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HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2007; **22**: 289–297.
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.856

Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers

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Introduction Rupatadine fumarate is a potent, selective, histamine H_1-receptor antagonist and PAF inhibitor with demonstrated efficacy for the relief of allergic rhinitis. Rupatadine does not easily cross the blood–brain barrier and is believed to be non-sedating at therapeutic doses. Consequently, rupatadine should show no impairment on car driving.
Objective This study compared the acute effects of rupatadine, relative to placebo and hydroxyzine (as an active control), on healthy subjects' driving performance.
Methods Twenty subjects received a single dose of rupatadine 10 mg, hydroxyzine 50 mg, or placebo in each period of this randomized, double-blind, three-way crossover study. Two hours postdosing, subjects operated a specially instrumented vehicle in tests designed to measure their driving ability. Before and after the driving tests ratings of sedation were recorded.
Results There was no significant difference between rupatadine and placebo in the primary outcome variable: standard deviation of lateral position (SDLP); however, hydroxyzine treatment significantly increased SDLP ($p < 0.001$ for both comparisons). Objective (Stanford sleepiness scale) and subjective sedation ratings (Visual Analogue Scales) showed similar results: subjects reported negative effects after hydroxyzine but not after rupatadine.
Conclusion Rupatadine 10 mg is not sedating and does not impair driving performance.

KEY WORDS — antihistamine; rupatadine; hydroxyzine; driving; safety

INTRODUCTION

Antihistamine therapy is the first choice in treatment in many allergic conditions with H_1 antihistamines being one of the largest classes of drugs in use in the world. Besides mediating targeted peripheral functions, it however also affects the central nervous system (CNS). The exact mechanism of action for histamine H_1-receptor antagonists still remains unknown but the role of histamine as a neurotransmitter has been firmly established. Histaminergic pathways are prominent in the CNS and are related to mechanisms that support alertness and vigilance (Nicholson, 1985; Qidwai *et al*., 2002). The sedative side effects of H_1-antagonists are caused by their affinity for the central H_1-receptors. The liposolubility of the older, 1st-generation H1-antagonists enables them to easily cross the blood–brain barrier (Meltzer, 1990; Timmerman, 2000). In the 1980's newer, 2nd-generation H_1-antagonists have been developed which possess less side effects such as the psychomotor impairment or sedation often found with the 1st-generation drugs (Rombaut and Hindmarch, 1994; Vuurman *et al*., 2004). These 2nd-generation drugs penetrate poorly into the CNS and are therefore relatively non-sedating (Bender *et al*., 2003; Timmerman, 2000). Also, in contrast to the 1st-generation antihistamines, the newer drugs have little or no affinity for muscarinic, cholinergic, adrenergic, and serotonergic receptors (Sangalli, 1997). This also contributes to the relative lack of other adverse CNS or peripheral effects reported after use of the 2nd-generation drugs (Kay, 2000). Both the pharmacodynamics and side effects

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Received 6 July 2006
Accepted 4 April 2007

profiles of the 2nd-generation H_1-antagonists suggest that these drugs offer a safety advantage over the 1st-generation drugs, particularly for ambulant patients who drive automobiles or operate other potentionally dangerous machinery. Although these newer-generation antihistamines were proven to be less sedative, most still show some level of CNS impairment, particularly at supraclinical dose levels (Casale *et al*., 2003; Holgate *et al*., 2003; Kay, 2000; Kay and Harris, 1999; Roberts and Gispert, 1999; Ridout and Hindmarch, 2003; Rosenzweig and Patat, 1999; Simons, 1999; Theunissen *et al*., 2004; Verster *et al*., 2003). Reviews of the experimental studies which have examined the effects of H_1-antagonists on performance measures from driving simulators and on-road driving generally have concluded that the 2nd-generation drugs pose little or no risk to safe driving (Ogden and Moskowitz, 2004; Verster and Volkerts, 2004), although individual adverse reactions cannot be ruled out.

More recently new drugs have been developed with claims of being free of any sedative side effects, due to the fact that they are incapable of crossing the blood–brain barrier. Amongst these new-generation antihistamines compounds are levocetirizine, fexofenadine, and desloratadine (Hindmarch *et al*., 2001; Ridout and Hindmarch, 2003). Although these new drugs show little or no negative effects on psychomotor performance or subjective rating of sedation, the claim that they are void of CNS effects cannot always be held. In some cases an improvement of psychomotor performance has been found, pointing to possible slightly stimulating effects of these compounds (Theunissen *et al*., 2006b; Vuurman *et al*., 2004). This would imply that these compounds do cross the blood–brain barrier or affect the CNS through an alternative mechanism.

Rupatadine (DCI) is a new chemical entity which possesses a potent PAF antagonist and antihistamine activity and has been selected from a series of *N*-alkylpyridine derivatives, that has demonstrated a potent dual antihistamine and PAF antagonist activity in animal an human models (Merlos *et al*., 1997). Rupatadine is marketed in Spain in a 10 mg od tablet formulation (Izquierdo *et al*., 2003), and has already been registered in several European countries and Brazil. Rupatadine is rapidly absorbed in humans when administered orally and extensively metabolized in the liver, mainly by CYP3A4. Rupatadine plasma half-life is 5.9 h. The efficacy of rupatadine for the treatment of allergic rhinitis (both intermittent and persistent) and chronic idiopathic urticaria has been well established in several controlled clinical studies (Stuebner *et al*., 2006). Another (Barbanoj *et al*., 2004) investigated possible CNS effects of rupatadine doses ranging between 10–80 mg. Using a battery of basic performance tests they found impairing effects of rupatadine only at doses above 40 mg, suggesting a good balance between the clinical dose and that producing untoward side effects. In a more recent study (Barbanoj *et al*., 2006) the combined effects of rupatadine (10 and 20 mg) and alcohol (0.8 g/kg) on cognitive performance were evaluated and compared to the effects of alcohol combined with hydroxyzine 25 mg and cetirizine 10 mg. The study showed that rupatadine 10 mg in combination with alcohol did not produce more cognitive and psychomotor impairment than alcohol alone. In contrast, cetirizine and hydroxyzine did significantly increase the effect of alcohol.

Although laboratory tests and driving simulators have often proven to be reliable and consistent in measuring driving-related skills, their predictive validity is only about 33% (Verster, 2002). In this study the possible effects of rupatadine 10 mg on driving are investigated, employing a unique and sensitive method to test drug effects on driving in real traffic.

METHODS

Subjects

The study enrolled 22 evaluable subjects (11♂, 11 ♀) through newspaper advertisements. Two subjects did not complete the study: one moved to a different town and one accepted job making participation impossible. Twenty subjects (10♂, 10 ♀) completed the study. Mean subject age(SD) was 27.2(3.5) years (range, 22–35 years) with a mean weight(SD) of 69.7(10.6) kg (range, 52–92 kg) and a mean height(SD) of 176.7(8.9) cm (range, 158–192 cm). Subjects were required to have had a driver's license for at least 3 years prior to the study and driving experience of at least 7500 km per year. Subjects with a history or symptoms of severe mental or physical disorders or substance abuse were excluded from the study, as were subjects with active allergic rhinitis. Subjects were screened by a medical history questionnaire and physical examination, including a 12 lead ECG, blood chemistry and haematology and urinary tests for drugs of abuse. Additional exclusion criteria included excessive smoking (>10 cigarettes per day) or consumption of caffeinated beverages (>5 cups/glasses per day); body weight more than 10% above the normal average for age, sex, and height; treatment with central nervous system medications or

DOI: 10.1002/hup

medications with sedative effects; and known allergic reactions to antihistamines. Women of childbearing potential were required to have a negative serum pregnancy test result at screening and to use an acceptable method of birth control before screening and during the study. Written informed consent was obtained from all subjects prior to participation. This study was conducted in accordance with Good Clinical Practice and the World Medical Association Declaration of Helsinki (1996) and subsequent revisions (Christie, 2000) and was approved by the Ethics Committee of Maastricht University.

Design

The study followed a single-center, randomized, double-blind, placebo and active-controlled, three-way crossover design. Rupatadine (10 mg), hydroxyzine (50 mg), and placebo were administrated orally in identical capsules once daily during treatment periods. Treatment periods were separated by a washout period of at least 7 days. Tests were performed between 2:00–4:30 h after dosing on each of the three test days.

Procedure

Subjects were individually trained 1 or 2 weeks prior to their first treatment to perform the driving tests and familiarize them with the experimental procedure. They were required to adhere to specific procedures prior to testing, including abstinence from alcohol or other recreational drugs the day before testing and retiring for sleep a minimum of 8 h prior to test days. On each test day subjects were collected from their homes in the morning and provided with a standard light breakfast at the study center. Sleep quality was measured upon arrival using the Groningen Sleep Quality Scale (Mulder Hajonides *et al*., 1980) and subjects only continued with the testing procedures if they reported good sleep quality (Groningen score <10) during the previous night. Additionally, subjects were limited to one cup of tea or coffee with breakfast on test days, and habitual smokers had to refrain from smoking for the duration of the testing (30 min before testing and until all tests were completed). Subjects were monitored at each visit for adverse events. At the end of each test day subjects were returned to their home by the experimenter.

Assessments

Highway-driving test. During the highway-driving test (O'Hanlon *et al*., 1982), the subject's task was to operate a specially instrumented vehicle over a distance of 100 km (61 miles) on a primary highway. A licensed driving instructor, who could intervene if necessary by using duplicate controls, accompanied the subject during the test. The subject was instructed to attempt to maintain a constant speed of 95 km (58 miles) per hour and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. The subject was allowed to deviate from this procedure in order to pass slower vehicles. The vehicle's speed and lateral position relative to the left lane delineation were continuously recorded, sampled, and stored on a computer system onboard. Offline editing routines involved removal of all data segments that revealed signal loss, disturbance, or overtaking manoeuvres. The remaining data were used to calculate means and standard deviations for lateral position (SDLP) and speed (SDSP). A minimum of 75% of 'clean' data was required for a reliable measurement. The primary measure was the SDLP, which measured 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 as low as 0.35 mg/mL [26,27]. The secondary outcome variable was SDSP, giving an indication how well subjects could maintain the designated speed. Details of the highway-driving test, including power calculations have been described fully elsewhere (O'Hanlon and Ramaekers, 1995).

Car-following test. The car-following test (Ramaekers *et al*., 2002) involved the use of two vehicles driving behind each other on a secondary highway for approximately 25 min. The subject controlled the following vehicle, while the investigator controlled the leading car. Again, a licensed driving instructor accompanied the subject in order to intervene when necessary. During the test the investigator in the leading car initiated sinusoidal speed changes. Between these maneuvers, the investigator in the leading car randomly lit up the brake lights of his car while the speed of the car remained constant. Subjects were instructed to maintain a 15–30 m distance to the leading car and to react as fast as possible to the brake lights by removing their foot from the accelerator pedal. Standard deviation of headway (SDHW) and brake reaction time (BRT) were the primary outcome variables of this car-following test.

DOI: 10.1002/hup

Subjective measures. Besides administering the driving tests, the following rating scales were presented to the subject on each test day:

- *Stanford sleepiness scale*. This is a well-known questionnaire and described fully elsewhere (Hoddes *et al*., 1972). The questionnaire indicates how 'sleepy' people are feeling and was presented twice on each test day: the first time prior to dosing to register a base-line value and once after performing the driving test.
- *Groningen Sleep Quality Scale* (Mulder Hajonides *et al*., 1980). The quality of sleep at home the night before each trial day was assessed by means of this questionnaire to ensure subjects were fit before they commenced a test day.
- *Subjective rating of Sedation*. Both the Subject as well as the Driving Instructor rated how 'sedated' the subject was during the driving test. This was done by a 100 point VAS scale.
- *Subjective rating of Driving Quality* (DQ). Both the Subject as well as the Driving Instructor rated the quality of the subject's driving. This was done by a 100-point VAS scale.

Statistical analysis. Sample size was based upon a power calculation of the primary outcome variable in the driving test, SDLP. With a sample size of 20 subjects, an α level of 0.05 (two-tailed), differences of 0.65 standardized units were detectable with a power of 85% (O'Hanlon and Ramaekers, 1995). Data analysis was performed employing the GLM routines from the SPSS statistical program series (Version 13, Norusis, 2004) on Windows-XP microcomputer. Efficacy variables were analyzed with an analysis of variance model (ANOVA) for crossover designs with terms for treatment, phase, and subject effects. Pairwise comparisons were performed using the least square means from the model. The active control group (hydroxyzine) was included for reference purposes. Since the study was oriented towards safety, a significance level of $\alpha = 0.05$ was used in all statistical tests to detect differences between treatment responses.

RESULTS

Missing data

Due to a technical error the data of subject #17 are incomplete for the hydroxyzine condition. The following analyses were therefore based on a dataset of 19 subjects in stead of the full 20 subjects: car-following test (BRT and SDHW; Subjective scales: Stanford sleepiness scale (STANFORD) and Driving Quality rating by the subject (DQ-S).

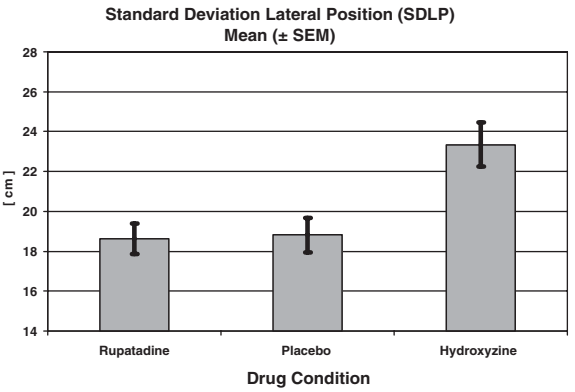

Figure 1. Mean (± SEM) standard deviation of lateral position (SDLP) scores for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 20$)

Standard deviation of lateral position (SDLP)

Figure 1 shows the mean SDLP (±SEM) for each of the three treatment conditions. The means of the rupatadine and placebo conditions were comparable (18.64 and 18.81 cm, respectively) and the SDLP in the hydroxyzine condition was much higher than the other two (23.35 cm). The higher SDLP indicated worse driving. ANOVA showed a significant overall effect of Treatment ($F_{2,36} = 21.57$; $p < 0.001$). Subsequent paired comparisons showed significant increase in SDLP after hydroxyzine treatment compared to both rupatadine ($F_{1,36} = 33.43$; $p < 0.001$) and placebo ($F_{1,36} = 25.57$; $p < 0.001$). There was no difference in SDLP between the rupatadine and placebo group ($F_{1,36} = 0.04$; $p = 0.848$). No effect of period was found, indicating a lack of learning or habituation to the driving test procedure.

Standard deviation of speed (SDSP)

The mean (±SEM) scores of the secondary outcome variable on the highway-driving test, SDSP are shown in Figure 2. Twenty evaluable data sets were available for the analysis. Subjects were instructed to maintain a steady speed at all times and the deviation from the mean speed was comparable for the rupatadine and placebo conditions. In the hydroxyzine condition subjects showed a larger variation in speed difference during the test. Overall ANOVA showed this to be highly significant ($F_{2,36} = 17.04$; $p < 0.001$).

DOI: 10.1002/hup

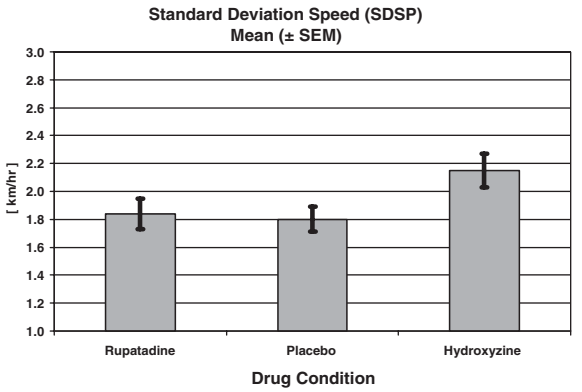

Figure 2. Mean (± SEM) standard deviation of speed (SDSP) scores for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 20$)

Subsequent pairwise comparisons showed that after treatment with hydroxyzine, subjects significantly varied in speed more compared to both rupatadine ($F_{1,36} = 21.75$; $p < 0.001$) as well as placebo ($F_{1,36} = 28.87$; $p < 0.001$) conditions. Scores in the rupatadine group were not different from scores in the placebo group ($F_{1,36} = 0.50$; $p = 0.482$). There was no effect of period on this variable, indicating subjects did not improve or degrade in time over the study.

Standard deviation of headway (SDHW)

The SDHW provides information on how 'well' subject keep an equal distance to the car in front of them. Figure 3 shows the means (±SEM) for all treatment conditions. The mean values for all conditions were similar and ANOVA revealed no effect of Treatment on SDHW ($F_{2,35} = 0.67$; $p < 0.517$). Pairwise comparisons showed no differences between means of either rupatadine and hydroxyzine ($F_{1,35} = 0.97$; $p < 0.333$), hydroxyzine and placebo ($F_{1,35} = 0.01$; $p < 0.986$), or rupatadine and placebo ($F_{1,35} = 1.04$; $p < 0.315$). A small positive, but significant effect was found for period ($F_{2,35} = 3.84$; $p = 0.031$), indicating a slight learning effect over the study.

Brake reaction time (BRT)

Figure 4 shows mean (±SEM) scores for the three treatment conditions. A higher score implied that subjects were slower to respond to the brake signal presented. The mean BRT was slightly lower for the rupatadine condition compared to both placebo and hydroxyzine. ANOVA did not show an overall treatment effect ($F_{2,35} = 1.59$; $p < 0.218$) and pairwise comparisons did not show an effect between either rupatadine and hydroxyzine ($F_{1,35} = 2.41$; $p < 0.130$), hydroxyzine and placebo ($F_{1,35} = 0.01$; $p < 0.957$), or between rupatadine and placebo ($F_{1,35} = 2.34$; $p < 0.135$). There was no effect of period on this variable, indicating subjects did not improve or degrade in time over the study.

Stanford sleepiness scale (STANFORD)

The Stanford sleepiness scale was administered twice on each of the three treatment days: the first time predosing as a baseline value and the second time after concluding the Driving tests. Figure 5 shows differences in Mean Compound Scores, a higher score indicating an increase in subjective sleepiness. Mean scores for the hydroxyzine treatment condition

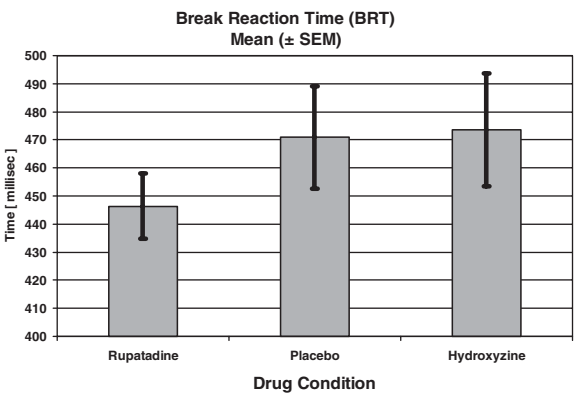

Figure 3. Mean (± SEM) brake reaction time (BRT) scores for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 19$)

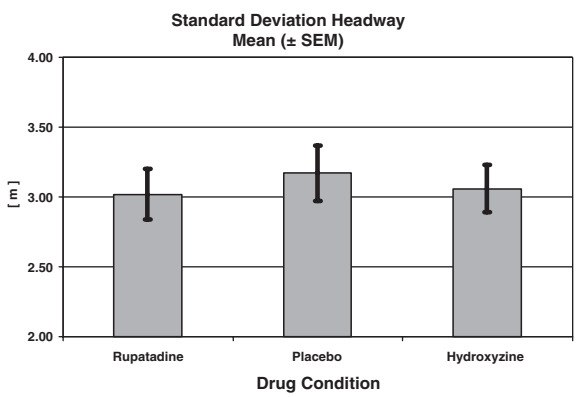

Figure 4. Mean (± SEM) standard deviation of headway (SDHW) scores for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 19$)

DOI: 10.1002/hup

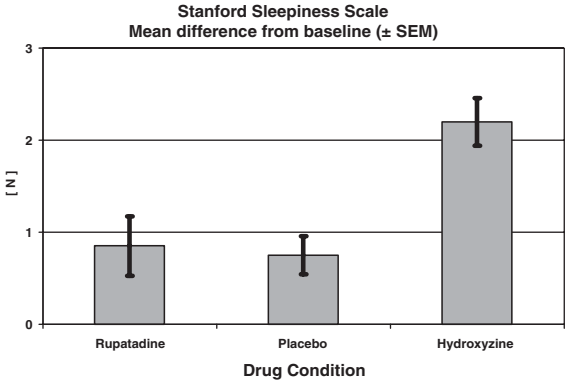

Figure 5. Mean (± SEM) difference scores on the Stanford scale for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 20$)

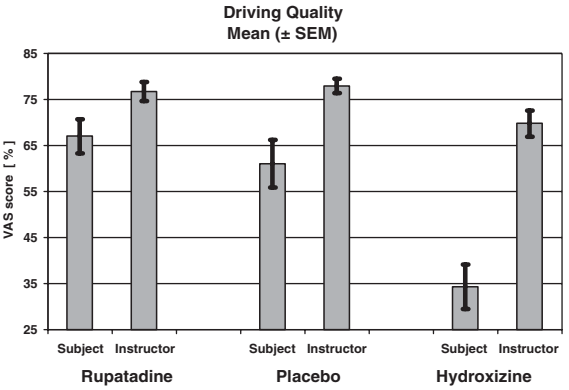

Figure 6. Mean (± SEM) rating of Driving Quality for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 20$ for instructor rated sedation and $N = 19$ for subject sedated rating)

were about twice as high compared to both the rupatadine and placebo treatment condition, and a significant overall effect for treatment was found ($F_{2,35} = 12.89$; $p < 0.001$). Pairwise comparisons showed that both the mean differences between rupatadine and hydroxyzine as well as placebo and hydroxyzine were significantly different ($F_{1,35} = 18.63$; $p < 0.001$ and $F_{1,35} = 20.48$; $p < 0.001$, respectively). The small difference between the placebo and rupatadine groups was not significant ($F_{1,35} = 0.04$; $p < 0.840$). No effect of period was found on this variable.

Driving Quality scale (subject and instructor)

Both the instructor as well as the subject rated how well the subject had performed in the driving test and rated this as the DQ on a Visual Analogue Scale running from 0–100. The higher the score the better the driving is rated.

Mean Subject rated Driving Quality (DQ-S) and Instructor rated Driving Quality (DQ-I) are shown in Figure 6 .The best mean score for DQ-S was seen in the rupatadine treatment condition, with a slightly lower rating for the placebo treatment condition. The scores in the hydroxyzine were almost 33% lower compared to the rupatadine group, indicating a large difference in rating. ANOVA showed a highly significant effect of treatment ($F_{2,35} = 23.73$; $p < 0.001$) with likewise significant effect for differences between rupatadine and hydroxyzine ($F_{1,35} = 42.20$; $p < 0.001$) and the difference between placebo and hydroxyzine ($F_{1,35} = 28.44$; $p < 0.001$). Mean scores of the rupatadine group did not differ from placebo ($F_{1,35} = 1.44$; $p < 0.239$).

The mean scores for DQ-I resembled those for DQ-S. Again the score is lowest in the hydroxyzine group; although the absolute differences are smaller, like the standard error. An overall treatment effect is found ($F_{2,36} = 4.72$; $p < 0.015$); with the hydroxyzine group rating worse compared to rupatadine ($F_{1,36} = 5.75$; $p < 0.022$) and placebo ($F_{1,36} = 8.20$; $p < 0.007$). No difference was found between the rupatadine and placebo groups ($F_{1,36} = 0.22$; $p < 0.644$). No effect for eriod was found for the DQ-S and DQ-I variables.

Perceived Sedation was recorded by presenting the subject and the instructor with a VAS rating scale directly after completing the Driving Test. Figure 7 shows the means of the Instructor rated Sedation (SED-I) and Subject rated Sedation (SED-S), indicating how much they judged the subject to be sedated.

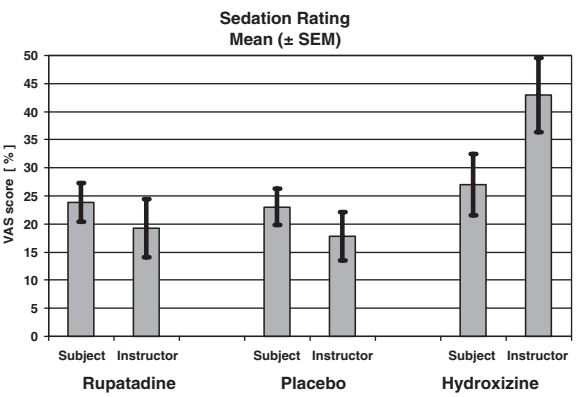

Figure 7. Mean (± SEM) rating of sedation for each treatment condition (rupatadine 10 mg, placebo, hydroxyzine 50 mg; $N = 20$ for instructor rated sedation and $N = 19$ for subject sedated rating)

DOI: 10.1002/hup

The results for SED-I showed an overall treatment but SED-S did not ($F_{2,36} = 12.56$; $p < 0.001$ and $F_{2,36} = 0.25$; $p < 0.782$, respectively). Paired comparisons only showed effects on SED-I, with hydroxyzine rated more sedative compared to both rupatadine as well as Placebo ($F_{1,36} = 17.40$; $p < 0.001$ and $F_{1,36} = 20.19$; $p < 0.001$, respectively).

Safety

A total of 16 adverse effects (AE) were reported for all 22 subjects that enrolled in the study. Most frequently 'tiredness' (5 reports) and 'drowsiness/sleepiness' (4 reports). Adverse events were reported after hydroxyzine (7 reports), rupatadine (3 reports), placebo (3 reports), and prior to dosing (1 report). Most reports of AE were expected and did not pose any serious safety hazard to the subjects' health. All AE's were resolved within 24 h after onset. In seven experimental procedures the actual driving was terminated for safety reasons. This meant that the Driving Instructor observed that the subject was getting too sedated or sleepy to continue safely and terminated the test. In two cases this was after treatment with rupatadine and in five cases after hydroxyzine. This is commonly seen in this test and has been documented in over 60 studies with other drugs affecting psychomotor behavior, especially after the subject has been driving over 40 min and vigilance effects become predominant (O'Hanlon and Ramaekers, 1995). In all cases enough data from the driving tests were available (>75%) to use the data for analysis.

DISCUSSION

Findings from the highway-driving test confirm the absence of drug-induced impairment in subjects who received rupatadine, with almost identical SDLP scores as placebo treated subjects. In contrast, the SDLP score in the hydroxyzine condition was significantly higher (4.54 cm) and relevant, having an impairing effect comparable to a Blood Alcohol concentration of 0.9% (Brookhuis, 1998). The results of the car-following test were less conclusive. In the hydroxyzine condition the BRT was not slower compared to the placebo condition. Also no effect for hydroxyzine was found on the SDHW. No straightforward explanation for this finding can be given. In previous studies with the same test the positive control condition did show effects (Ramaekers *et al*., 2002; Vuurman *et al*., 2004). Nonetheless there was also no impairment in the rupatadine treatment condition. Results of the subjective scales and questionnaires support the findings of the driving tests. Rupatadine showed no effect on driving performance related scales in contrast with the sedating effect of hydroxyzine on both the Stanford sleepiness scale and the rating of DQ. An interesting finding was the large difference in rating of sedation between the instructor and the subject in the hydroxyzine condition. The instructor clearly rated the sedation to be much worse than the subject. Judging from the performance data the subjects underrated their sedation in the hydroxyzine condition.

The effects of other 2nd-generation antihistamines have also been investigated in studies that utilized similar driving and psychomotor performance test methodology (Brookhuis, 1998; O'Hanlon and Ramaekers, 1995). Overall, the results of these studies demonstrated that driving and psychomotor performance impairment varies between 1st- and 2nd-generation antihistamines and possibly among such 2nd-generation agents as loratadine and cetirizine as well. Previous studies (Theunissen *et al*., 2006a; Vermeeren and O'Hanlon, 1998; Vuurman *et al*., 2004; Vuurman *et al*., 1994; Theunissen *et al*., 2006a) show that treatment with the recommended therapeutic dose of 2nd-generation antihistamines such as mizolastine ebastine, desloratatadine, mequitazine, or fexofenadine results in mean SDLP values comparable with placebo. However, sedation or somnolence are also reported in trials with new antihistamines such as levocetirizine (Bachert *et al*., 2004). Driving studies with the recommended therapeutic dose of cetirizine are less straightforward and show either moderate impairment (Ramaekers *et al*., 1992) or lack of impairment (Volkerts and van Laar, 1995). However, most antihistamines affect driving performance when given at twice the recommended therapeutic dose. The effect seems to be beneficial with fexofenadine; (Vermeeren and O'Hanlon, 1998) in contrast, cetirizine and loratadine cause a less favorable sedative effect. The differential effects on driving performance suggest the 2nd-generation antihistamines may have different mechanisms of action. As for the compound under investigation in this study, Barbanoj *et al*. (2004) showed a dose dependent relation of higher doses of rupatadine with reported sedation, although psychomotor impairment on the used tests is only seen after a 80 mg dose of rupatadine. This does however support the notion that rupatadine has some CNS effects at higher doses too. The effects are however only apparent at doses well above those administered clinically, giving the drug a large margin of safety. One noteworthy finding was the large difference between

DOI: 10.1002/hup

subject rated quality of driving and sedation on one hand (Figures 6 and 7) and instructor rated quality of driving and sedation on the other hand in the hydroxyzine condition. This suggests that subjects taking this older antihistamine underrated the effects of the drug.

Most discussions on sedative effects of different classes of antihistamines ascribe differences in the sedative potentials to receptor occupancy, receptor selectivity, and brain penetration (Handley and Graff, 1998; Simons, 1994). The inability to penetrate the blood–brain barrier has been put forward as the major advantage of 2nd- and the new-generation antihistamines over the older ones (Hindmarch and Shamsi, 1999). Recently, both animal and in-vitro studies suggest a more complex system regulation of the brain distribution of antihistamine drugs (Chen *et al.*, 2003; Devillier, 2006; Mahar Doan *et al*., 2004). In these studies the role of the P-glycoprotein (Pgp) efflux system and plasma protein binding have been described for a large number of antihistamines. The authors provide theoretical pharmacokinetic properties that antihistamines should possess to limit its CNS activity. Combining these insights with efficacy data and side effect, profiles should ultimately lead to a better understanding of the mechanism of action on the CNS and will provide a sounder scientific basis than dose ranging studies alone.

In this study rupatadine was well tolerated. Three subjects reported AE's while receiving rupatadine and two subjects did not complete the driving test, compared to the hydroxyzine group where five driving tests were not completed. In conclusion we can state that rupatadine, given at 10 mg, does not impair actual driving performance, is well tolerated, and comparable with the more recent antihistamines compounds.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs Mariska van der Heijden from Trial Form Support Barcelona for her assistance in setting up the study and monitoring the study. This work was financed by a grant from Grupo Uriach (Barcelona, Spain).

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