear to be mild and are mostly not even noted by patients. Future drug research should elaborate on these stimulating antihistamines, so that patients, who already experience sedating effects of the allergic condition itself, can continue functioning at an optimal level.

In *chapter 1*, some background information is given related to the topics discussed in this dissertation. The subjects of this chapter include the function of histamine in allergic reactions and its function in the central nervous system, and the therapeutic action of antihistamines in the periphery as well as the central action of antihistamines. Subsequently, the traditional classification of antihistamines into first and second generation antihistamines is outlined. Antihistamines which do not fit in this classification system are discussed afterwards. This chapter ends with the aim and outline of this dissertation.

Chapter 2 presents the results of a study into the effects of different doses of mequitazine (5, 10 and 15 mg). Mequitazine has been considered to be a second generation antihistamine even though it was never firmly established that this drug's sedative potential actually differs from the first generation antihistamines. Eighteen healthy volunteers were treated with three doses of mequitazine in a cross-over study. The sedative effects of mequitazine on actual driving, psychomotor performance and memory were compared with those of a first and a second generation antihistamine; dexchlorpheniramine and cetirizine, respectively. The results of the highway driving test revealed that dexchlorpheniramine impaired driving performance as indicated by a significant rise in the Standard Deviation of Lateral Position (SDLP). Mequitazine significantly increased SDLP in a dose related manner, but the

separate dose effects failed to reach statistical significance. Mequitazine caused a dose related increase in reaction time in a divided attention task and the high dose was significantly different from placebo. Subjects reported to be less alert after treatment with dexchlorpheniramine. Cetirizine did not affect performance in any of the tasks. It was concluded that mequitazine is mildly sedating. The effects of mequitazine are comparable to those of other second generation antihistamines, in that it causes mild driving impairment, particularly at higher doses.

In *chapter 3* the effects of repeated doses of mequitazine 10 mg are investigated on driving and psychomotor performance of healthy subjects. In *chapter 2* it was demonstrated that mequitazine produces mild sedation after single doses. It is not known, however, whether the acute sedation persists after repeated dosing. The effect of repeated doses of mequitazine was studied in sixteen healthy volunteers and compared to the effects of cetirizine, dexchlorpheniramine and placebo. Treatments were continued for 8 days and drug effects were assessed on day 1 and day 8 using two on the road driving tests, psychomotor tests and a subjective questionnaire. Driving performance in the highway driving test was significantly impaired after dexchlorpheniramine and mequitazine treatment on day 1. After 8 days of treatment, these effects on driving performance disappeared. There were no effects of treatment on any of the other measures, including car following, tracking and divided attention. Although subjective ratings confirmed that subjects knew their driving had been impaired in the mequitazine and dexchlorpheniramine condition after completion of the highway driving test on day 1, they did not expect their driving to be affected before the start of the test. It was concluded that single doses of mequitazine 10 mg and dexchlorpheniramine cause mild driving impairment. However, when taken over several days, the impairing effect wears off, possibly as a result of tolerance.

Chapter 4 - First and second generation antihistamines are associated with different degrees of sedation. Sporadically however, evidence of stimulating effects of antihistamines appeared in the literature. This chapter reviews the studies that demonstrated stimulating effects of antihistamines and postulates several hypotheses trying to explain the mechanism by which antihistamines cause these stimulating effects. The reports of antihistamines with mild stimulating properties concentrate around four H1-antagonists: terfenadine, ebastine, fexofenadine and desloratadine. The stimulating effects were mostly demonstrated in tasks involving high levels of attention, e.g. divided attention tasks, vigilance tasks and driving tasks. The stimulating effects of these antihistamines were also often dependent of the given dose; however the relation was not always linear. The mechanism responsible for the stimulating effects of these four antihistamines is still unclear. Two hypotheses suggest that it is caused by increased levels of dopamine either through blocking the dopamine transporter or through GABA inhibition. A third hypothesis suggests that the stimulating effect is caused by increased levels of histamine, due to blocking of the H3 histamine receptor. Further research is needed to clarify the ambiguous role of histamine in processes of arousal.

In *chapter 5*, a study into the stimulating effects of fexofenadine is presented. Previously, some studies reported mild stimulant effects of fexofenadine. In this study, the stimulating effects of high doses of fexofenadine (180 and 360 mg) were studied and it was determined

whether such effects are related to workload. The effects of fexofenadine were studied in 16 healthy volunteers and compared with placebo. A divided attention task (DAT), continuous performance task (CPT) and motor choice reaction time test (MCRT), all with increasing levels of workload were used to determine drug effects. The underlying neurophysiological processes in the DAT and CPT were measured using Event Related brain Potentials (ERP's). Results demonstrated that performance on the DAT was less affected by increments in workload after fexofenadine treatment. The results of the event related potentials indicated faster attentional and information processing latencies following fexofenadine treatment. Treatment did not influence performance in the CPT task or in the ERP's measured during this task. The MCRT demonstrated faster movement times following fexofenadine treatment. Together, these results suggest that although the neurophysiological data indicate CNS activation after fexofenadine treatment, the magnitude of the centrally activating effects is too small to produce relevant performance improvement at the behavioral level.

Chapter 6 – Previous studies demonstrated mild stimulating effects of fexofenadine, probably due to its interaction with the dopamine system. The study described in chapter 6 investigates the effects of a high dose of fexofenadine on cognitive performance, motor impulsivity, physiological measures and subjective experience. Forty subjects were included in this between subject study. Half of the participants received fexofenadine 360 mg while the other half received placebo. Cognitive performance and motor impulsivity were measured using the digit symbol substitution test (DSST) and a stop signal task (SST), respectively. One hour after drug intake, performance on the DSST was improved in the fexofenadine group. Fexofenadine did not affect motor impulsivity, subjective experience or physiological measures. From these results it was concluded that fexofenadine has mild stimulant effects which are short-lived and not comparable to the effects of psychostimulants.

Chapter 7 – In the previous chapters, the mild stimulating effect of fexofenadine has been demonstrated. In the present chapter the hypothesis that this stimulating effect is caused by a blocking of the dopamine transporter (DAT), is investigated. Sixteen healthy volunteers participated in this between subject study. Subjects received either fexofenadine 360 mg or placebo, and were subsequently injected with the radiotracer [123I]FP-CIT. FP-CIT has a high affinity for the dopamine transporter. The binding potential of FP-CIT was measured using SPECT-scan. Results of this study demonstrated that there was no difference in binding potential of FP-CIT at the dopamine transporter between the placebo and fexofenadine group. Therefore we could not confirm our hypothesis. It could however be that fexofenadine's binding at the DAT was broken by the strong binding of FP-CIT at this receptor.

Chapter 8 – In this chapter the most important findings of this dissertation are discussed in a broader perspective: objective and subjective measures for assessing the sedating effects of antihistamines are evaluated; attention is given to the use of the standardized test for measuring impairment caused by antihistamines and other psychoactive drugs; the significance of the stimulating effects of antihistamines is discussed; the role of histamine in arousal as well as the role of other neurotransmitters involved in the psychoactive effects of

antihistamines are dealt with in addition to the practical relevance of the findings for allergy patients. From this chapter it becomes clear that future research should in addition to the histamine system concentrate on other neurotransmitter systems that might explain the variation in the sedating effects of antihistamines and the stimulating effects of a few antihistamines.

Samenvatting

Een groot deel van de bevolking heeft last van allergieën, en gebruikt bijgevolg antihistamines om de symptomen tegen te gaan. Het feit dat psychoactieve drugs zoals slaapmiddelen, antidepressiva en illegale drugs de prestaties van de gebruiker kunnen beïnvloeden is algemeen bekend. Minder mensen zijn zich bewust van het effect dat antihistamines kunnen hebben op alledaagse activiteiten zoals autorijden.

De eerste antihistamines die ontwikkeld werden voor de bestrijding van allergieën produceerden behoorlijke sedatie, hetgeen de farmaceutische industrie ertoe verplichtte om betere geneesmiddelen met minder bijwerkingen te ontwikkelen. In de jaren tachtig werden nieuwe antihistamines geïntroduceerd die men vervolgens de tweede generatie antihistamines noemde. De veronderstelling dat alle tweede generatie antihistamines niet-sederend zijn, klopt echter niet. Voorafgaande studies hebben aangetoond dat bijna alle tweede generatie antihistamines sedatie kunnen veroorzaken, hoewel doorgaans in mindere mate dan de eerste generatie. De sederende effecten zijn in grote mate afhankelijk van de toegediende dosis en verdwijnen in de meeste gevallen wanneer de behandeling over langere tijd wordt voortgezet. Wanneer de effecten van antihistamines op een standaard rijtest op de snelweg vergeleken worden met de effecten van alcohol, blijkt dat de verslechtering die veroorzaakt wordt door de eerste generatie antihistamines groter is dan de verslechtering als gevolg van de wettelijke alcohol limiet (BAC 0.5 mg/ml). De rijverslechtering veroorzaakt door tweede generatie antihistamines is van een vergelijkbare omvang als de wettelijke alcohol limiet. Het is echter verontrustend dat de meeste patiënten zich niet bewust zijn van de invloed die deze geneesmiddelen hebben op hun dagelijks functioneren. Vragenlijstonderzoeken naar de subjectieve sedatie of subjectieve prestatie, kunnen meestal de effecten van tweede generatie antihistamines niet aantonen. Het is daarom aan te raden dat alle antihistamines getest worden met objectieve tests die gevoelig zijn voor kleine sedatieve effecten.

Incidenteel is aangetoond dat bepaalde antihistamines in staat zijn om de prestatie op sommige tests te stimuleren. Het is evenwel niet duidelijk door welk mechanisme de H1-antagonisten deze prestaties bevorderen. Niettegenstaande is het duidelijk dat stimulerende antihistamines door patiënten verkozen worden boven de sederende. Op dit ogenblik lijken de stimulerende effecten van deze antihistamines mild en bijna niet merkbaar voor de patiënten. Het is aan te raden dat toekomstig geneesmiddelonderzoek doorgaat met het onderzoeken van deze stimulerende antihistamines, zodat patiënten die reeds sederende effecten ervaren van de allergische aandoening op zich, kunnen blijven functioneren op een optimaal niveau.

In *hoofdstuk 1* wordt achtergrondinformatie gegeven gerelateerd aan de onderwerpen die in dit proefschrift besproken worden. De onderwerpen van dit hoofdstukken omvatten de functie van histamine in allergische reacties en in het centrale zenuwstelsel, de therapeutische werking van antihistamines in de periferie en de centrale werking van antihistamines. Vervolgens wordt de traditionele classificatie van antihistamines in eerste en tweede generatie antihistamines uitgelegd. Antihistamines die niet in dit classificatiesysteem passen worden naderhand besproken. Het hoofdstuk eindigt met de doelstelling en opbouw van dit proefschrift.

In *hoofdstuk 2* worden de resultaten van een studie naar de effecten van verschillende doses mequitazine (5, 10 en 15 mg) gepresenteerd. Hoewel nooit voldoende onderbouwd werd vastgesteld dat de sedatieve effecten van mequitazine feitelijk verschillen van de eerste

generatie antihistamines, werd het geneesmiddel bij de tweede generatie antihistamines gerekend. Aan dit cross-over onderzoek namen achttien gezonde vrijwilligers deel. De deelnemers kregen drie verschillende doses mequitazine toegediend. De sedatieve effecten van mequitazine op rijvaardigheid, psychomotorische prestatie en geheugen werden vergeleken met die van een eerste en een tweede generatie antihistamine, respectievelijk dexchlorpheniramine en cetirizine. De resultaten van de rijtest op de snelweg toonden aan dat dexchlorpheniramine een significante toename in Standaard Deviatie van de Laterale Positie (SDLP) veroorzaakte, hetgeen duidt op een verslechtering in de rijvaardigheid. Mequitazine verhoogde de SDLP op een dosis-afhankelijke manier, zonder dat de afzonderlijke doses statistisch significant waren. Mequitazine veroorzaakte een dosis gerelateerde toename in reactietijd in de verdeelde aandachtstaak en de hoogste dosis was significant verschillend van placebo. Proefpersonen rapporteerden minder alert te zijn na toediening van dexchlorpheniramine. Cetirizine beïnvloedde de prestatie in geen van de taken. Er werd geconcludeerd dat mequitazine mild sederend is. Mequitazine veroorzaakt lichte verslechtering van de rijvaardigheid met name na hoge doses en is daardoor vergelijkbaar met andere tweede generatie antihistamines.

In *hoofdstuk 3* worden de effecten van herhaalde doses mequitazine 10 mg op de rijvaardigheid en psychomotorische prestatie van gezonde vrijwilligers onderzocht. In *hoofdstuk 2* was aangetoond dat mequitazine milde sedatie produceert na een enkele dosis. Het is echter nog onbekend of de acute sedatie standhoudt bij herhaalde toediening. De effecten van een herhaalde dosis mequitazine werden bestudeerd bij zestien gezonde vrijwilligers en vergeleken met de effecten van cetirizine, dexchlorpheniramine en placebo. De geneesmiddelen werden gedurende acht dagen toegediend, en de effecten werden gemeten op dag 1 en dag 8 door middel van twee rijtesten, psychomotorische testen en een subjectieve vragenlijst. Op dag 1 was de rijvaardigheid op de snelweg significant slechter na dexchlorpheniramine en mequitazine toediening. Na 8 dagen toediening waren deze effecten op rijvaardigheid niet langer aanwezig. Er waren geen effecten van de geneesmiddelen op een van de andere maten. Uit de subjectieve vragenlijst bleek dat proefpersonen op dag 1 zich na het uitvoeren van de rijtest bewust waren van hun slechtere rijprestatie in de mequitazine en dexchlorpheniramine conditie, maar dat ze dit voorafgaand aan de rijtest niet voorspeld hadden. Er werd geconcludeerd dat een enkele dosis mequitazine 10 mg en dexchlorpheniramine een milde rijverslechtering veroorzaken. Echter, wanneer de geneesmiddelen gedurende verschillende dagen toegediend werden, nam de verslechtering af, mogelijk als gevolg van tolerantie.

Hoofdstuk 4 – Eerste en tweede generatie antihistamines worden geassocieerd met verschillende mate van sedatie. Sporadisch zijn er bewijzen voor stimulerende effecten van antihistamines in de literatuur verschenen. Dit hoofdstuk beschrijft studies die stimulerende effecten van antihistamines hebben aangetoond en postuleert verschillende hypothesen omtrent het mechanisme verantwoordelijk voor de stimulerende effecten van antihistamines. De meldingen van antihistamines met milde stimulerende eigenschappen concentreren zich rond vier H1-antagonisten: terfenadine, ebastine, fexofenadine en desloratadine. De stimulerende effecten werden veelal aangetoond in taken waarbij een hoge mate van aandacht noodzakelijk is, bijvoorbeeld verdeelde aandacht, volgehouden aandacht en rijvaardigheid. De stimulerende effecten van deze antihistamines waren meestal ook afhankelijk van de gegeven dosering, hoewel de relatie niet altijd lineair was. Het is nog onduidelijk

welk mechanisme verantwoordelijk is voor de stimulerende effecten van deze vier antihistamines. Twee hypothesen suggereren dat het effect veroorzaakt wordt door een verhoogd dopamineniveau, als gevolg van blokkade van de dopamine transporter ofwel door inhibitie van GABA. Een derde hypothese stelt dat het effect veroorzaakt wordt door een verhoogd histamineniveau als gevolg van een blokkade van de histamine H₃-receptor. Verder onderzoek is noodzakelijk om de ambigue rol van histamine in arousal processen te verklaren.

In hoofdstuk 5 wordt een onderzoek naar de stimulerende effecten van fexofenadine gepresenteerd. Voorheen hebben enkele studies mild stimulerende effecten van fexofenadine aangetoond. In dit onderzoek werden de stimulerende effecten van een hoge dosis fexofenadine (180 en 360 mg) onderzocht en er werd bepaald of zulke effecten gerelateerd zijn aan de werklust. De effecten van fexofenadine werden bestudeerd bij 16 gezonde vrijwilligers en vergeleken met placebo. Er werd gebruik gemaakt van de 'divided attention taak' (DAT), 'continuous performance taak' (CPT) en 'motor choice reaction time test' (MCRT), allen met een toenemende werklust, om de effecten van het geneesmiddel te bepalen. De onderliggende neurofysiologische processen werden tijdens de DAT en CPT gemeten met behulp van Event Related brain Potentials (ERP's). De resultaten toonden aan dat de prestatie op de DAT minder beïnvloed werd door toename in werklust na fexofenadine behandeling. De resultaten van de event related potentials duiden op snellere aandachts- en informatieverwerkingsprocessen na fexofenadine toediening. Fexofenadine had geen invloed op de prestatie op de CPT of op de ERP's die gemeten werden tijdens deze taak. De MCRT toonde snellere bewegingstijden aan na fexofenadine toediening. Samengevat suggereren deze resultaten dat hoewel de neurofysiologische data wijzen op een activatie van het centrale zenuwstelsel als gevolg van fexofenadine toediening, de omvang van de centraal activerende effecten te klein zijn om relevante prestatie verbeteringen te produceren.

Hoofdstuk 6 – Voorgaande onderzoeken hebben mild stimulerende effecten van fexofenadine aangetoond, waarschijnlijk als gevolg van een interactie met het dopamine systeem. Het in hoofdstuk 6 beschreven onderzoek bestudeert de effecten van een hoge dosis fexofenadine op cognitief functioneren, motor impulsiviteit, fysiologische maten en subjectieve beleving. Veertig proefpersonen namen deel aan dit 'between subjects' onderzoek. De helft van de deelnemers kreeg fexofenadine 360 mg toegediend, terwijl de andere helft placebo kreeg toegediend. Cognitief functioneren en motorische impulsiviteit werden respectievelijk gemeten met behulp van de 'digit symbol substitution test' (DSST) en een 'stop signal taak' (SST). Eén uur na inname was de prestatie op de DSST verbeterd in de fexofenadine groep. Fexofenadine had geen invloed op motor impulsiviteit, subjectieve beleving of op de fysiologische maten. Aan de hand van deze resultaten werd geconcludeerd dat fexofenadine milde en kortdurende stimulerende effecten heeft die niet vergelijkbaar zijn met de effecten van psychostimulanten.

Hoofdstuk 7 – In de vorige hoofdstukken werden mild stimulerende effecten van fexofenadine aangetoond. In dit hoofdstuk wordt de hypothese getest dat dit stimulerend effect veroorzaakt wordt door een blokkade van de dopamine transporter (DAT). Zestien gezonde vrijwilligers namen deel aan dit 'between subjects' onderzoek. Proefpersonen kregen ofwel fexofenadine

360 mg of placebo toegediend, en kregen vervolgens de radiotracer [123I]FP-CIT geïnjecteerd. FP-CIT heeft een hoge affiniteit voor de dopamine transporter. De binding van FP-CIT werd gemeten met behulp van SPECT-scans. De resultaten van dit onderzoek lieten zien dat er geen verschil was tussen de placebo en fexofenadine groep in binding van FP-CIT aan de dopamine transporter. Daardoor konden we de gestelde hypothese niet bevestigen. Het is echter niet uit te sluiten dat de binding van fexofenadine aan de dopamine transporter verbroken werd door een sterke binding van FP-CIT aan deze receptor.

Hoofdstuk 8 – In dit hoofdstuk worden de belangrijkste bevindingen van dit proefschrift in een perspectief geplaatst: objectieve en subjectieve maten voor het bepalen van sederende effecten van antihistamines werden geëvalueerd; gestandaardiseerde testen voor het meten van prestatieachteruitgang door antihistamines en andere psychoactieve drugs werd belicht; de significantie van de stimulerende effecten van antihistamines werd besproken; zowel de rol van histamine in arousal processen als de rol van andere neurotransmitters betrokken in de psychoactieve effecten van antihistamines werden behandeld alsook de praktische relevantie van de bevindingen voor allergiepatiënten. Dit hoofdstuk maakt duidelijk dat onderzoek in de toekomst zich naast het histamine systeem moet concentreren op andere neurotransmittersystemen zodat de variatie in sederende effecten van antihistamines en de stimulerende effecten van enkele antihistamines verklaard kan worden.

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Curriculum Vitae

Eef Theunissen werd op 1 mei 1977 geboren. In 1995 behaalde zij het diploma moderne talen – menswetenschappen aan het KSO te Borgloon. Aansluitend begon zij met de studie Psychologie aan de Universiteit Maastricht, waarbij ze koos voor de afstudeerrichting ontwikkelingspsychologie. Ze beëindigde de opleiding met een extra stage aan het Centre de Recherche Cerveaux et Cognition in Toulouse. Het doctoraal diploma psychologie behaalde ze in januari 2001. In april van hetzelfde jaar startte ze als assistent in opleiding bij het instituut Hersenen en Gedrag binnen de vakgroep Neurocognitie. Daar heeft zij onderzoek verricht naar de effecten van antihistaminica op cognitieve en psychomotorische functies, onder leiding van dr. J. Ramaekers en Prof. dr. W. Riedel. Momenteel is zij werkzaam als post-doc bij de vakgroep Neurocognitie, faculteit Psychologie aan de Universiteit Maastricht.

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