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Evaluation of the cognitive, psychomotor and pharmacokinetic profiles of rupatadine, hydroxyzine and cetirizine, in combination with alcohol, in healthy volunteers

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Introduction The Central Nervous System (CNS) impairment induced by moderate alcohol (ALC) ingestion may be enhanced if other drugs are taken simultaneously. Rupatadine (RUP) is a new H_1-antihistamine which also inhibits platelet activating factor (PAF) release in inflammatory reactions.
Objective The main aim of the study was to assess the effects of ALC 0.8 g/Kg on RUP (10 mg and 20 mg) CNS effects. An evaluation of alcohol and RUP pharmacokinetics was also attained.
Methods Eighteen healthy young volunteers of both sexes participated in a phase I, randomised, crossover, double-blind, placebo-controlled study. At 2-week intervals they received six treatments: (a) placebo (PLA), (b) ALC alone and ALC in combination with: (c) hydroxyzine 25 mg (HYD), (d) cetirizine 10 mg (CET), (e) RUP 10 mg or (f) RUP 20 mg. At baseline and several times thereafter, seven psychomotor performance tests (finger tapping, fine motoric skills, nystagmus, temporal estimation, critical-flicker-fusion frequency, 'd2' cancellation, simple reaction) and eleven subjective self-reports (drunkenness, sleepiness, alertness, clumsiness, anger, inattentiveness, efficiency, happiness, hostility, interest and extraversion) were carried out. Two-way (treatment, time) ANOVAs for repeated measures to each variable together with a multivariate non-parametric approach were applied. Plasma concentrations of alcohol, and of RUP and its metabolites, were quantified by validated immunofluorescence and LC/MS/MS methods, respectively. Plasma-time curves for all compounds were analysed by means of model-independent methods.
Results The combination of alcohol with HYD, CET and RUP 20 mg produced more cognitive and psychomotor impairment as compared to alcohol alone, being the combination of alcohol and HYD the one which induced the greatest deterioration. The combination of alcohol and RUP 10 mg could not be differentiated from ALC alone. Subjective self-reports reflect effects on metacognition after the combination of alcohol with HYD and CET i.e. the increased objective impairment observed was not subjectively perceived by the subjects. No significant differences were obtained when comparing alcohol plasma concentrations assessed after the treatments evaluated. RUP showed a lineal kinetic relationship after 10 and 20 mg with a higher exposition to both metabolites assayed.
Conclusions Present results showed that single oral doses of rupatadine 10 mg in combination with alcohol do not produce more cognitive and psychomotor impairment than alcohol alone. Higher doses of rupatadine, in combination with alcohol, may induce cognitive and psychomotor deterioration as hydroxyzine and cetirizine at therapeutic doses. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — cognition; psychomotor performance; subjective effects; pharmacokinetics; rupatadine; hydroxyzine; cetirizine; alcohol; interaction; healthy volunteers

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INTRODUCTION

Sedation is a common side effect of many first-generation antihistamines. It complicates or precludes their use by people engaged in activities requiring mental alertness, such as driving a car or operating complex machinery. Furthermore, the sedative effect is unpleasant to many patients and may reduce their compliance with a therapeutic regimen. In view of the fact that antihistamines are generally used by a relatively healthy population, concurrent use of these drugs with alcohol is likely to occur.

Rupatadine is a new second-generation antihistamine compound. It has been shown to have a potent dual activity as histamine and platelet activating factor (PAF) antagonist, without sedative effects in experimental animals (Merlos *et al*., 1997). This joint blockage would be expected to provide more clinical efficacy than the blockage of each of them alone, thereby justifying the development of such new entities. To date, rupatadine is the only of such compounds that has become available on the market.

Doses of 10 and 20 mg of rupatadine seem unlikely to produce sedation of practical consequences (Barbanoj *et al*., 2004). This suggests a discrepancy between the central and peripheral effects of the drug, particularly considering that therapeutically successful doses have been identified to fall within this dose range (Perez *et al*., 2002). However, even the minimal potential of a drug to produce sedation is important, since it might add to or potentiate the sedative effect of another drug or alcohol taken concomitantly. The expression of single or combined sedative drug effects in causing inadequate performance of an inherently dangerous task is a matter of common concern. It is therefore important to be sure that the central depressant action of other drugs is not increased by concurrent administration of rupatadine, particularly by the social drug alcohol.

The present investigation was primarily undertaken to assess the effects of alcohol 0.8 g/kg on rupatadine (10 mg and 20 mg) central nervous system (CNS) effects. An evaluation of alcohol and rupatadine pharmacokinetics was also attained. CNS activity was evaluated through standard objective laboratory tests measuring drug effects on a variety of cognitive and psychomotor functions (Hindmarch, 1980, 1988; Meltzer, 1990; Barbanoj *et al*., 2002), and also through subjective reports on visual analogue scales (VAS) which are validated measures of the subjective experience (Luria, 1975; Hindmarch and Gudgeaon, 1980). By including two positive controls (hydroxyzine and cetirizine), we achieved results following administration of drugs of the same therapeutic group with which to compare the pharmacodynamic results from the experimental treatments. In addition, rupatadine kinetics for the parent compound and two active metabolites were described.

METHODS

Study population

Healthy young participants of either gender were selected from the pool of volunteers at the Pharmacology Research Unit (Research Institute), Santa Creu i Sant Pau Hospital, Barcelona (Spain). A medical interview, complete physical examination and relevant tests (clinical chemistry, haematology, urinalysis, ECG) were performed within 21 days prior to study initiation. Pre-study examinations also included drug screening, serological testing (for hepatitis B and C and HIV) and a serum pregnancy test for women. Exclusion criteria included any history of medical or psychiatric illness. Likewise, those subjects with null/abusive consumption of alcohol and/or a psychomotor performance level outside the expected values for their age were also excluded. Alcohol and coffee were not allowed in the 24 h prior to the study or in the 24 h after the study. Participants were requested not to take any medications during the study without the previous knowledge of the investigator.

The study was approved by the study centre's Research Ethics Committee and the Spanish Medicines Agency, and was conducted following the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines. All volunteers gave written informed consent prior to entering the clinical trial and were paid for their participation in the study.

Study design

The study was conducted according to a randomised, double-blind, double-dummy, crossover design controlled with placebo and two positive standards. All subjects participated in six experimental sessions. In a sequential and randomised manner, separated by a minimum period of 14 days, they received a drink with alcohol content (0.8 g of alcohol $\times$ kg of body weight) simultaneously with single oral capsules (at the beginning of the drink intake) of rupatadine 10 mg (RUP_10), rupatadine 20 mg (RUP_20), cetirizine 10 mg (CET), hydroxyzine 25 mg (HYD) and placebo (ALC). In addition, placebo was administered together with an alcohol-free drink (PLA) in an experimental session.

The study medication was administered in the early morning in the fasting state, concomitantly with the alcoholic drink. Drinks were prepared immediately prior to their intake. The corresponding dose of alcohol was obtained by diluting alcohol to a concentration of 40% (vodka) in orange juice to reach a total volume of 400 ml. For the alcohol placebo condition, the corresponding volume of vodka was replaced by water, and orange juice was added to reach the total volume of 400 ml. To mask the content of the drink as far as possible, 2 ml of supernatant alcohol was always added to avoid identification by flavour. The drinks were then administered in six portions equally distributed over a drinking period of 30 min (5-min intervals with drinking behaviour as homogeneous as possible). The subjects fasted until +3 h post-administration after which they received small snacks at 2-h intervals in order to avoid a decrease in vigilance induced by heavy meals.

A few days before the first experimental session all participants were adequately trained so as to become familiar with the whole study procedures. On each experimental day, subjects were hospitalised from early morning until +12 h post-administration. CNS effects of the different treatment conditions were evaluated at baseline and at +1 h, +2 h, +4 h, +6 h, +8 h and +10 h post-administration. In order to measure alcohol plasma levels and to allow for subsequent characterisation of kinetic parameters of the study drug (rupatadine and its metabolites), blood samples were taken before and at several time points after treatment intake (+0.5 h, +1 h, +1.5 h, +2 h, +4 h, +6 h, +8 h, +10 h, +24 h and +48 h). Clinical tolerability and safety were assessed by continuous recording of adverse events and daily evaluation of vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and axilar temperature). Furthermore, laboratory tests and ECG were performed at baseline and at +24 h post-administration in each experimental period.

Central nervous system effects

CNS effects were assessed by a cognitive psychomotor performance test battery (7 standard objective laboratory tests), subjective reports (11 visual analogue scales) and topographic 16-lead EEG recordings (the results of the latter will be published in a separate paper). Procedures were performed consecutively, each time in the same order. The full battery of objective tests together with the subjective visual analogue scales lasted round 15 min. Objective laboratory tests: (a) Motor activity; (1) Finger tapping test (FTT) used to measure a subject's ability to perform fast wrist and finger movements; the primary parameter evaluated was the mean number of strikes/second in a 30-s period. (2) Fine motoric test (FMT) was used as a measure of the ability to perform quick precise movements requiring good eye-hand co-ordination; the primary parameter evaluated was the number of squares correctly dotted in 15 s for each hand. (3) Nystagmus test (NYS) used to measure the extent of a sudden characteristic spasmodic movement of the eye at the start and at the end of a rotation period; the primary parameter evaluated was the degree of appearance of nystagmus. (b) Perceptive evaluation; (1) Temporal estimation (TE) used to measure the subjective perception of time by repeated estimations (5 trials) of a time period of pre-established duration (15 s interval) with non-objective external cue; the primary parameter evaluated was the mean in seconds of the five estimations made. (2) Critical flicker-fusion frequency test (CFF) used as indicator of cortical arousal, a measure of the CNS information processing speed; the primary parameter evaluated was the mean threshold of flicker-fusion frequency to four up and down trials. (c) Attentional assessments; (1) 'd2' cancellation test (D2T) as measure of attention and recognition of sensory information; the primary parameter evaluated was the number of correct responses during an interval of 280 s. (d) Associative tasks (1) Simple reaction time test (SRT) to measure the speed at which a subject responds to a sensory cue (visual) by some motor action (pressing a bottom); the primary parameter evaluated was the mean reaction time to 30 stimuli randomly presented at 500- to 3000-ms intervals.

While some evaluations were conducted using a microcomputer, Multipsy 821 -BIO-DATA- (FTT, TE, CFF and SRT) or an appropriate evaluation instrument (NYS), others involved paper and pen- based tests (D2T and FMT).

Subjective reports. These were assessed by eleven 100-mm-long horizontal visual analogue scales (VAS) on which the subjects had to locate their position between two extreme states. The volunteers did not have access to their previous responses. The pairs of extremes used were sober/drunk, awake/drowsy, sleepy/alert, quick/slow, glad/angry, attentive/inattentive, incompetent/efficient, sad/happy, kind/hostile, bored/interested, introverted/extraverted. They were quantified in such a way that scores for drunkenness, sleepiness, alertness, clumsiness, anger, inattentiveness, efficiency, happiness, hostility, interest and extroversion were computed and expressed as mm.

Pharmacokinetic assessments

For plasma level determinations, an indwelling catheter was inserted in an antecubital vein and kept patent throughout the study. At each above-described time, 10 ml venous blood samples were collected in glass tubes with lithium heparin. They were centrifuged at 2500 rpm for 15 min at 4°C. Plasma was then separated and stored at −20°C until its posterior analysis.

Plasma concentrations of alcohol were assayed according to an enzyme method with yeast dehydrogenase alcohol, measuring at final point the increase of absorbance at 378 nm of NADH formed (Heise, 1966). The calibration was made in each analytical series using distilled water and a calibration material of 49.3 nmol/l (supplied by Roche Diagnostic Systems). The inter-serial precision of the method was 1.3%–18 mmol/l and 0.7%–44 mmol/l. The dynamic interval of measurement was 0–130 mmol/l (0–6 g/l). The analytical sensitivity (increased absorbance, ΔA, vs substance concentration) was 1.3×10^{-2} ΔA/mmol/l.

Plasma concentrations of RUP and its active metabolites (UR–12790 and UR–12788) were determined by a previously validated liquid chromatography/APCI tandem mass spectrometric (LC/MS/MS) method. Treatment of the samples involved an enzymatic hydrolysis of 500 µl of plasma with β-glucuronidase followed by a liquid–liquid extraction. The LC/MS/MS system consisted of a Series 200 HPLC (Perkin Elmer) and a mass spectrometer API 365 with a heated nebulizer probe (Applied Biosystems). Chromatography was performed in a reverse-phase column and detection was done in multiple reaction monitoring (MRM) mode of positive ions. The method was linear from 0.2 to 40 µg/L of each compound. The lowest limit of quantification was established at 0.2 µg/L for all the analytes and no endogenous compounds were found to interfere with the analysis. The described method met regulatory requirements for selectivity, sensitivity, goodness of fit, precision and accuracy. Analysis were carried out in accordance with the principles of Good Laboratory Practices (GLP).

Tolerability and safety evaluations

Clinical tolerability and safety were assessed by daily recording of adverse events and of vital signs (supine systolic and diastolic blood pressures, heart rate, respiratory rate and axilar temperature). Furthermore, laboratory tests (haematology, biochemistry) and ECG were performed at baseline and at +24 h post-administration in each experimental period.

Statistics

Univariate (each parameter independently) analysis was based in the comparisons of baseline performance and single dose effects. Baseline performance (at predose) was compared using ANOVAs which included the treatments and the subjects as main effects. Single dose effects were evaluated for changes to baseline (effects of treatment) and for row data (effects of interaction treatment by time), by applying ANOVAs which included the treatment regimens, the times and the subjects as main effects. When suitable, descriptive pairwise comparisons were performed using paired *t*-tests, not adjusting for multiple testing. Because the study was designed to test for pharmacodynamic effects, the analysis was based on completed data rather on an intention-to-treat analysis.

To obtain a general vision of the results, a multivariate, non-parametric approach was also applied (Lorenzo and Barbanoj, 2002). Treatment-effect relations, separately for objective and subjective assessments, were evaluated by means of Friedman's rank ANOVA and Wilcoxon tests of changes from premedication values using 9 objective combined variables obtained from the 7-cognitive psychomotor performance tests, and 11 combined variables obtained from the visual analogue scales, respectively. Transformations were applied so that a lower Friedman's rank means a higher cognitive psychomotor impairment (i.e. decreases in FTT, CFF, NT, D2T, FMT and increases in TE and SRT) or higher subjective effects (i.e. decreases in alertness, efficiency, happiness and interest, and increases in drunkenness, sleepiness, clumsiness, anger, innattentiveness, hostility and extroversion).

The pharmacokinetic profile for alcohol and for rupatadine and its two metabolites: UR–12790, UR–12788 was defined by calculating the area under the concentration-time curve (AUC) from time zero to the last sample using the trapezoidal method. In addition, the peak plasma concentration (C_{max}) and the time required to achieve the latter (t_{max}) were determined directly from the experimental data (Shumaker, 1986). Comparisons of parameters (AUC and C_{max}) for alcohol were assessed by ANOVAs which included the treatments and the subjects as main effects. For the 2 doses of RUP these kinetic parameters were compared by paired *t*-tests. Potential differences in the t_{max} were analysed by the non-parametric Friedman and Wilcoxon tests for alcohol and RUP, respectively. Pharmacokinetic data processing was performed with the WinNonlin (version 2.1) software.

All variables were statistically analysed using SPSSWIN version 6.1. Results are reported as mean values of changes from pre-drug data (Δ values) or as mean values $\pm$ SD computed for the original values of the variables, for treatments and test times, respectively. Differences were considered significant when the probability of type I error was less than 0.05.

RESULTS

Study population

Twenty young healthy volunteers were enrolled and eighteen subjects completed all six periods of the study. The main demographic characteristics of the final experimental sample (9 males and 9 females) as mean ($\pm$ SD) were: 23.5 years (2.1), 168 cm (10) and 64.3 Kg (9.7). No significant differences were observed among these demographic characteristics between the experimental and the enrolled samples. Two participants dropped out of the study. In one case this was due to personal reasons while the second participant had persistent low haemoglobin values. She was diagnosed of iron-deficiency anaemia and was excluded from the study due to concomitant disease requiring treatment. All subjects who completed the trial were compliant with the study protocol and all active treatments were well tolerated.

Central nervous system pharmacodynamics

Baseline assessments. Baseline scores, both those obtained for objective laboratory tests and those for subjective reports (Table 1), did not differ across treatments, demonstrating similar experimental conditions at the starting point for each treatment.

Objective laboratory tests

Parametric univariate analysis. All active treatments induced significant impairments in the tapping test (p-drug: 0.004, p-interaction: <0.0001), though of different magnitude. Single ALC intake only caused decreases in the number of taps/s at +1 h and +2 h peaking at the first hour (mean decrease: 0.86 taps/s). This impairment recovered thereafter. The maximum decrease in performance in this task was found in the experimental sessions where RUP_20 or HYD were administered (mean peak decrease: 1.18 and 1.29 taps/s, respectively). Baseline values were not fully recovered. RUP_10 and CET showed lower impairments with a faster recovery, though baseline values were not obtained until the last assessments.

In the fine motor skill test, there were no significant changes in the total number of dotted rectangles [p-drug: 0.501, p-interaction: 0.133]. However, significant effects were observed in the number of correctly dotted

Table 1. Baseline values on objective laboratory tests and subjective reports. Mean $\pm$ SD values obtained in 18 healthy subjects before drug intake

	Placebo	Alcohol 0.8 g/kg	Rupatadine 10 mg + Alcohol 0.8 g/kg	Rupatadine 20 mg + Alcohol 0.8 g/kg	Cetirizine 10 mg + Alcohol 0.8 g/kg	Hydroxyzine 25 mg + Alcohol 0.8 g/kg
Objective tests						
FTT	6.89 ± 0.91	6.69 ± 1.04	7.01 ± 0.69	6.99 ± 0.84	6.94 ± 0.77	6.88 ± 0.73
FMT	88.39 ± 19.11	91.72 ± 13.58	89.89 ± 15.03	90.72 ± 15.70	88.83 ± 12.59	88.06 ± 10.69
NYS	57.36 ± 2.90	57.78 ± 3.08	56.94 ± 2.51	57.92 ± 2.88	57.92 ± 3.00	57.36 ± 2.50
TE	16.27 ± 3.28	16.69 ± 2.38	16.66 ± 2.42	15.91 ± 2.07	16.75 ± 3.39	16.78 ± 2.84
CFF	40.76 ± 2.61	40.48 ± 3.80	40.71 ± 3.47	40.64 ± 4.13	40.93 ± 3.68	41.08 ± 3.75
D2T	312.72 ± 52.80	320.78 ± 46.77	331.22 ± 55.03	322.50 ± 40.67	323.89 ± 52.32	322.56 ± 52.37
SRT	210.94 ± 33.50	205.33 ± 34.51	209.89 ± 35.14	207.17 ± 32.91	200.44 ± 20.34	207.33 ± 21.68
Subjective scales						
Drunkenness	0.72 ± 1.56	0.83 ± 2.48	2.44 ± 4.87	2.61 ± 8.49	2.44 ± 8.68	1.89 ± 6.80
Sleepiness	31.78 ± 27.83	28.28 ± 21.80	31.78 ± 27.50	32.28 ± 29.43	35.83 ± 30.07	43.50 ± 25.75
Alerteness	61.78 ± 30.15	68.39 ± 22.99	66.78 ± 22.38	66.33 ± 29.59	60.00 ± 27.78	56.17 ± 26.85
Clumsiness	35.06 ± 24.52	27.94 ± 14.87	37.11 ± 19.86	33.06 ± 26.51	37.89 ± 25.02	40.22 ± 22.84
Anger	33.06 ± 18.59	30.44 ± 16.15	32.83 ± 21.14	29.33 ± 20.00	34.89 ± 21.87	35.39 ± 19.45
Inattentiveness	29.89 ± 20.50	30.06 ± 17.90	36.44 ± 19.41	29.44 ± 22.58	41.22 ± 23.96	39.50 ± 21.75
Efficiency	72.00 ± 25.12	71.44 ± 18.17	64.56 ± 23.44	69.67 ± 24.20	67.83 ± 24.95	62.22 ± 23.46
Happiness	32.78 ± 18.21	31.56 ± 18.70	34.78 ± 18.16	32.00 ± 19.50	34.39 ± 20.08	37.72 ± 20.07
Hostility	71.33 ± 21.71	73.72 ± 19.73	69.33 ± 21.98	70.72 ± 25.09	71.78 ± 22.08	67.50 ± 22.89
Interest	37.06 ± 21.16	30.83 ± 17.03	35.56 ± 21.32	32.61 ± 20.96	30.11 ± 19.12	40.56 ± 22.05
Extraversion	58.56 ± 26.83	63.89 ± 26.24	63.06 ± 24.28	62.94 ± 24.87	60.72 ± 25.53	59.67 ± 25.67

FTT, finger tapping test (strikes/s); FMT, fine motoric test (no. of correct responses); NYS, nystagmus test (degree of appearance); TE, temporal estimation (s); CFF, critical flicker-fusion frequency (Hz); D2T, 'd2' cancellation test (no. of correct responses); SRT, simple reaction time (ms); Subjective scales (mm).

rectangles [*p*-drug: 0.019, *p*-interaction < 0.0001]. All active treatments decreased performance in a similar magnitude (mean decreases: 18 correct dotted rectangles), clearly peaking at +1 h after ALC alone, but similar between +1 and +2 h with all the combination treatments. A trend to recovery starting at +4 h was obtained after all active treatments.

All active treatments induced significant impairments in the nystagmus test [*p*-drug < 0.0001, *p*-interaction: <0.0001], these being of similar magnitude. The decreases peaked at +1 h (mean decreases: 10 s) and were significant until +4 h. No significant changes were obtained in the time estimation test [*p*-drug: 0.299, *p*-interaction: 0.778].

Significant effects were observed in the critical flicker-fusion frequency test [*p*-drug: 0.111, *p*-interaction <0.0001]. There was a decrease after all active treatments which peaked at +2 h. The greatest impairment was obtained after HYD (mean maximum decrease: 3.87 Hz), not fully recovering until +8 h. The remaining active treatments showed a similar magnitude of impairment (mean maximum decreases: 1.89 Hz) starting the recovery at +4 h after ALC, RUP_10 and CET, but persisting until +8 h after RUP_20.

In the 'd2' cancellation test, significant changes were obtained both in the total number of cancelled letters [*p*-drug < 0.0001, *p*-interaction: 0.002] and in the number of correctly cancelled letters [*p*-drug < 0.0001, *p*-interaction < 0.0001]. These two variables showed the same pattern of results. A trend to improved performance was observed after PLA (maximum mean increase at +10 h: 17.28 correct letters). While ALC treatment induced the lowest impairment, peaking at +1 h (mean decrease: 35.67 correct letters) with a fast recovery, HYD induced the highest alteration, peaking at +2 h (mean decrease: 70.84 correct letters). It was also more sustained over time. The administration of CET, RUP_10 and RUP_20 induced an intermediate reduction between that induced by ALC and HYD in both magnitude and recovery.

Significant effects were observed in the simple reaction time [*p*-drug: 0.006, *p*-interaction <0.0001], with an increase after all active treatments (Figure 1). The greatest impairment was obtained after HYD, peaking

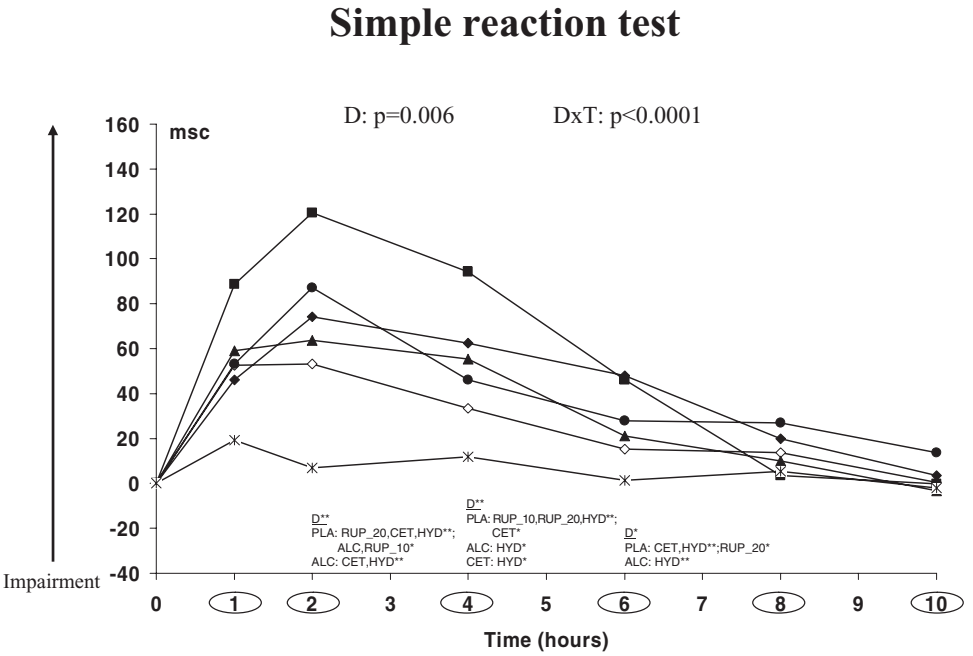

Figure 1. Time course of the effects on an objective behavioural task after the administration of placebo (✳ PLA), alcohol 0.8 mg/Kg (◇, ALC), rupatadine 10 mg + alcohol 0.8 mg/kg (▲, RUP_10), rupatadine 20 mg + alcohol 0.8 mg/kg (◆, RUP_20), cetirizine 10 mg + alcohol 0.8 mg/kg (●, CET) and hydroxyzine 25 mg + alcohol 0.8 mg/kg (■, HYD). Values are means ($n = 18$) of Δ values (changes from baseline). Statistical results after ANOVA: D = treatment factor, D × T = interaction factor. *p < 0.05, **p < 0.01. The greatest impairment was obtained after HYD. The other active treatments showed a similar magnitude of impairment at +1 h. This was increased until +2 h after CET and RUP_20, and sustained after ALC and RUP_10. It started to recover on +4 h after

Table 2. Treatment/effects relations on objective laboratory tests. Based on Friedman's rank ANOVA and Wilcoxon test of changes from pre-medication values using 9 objective combined variables obtained from 7-psychomotor performance tests. Transformations were applied in order that a lower Friedman's rank means a higher psychomotor impairment

Time	Placebo	Alcohol 0.8 g/kg	Rupatadine 10 mg + Alcohol 0.8 g/kg	Rupatadine 20 mg + Alcohol 0.8 g/kg	Cetirizine 10 mg + Alcohol 0.8 g/kg	Hydroxyzine 25 mg + Alcohol 0.8 g/kg	$\chi 2$	p
+1 h	53.01	32.04*	21.51*	27.99*	23.04	31.50*	20.54	0.0010
+2 h	51.03	44.01	38.97	18.00**	25.02*	11.97**	38.02	0.0000
+4 h	52.02	44.01	28.53*	23.40*	32.04	9.54**	36.25	0.0000
+6 h	46.53	36.00	36.54	24.03	29.97	16.02*	18.06	0.0029
+8 h	45.99	35.01	38.97	15.03*	16.02*	37.98	26.46	0.0001
+10 h	46.98	38.97	27.00	27.99	21.96*	26.01	14.27	0.0140
Total	295.56	230.04*	191.52*	136.44**	148.05**	133.02**	110.35	<0.01

Wilcoxon tests: *$p<0.05$ vs placebo; **$p<0.05$ vs placebo and alcohol.

at +2 h (mean maximum increase: 120.56 ms) and not fully recovering until +8 h. The other active treatments showed a similar magnitude of impairment at +1 h. This impairment increased until +2 h after CET and RUP_20 (mean maximum increases: 81 ms), but remained unchanged after ALC and RUP_10 (mean increases: 58 ms). Recovery started at +4 h.

Non-parametric multivariate analysis. Treatment-effect relations are detailed in Table 2. Based on rank sums, there were significant differences between treatments in global magnitude of impairment ($\chi^2 = 110.35$; $p < 0.0001$). Specifically, all treatments with alcohol, either alone or in combination with an active compound, were significantly different from PLA. ALC was the intervention which produced less objective psychomotor impairment and this was significantly different from that observed after HYD, CET and RUP_20. The highest objective impairment was induced by HYD, and it differed significantly from that obtained after RUP_10.

Subjective visual analogue scales

Parametric univariate analysis. No statistically significant differences in either the treatment factor or the treatment-by-time factor were evidenced in the following scales: anger (p-drug: 0.739, p-interaction: 0.289), happiness (p-drug: 0.845, p-interaction: 0.244), hostility (p-drug: 0.738, p-interaction: 0.289), interest (p-drug: 0.066, p-interaction: 0.051) and extraversion (p-drug: 0.806, p-interaction: 0.612). In addition, maximum mean changes observed throughout the trial were of low magnitude: anger (after RUP_20 at +8 h: +16.61 mm), happiness (after CET at +6 h: +12.33 mm), hostility (after HYD at +2 h: −9.39 mm), interest (after ALC at +6 h: +21.73 mm) and extraversion (after RUP_20 at +6 h: −10.55 mm).

Significant differences in both the treatment factor and the treatment-by-time factor were obtained in the scales assessing drunkenness (p-drug < 0.0001, p-interaction < 0.0001), sleepiness (p-drug: 0.023, p-interaction < 0.001), alertness (p-drug: 0.005, p-interaction: 0.015) and clumsiness (p-drug: 0.006 p-interaction: < 0.0001). In the inattentiveness (p-drug: 0.279, p-interaction: 0.001) and efficiency (p-drug: 0.068, p-interaction < 0.0001) scales, the only significant effects were evidenced in the interaction term.

Similar values were obtained in the drunkenness scales in all sessions where alcohol was taken, regardless of concomitant administration of a drug or not. They clearly peaked at +1 h (mean maximum increase: +82.73 mm) and decreased thereafter, but were still significant until +6 h (Figure 2).

Subjects reported to be significantly more sleepy and less alert from the 1st until the 6th h and more clumsy only until the 4th h after all treatments with alcohol, either alone or together with an active compound, in comparison with PLA. These effects showed a plateau between +2 and +6 h, slightly peaking at +4 h (mean maximum changes: +37 mm for sleepiness, −42 mm for alertness and +34 mm for clumsiness). Differences between treatments containing alcohol were observed in the sleepiness scale at +1 h, where the significant increases were only observed after RUP_20 and CET, and in the alertness scales at +1 and +6 h, where only decreases obtained after RUP_20 and RUP_10 were significantly differentiated from PLA (Figure 3).

In the inattentiveness and efficiency scales significant changes were only observed in the 1st and 2nd h (mean maximum changes: +28 mm for inattentiveness, −31 mm for efficiency). In the 1st h, subjects reported feeling significantly more inattentive in relation to PLA after ALC, RUP_20 and RUP_10 and less efficient in relation to PLA after ALC, RUP_20, RUP_10 and

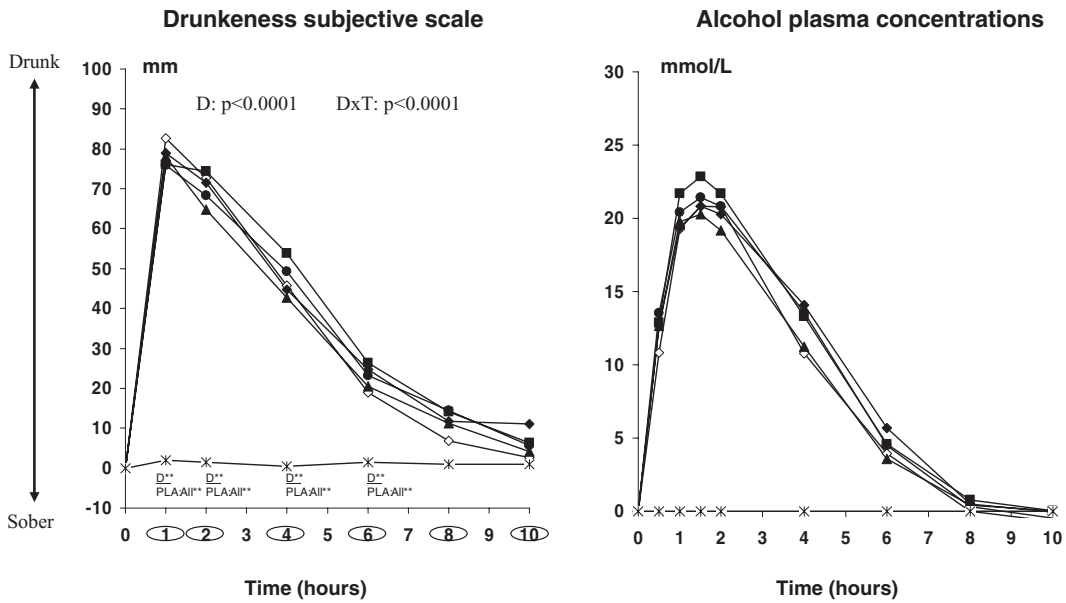

Figure 2. The time course of the drunkenness subjective scales and the alcohol plasma levels after the administration of placebo (✳, PLA), alcohol 0.8 mg/Kg (◇, ALC), rupatadine 10 mg + alcohol 0.8 mg/kg (▲, RUP_10), rupatadine 20 mg + alcohol 0.8 mg/kg (◆, RUP_20), cetirizine 10 mg + alcohol 0.8 mg/kg (●, CET) and hydroxyzine 25 mg + alcohol 0.8 mg/kg (■, HYD). Left panel: Values are means ($n = 18$) of Δ values (changes from baseline). Statistical results after ANOVA: D = treatment factor, D × T = interaction factor. *$p < 0.05$, **$p < 0.01$. Similar values were obtained in the drunkenness scale in all sessions where alcohol was taken, clearly peaking at +1 h and decreasing thereafter, but still significant until +6 h. Right panel: values are means ($n = 18$) of row data (mmol/L). AUC, C_{max} and t_{max} for alcohol when administered alone or combined with any active compounds showing no statistical differences between conditions

CET. These effects were significantly higher than those observed after HYD. At +2 h, all treatments with alcohol, either alone or together with an active compound, were significantly different from PLA.

Non-parametric multivariate analysis. Treatment-effect relations are detailed in Table 3. Based on rank sums there were significant differences in the global magnitude of subjective changes between treatments ($\chi^2 = 63.67$; $p < 0.0001$). Specifically, all treatments with alcohol, either alone or in combination with an active compound, were significantly different from PLA. Subjective changes obtained after HYD and CET were significantly lower than those observed after ALC.

Pharmacokinetics

Alcohol. The mean plasma concentration-time course of alcohol after a single oral administration, either alone (ALC) or together with the active compounds (HYD, CET, RUP_20 and RUP_10), is plotted in Figure 2.

The AUC for alcohol when administered alone or combined with any active compounds showed no statistical differences between conditions. Mean values ranged between 65.78 and 82.25 mmol × h/l. Neither did alcohol bioavailability rates show any significant differences, either in Cmax, with values ranging between 21.30 and 24.12 mmol/l, or in t_{max}, with all treatments presenting median values of 1.5 h (Table 4).

Rupatadine. The mean plasma concentration-time course of rupatadine (administered compound) and two metabolites: UR-12788 and UR-12790, after a single oral administration of rupatadine 10 and 20 mg together with 0.8 g/kg alcohol, is plotted in Figure 4.

Pharmacokinetic parameters obtained after both doses of rupatadine are shown in Table 5. Significant differences were obtained in AUC and C_{max} for

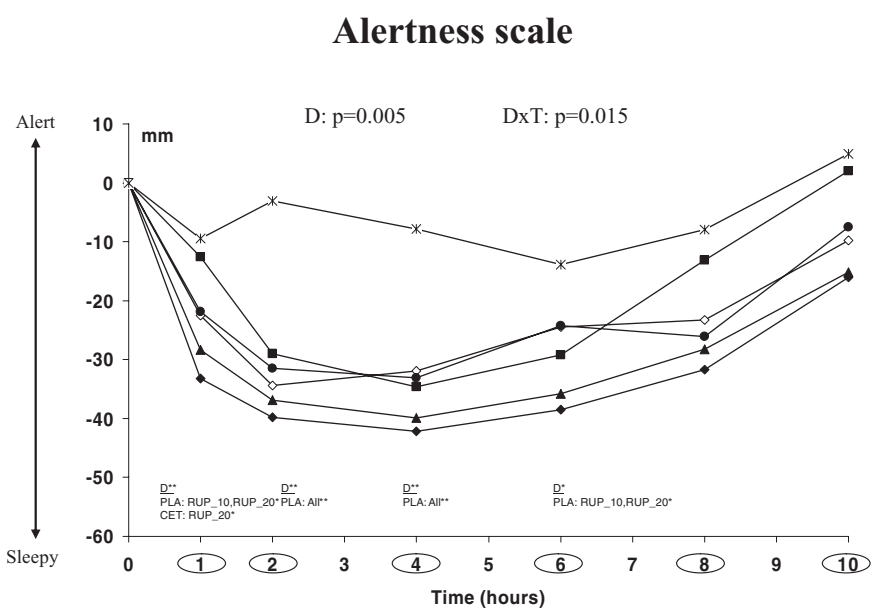

Figure 3. Time course of the effects on a subjective visual analogue scale after the administration of placebo (✳, PLA), alcohol 0.8 mg/Kg (◇, ALC), rupatadine 10 mg + alcohol 0.8 mg/kg (▲, RUP_10), rupatadine 20 mg + alcohol 0.8 mg/kg (◆, RUP_20), cetirizine 10 mg + alcohol 0.8 mg/kg (●, CET) and hydroxyzine 25 mg + alcohol 0.8 mg/kg (■, HYD). Values are means ($n = 18$) of Δ values (changes from baseline). Statistical results after ANOVA: D = treatment factor, D × T = interaction factor. *$p < 0.05$, **$p < 0.01$. Subjects reported significantly less alertness from the 1st until the 6TH h after all treatments with alcohol. These effects showed a plateau between +2 and +6 h. Differences between treatments containing alcohol were observed at +1 and +6 h when only decreases obtained after RUP_20 and RUP_10 could be significantly differentiated from PLA

Table 3. Treatment/effects relations on subjective visual analogue scales. Based on Friedman's rank ANOVA and Wilcoxon test of changes from pre-medication values using 11 subjective combined variables obtained from 11 visual analogue scales. Transformations were applied in order that a lower Friedman's rank means a higher subjective effect

Time	Placebo	Alcohol 0.8 g/kg	Rupatadine 10 mg + Alcohol 0.8 g/kg	Rupatadine 20 mg + Alcohol 0.8 g/kg	Cetirizine 10 mg + Alcohol 0.8 g/kg	Hydroxyzine 25 mg + Alcohol 0.8 g/kg	$\chi 2$	p
+1 h	55.00	22.99**	35.97	25.96**,†	40.04	51.04*	21.65	0.0006
+2 h	56.98	23.98**	44.00	31.02**	37.95	36.96	16.66	0.0052
+4 h	55.99	30.99**	34.98	30.03**	44.99	31.02**	13.23	0.0213
+6 h	55.99	33.00**	43.01	25.96**	33.00	40.04	14.17	0.0146
+8 h	48.95	30.03	41.03	22.00**	43.01	45.98	13.96	0.0159
+10 h	42.46	36.52	36.96	22.00†	42.46	50.49	11.81	0.0376
Total	315.37	177.51**	235.95**	156.97**	241.45***·	255.53***·	63.67	< 0.01

Wilcoxon tests: *$p < 0.05$ vs alcohol; **$p < 0.05$ vs placebo; †$p < 0.05$ vs hydroxyzine.

Table 4. Kinetic parameters of alcohol plasma levels. Mean (SD) values obtained after single oral intake of alcohol 0.8 g/kg either alone or concomitantly with single oral dose of hydroxyzine 25 mg, cetirizine 10 mg and rupatadine (10 mg and 20 mg) in 18 healthy subjects

	Alcohol 0.8 g/kg	Rupatadine 10 mg + Alcohol 0.8 g/kg	Rupatadine 20 mg + Alcohol 0.8 g/kg	Cetirizine 10 mg + Alcohol 0.8 g/kg	Hydroxyzine 25 mg + Alcohol 0.8 g/kg
AUC (mmol × h/l)	73.89 (29.44)	65.78 (28.50)	79.43 (33.13)	82.25 (32.59)	77.48 (32.33)
C_{max} (mmol/l)	23.62 (3.80)	21.30 (4.53)	22.90 (4.86)	23.52 (4.61)	24.12 (4.78)
*t_{max} (h)	1.5 (1, 2)	1.5 (1, 2)	1.5 (0.5, 4)	1.5 (1, 2)	1.5 (1, 2)

*median (minimum, maximum values).

Time course plasma concentrations

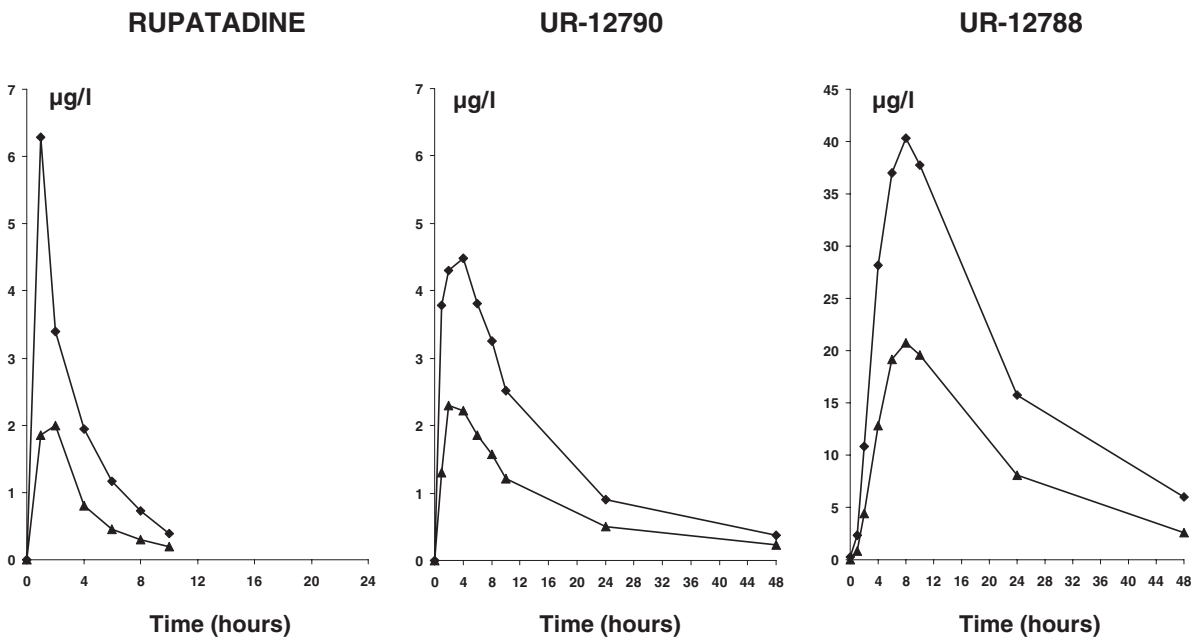

Figure 4. Time course of plasma concentrations of rupatadine (left panel), UR–12790 (middle panel) and UR–12788 (right panel) after the administration of rupatadine 10 mg + alcohol 0.8 mg/kg (▲) and rupatadine 20 mg + alcohol 0.8 mg/kg (◆). Values are means ($n = 18$) of raw data (µg/L). AUC and C_{max} of both parent compound and active metabolites were proportional to the doses, showing the following order of drug disposition: rupatadine < UR–12790 < UR–12788

Table 5. Kinetic parameters of rupatadine and its metabolites. Mean (SD) values obtained after single oral dose (10 mg and 20 mg) of rupatadine administered concomitantly with alcohol 0.8 g/Kg in 18 healthy subjects

	Rupatadine		UR–12790		UR–12788	
	Dose 10 mg	Dose 20 mg	Dose 10 mg	Dose 20 mg	Dose 10 mg	Dose 20 mg
AUC (µg × h/l)	7.79 (4.46)	20.63 (12.79)	34.31 (14.68)	77.80 (26.83)	455.24 (186.18)	923.68 (294.60)
C_{max} (µg/l)	2.69 (1.74)	6.93 (5.22)	2.76 (0.96)	5.51 (1.26)	22.72 (10.86)	42.14 (15.37)
*t_{max} (h)	2 (1, 2)	1 (1, 2)	2 (1, 4)	2 (1, 6)	8 (6, 10)	8 (6, 10)

*median (minumum, maximum values).

all three compounds (rupatadine: $p < 0.0001$, $p = 0.002$, respectively; UR-12788: $p < 0.0001$, $p < 0.0001$, respectively; UR-12790: $p < 0.0001$, $p < 0.0001$, respectively). Overall results showed the following order of drug disposition: rupatadine < UR–12790 < UR–12788. C_{max} for rupatadine and UR–12790 were similar and both clearly lower than for UR–12788. Analysis of the differences in t_{max} after both administered doses did not show any significances in any of the comparisons. The metabolite UR–12788 was found to reach its maximum concentration later than rupatadine and UR–12790.

Tolerability and safety

A total of 21 adverse events were reported during the study (6 after ALC, 5 after HYD, 4 after RUP_20, 3 after RUP_10, 1 after PLA and 2 during the washout period). Eight of twenty subjects reported at least one adverse event throughout the course of the study. Headache was the most commonly reported event,

followed by nausea, vomiting, dizziness and diarrhoea. Their causal relationship with the treatment was considered 'a possibility', either in relation to the drug administered or to the alcohol intake. The two adverse events, which occurred during the washout window (tonsillitis and pedestrian accident), were considered not to be drug-related. No serious adverse events were reported, and no subject withdrew due to drug intolerance.

No clinical significant trends or values were observed during the study either in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and axial temperature) or in ECG parameters (QT and QTc intervals). Although there were a number of laboratory findings outside the normal range, these deviations were generally minor and were not considered to be clinically relevant.

DISCUSSION

The present study in healthy young volunteers compares the cognitive psychomotor and subjective effects of acute alcohol 0.8 g/kg when taken alone or together with a single oral intake of hydroxyzine 25 mg, cetirizine 10 mg, or two doses of rupatadine (10 and 20 mg) (a new H_1 antihistamine and PAF antagonist compound) and placebo. Plasma concentrations of alcohol, rupatadine and two active metabolites were also evaluated. The employed procedures are a well-documented approach and reliable method for assessing CNS effects in humans, comparing either relative potency or their time of onset and duration of action (Hindmarch, 1980; Hindmarch and Gudgeaon, 1980; Barbanoj *et al.*, 2002). Activity was studied in a time-response manner. A crossover design was chosen to minimise variability. We used a mixed-gender sample to determine antihistamine effects on performance because the repeatedly observed gender difference in antihistamine central effects is matter of controversy (Vermeeren *et al.*, 2002).

Alcohol not only served as a challenging agent to evaluate antihistamine effects, but also as the positive control. Alcohol dosing was adjusted to body weight (0.8 g/kg) in order to reach blood alcohol concentrations close to the alcohol limit for driving in force in Spain at the time: 17.39 mmol l^{-1} (0.8 g/l). The legal limit has since been reduced to 10.87 $mmol^{-1}$ (0.5 g/l), but it remains at the previous point in some other EU countries such as UK, Ireland, Luxembourg and Malta (INRETS, 2004). In fact, mean blood alcohol concentrations in the present study ranged from 11.34–22.96 mmol l^{-1} between 30 and 240 min. This relatively high dose of alcohol was intended to produce significant depressants effects on CNS function in most objective laboratory tests and to avoid possible failure, as reported in studies with lower doses of alcohol (Ridout *et al.*, 2003). Indeed we observed statistically significant impairments in the majority of objective laboratory tests, such as finger tapping, fine motor, nystagmus, critical flicker-fusion frequency, 'd2' cancellation and simple reaction time. Only in the time estimation test no significant effects were obtained. As expected, volunteers self-rated level of drunkenness throughout the experimental session.

These results are in agreement with previous experimental data reported in several studies. The administration of alcohol doses ranging from 0.5 mg kg^{-1}–1.5 mg kg^{-1} causes impairment of cognitive and psychomotor performance tasks (Seppala *et al.*, 1979; Hindmarch *et al.*, 1992; Kerr and Hindmarch, 1998; Ridout *et al.*, 2003). The effects are variable in the lower range, due to the different measures and methods employed by the researchers and to the large interindividual and interoccasional differences in the effects of alcohol. However, the effects are greater and more consistent as the doses increase and as the tasks become more complex. Subjectively, in studies that used scales to measure the degree of inebriation, subjects reported feeling drunk (Laisi *et al.*, 1979; Strömberg and Mattila, 1985) and when different doses of alcohol were administered, this feeling was reported in a dose-related manner. In our study alcohol was successfully masked only at the onset of ingestion. Volunteers were soon able to differentiate it from placebo, so a subjective bias cannot be completely ruled out.

Regarding the combination treatments, more impairment in objective cognitive and psychomotor performance tests was obtained when hydroxyzine 25 mg, cetirizine 10 mg or rupatadine 20 mg were combined with alcohol as compared to alcohol alone. The administration of rupatadine 10 mg plus alcohol 0.8 was the combination which could not be differentiated from alcohol alone. The co-administration of hydroxyzine and other 'first generation' antihistamines (phenothiazines, ethanolamines or ethylenediamines compounds for example) is known to enhance the actions of alcohol (Hughes and Forney, 1964; Landauer and Milner, 1971; Baugh and Calvert, 1977; Burns and Moskowitz, 1980). In relation to cetirizine, although most studies conclude it is unlikely to produce sedation of practical consequences, they abstain from stating that the drug is free of all sedative potential, as when it was evaluated taken concomitantly with alcohol, same additional psychomotor impairments in comparison to those assessed

after alcohol alone were observed (Meltzer, 1991; Ramaekers *et al.*, 1992; Simons, 1994; Patat *et al.*, 1995). These findings were also clearly shown in the present study. Our results reveal a similar profile in relation with rupatadine. Previous data evaluating the dose-range central effects of rupatadine showed that significant impairments were obtained at the highest dose (80 mg), while lower doses (20 and 10 mg), those which were therapeutically relevant (Izquierdo *et al.*, 2003), were similar to placebo (Barbanoj *et al.*, 2004). In the present study the 20 mg dose showed more impairment as compared to alcohol alone and the 10 mg authorised dose did not.

Subjectively, it is interesting to notice that those scales which were more related with mood (anger, happiness, hostility, interest and extraversion) did not show any statistically significant differences, while those most closely related to the subjective perception of performance (sleepiness, alertness, clumsiness, inattentiveness and efficiency) did so. It has been argued that there are qualitative differences between antihistamines and benzodiazepines sedative actions, diazepam causing a subjectively pleasant impairment of performance, whilst hydroxyzine-induced sedation had an unpleasant character, rendering the subjects sad and antagonistic (Mattila *et al.*, 1986). The euphoric subjective profile induced by alcohol (Morgan and Badawy, 2001; Blomquist *et al.*, 2002) is well-known, so a possible mood counteracting phenomenon cannot be completely excluded.

Regarding the global subjective assessments, a clear difference was observed between the rupatadine and the hydroxyzine, cetirizine intakes together with alcohol; the changes obtained after the latter were significantly lower than those observed after alcohol alone. When the drug concomitantly administered with alcohol was rupatadine no significant differences were obtained in relation to alcohol alone. A clear dissociation between the magnitude of the impairment caused by a treatment when evaluated objectively and when the subjective perception of this involvement was assessed was evident after cetirizine plus alcohol, but was considerably more noteworthy after hydroxyzine plus alcohol. These results contrast with what would be expected as it is known that the antihistamine concentration thresholds needed to produce subjective reported drowsiness are lower than those needed to produce objective impairment (Gengo *et al.*, 1989). However, a dissociation like that encountered in this study has previously been described in the literature (Lister *et al.*, 1988; Barbanoj, 1991). It has been outlined as an impairment in the ability of self-perception of cognitive deficits, in other words, an impairment in metacognition. As a result, patients might find that their subjective feelings do not provide a reliable indication of the effect of antihistamines plus alcohol on objective performance.

Alcohol concentrations obtained in our study were in accordance with previously published data (Azcona *et al.*, 1995; Farré *et al.*, 1997) and we observed that they were unaffected by concurrent antihistamine and alcohol intake. The increased effects described were therefore likely to have a pharmacodynamic origin in the CNS.

It is known that clinical effects of rupatadine are due to the combination of both parent compound and its metabolites. Rupatadine contributes around 25% to the total systemic exposure of active substances and the rest is provided by several active metabolites. Rupatadine itself provides a rapid onset of action but the main active metabolites (UR–12790 and its hydroxylated metabolite UR–12788) retain an antihistaminic activity and may partially contribute to the overall efficacy of the drug, maintaining activity for 24 h (Izquierdo *et al.*, 2003). Definitive statements about rupatadine pharmacokinetics cannot be drawn as the drug was administered together with alcohol. However, the AUC and peak plasma concentrations obtained with both the parent compound and active metabolites were proportional to the doses. This indicates that rupatadine would show linear kinetics within the dose range studied (10–20 mg). In addition, due to the design of the study we can not exclude the possibility that the absorption or metabolism of the antihistamines was not affected by alcohol. Previous research has found that alcohol enhanced the intestinal absorption of hydroxyzine (Moriya and Nanikawa, 1990). Moreover, alcohol in acute doses has also been shown to inhibit drug metabolism (Sellers and Holloway, 1978).

The adverse events reported during the course of the study were few and not severe, being the most commonly reported headache. No increased incidence or additional events were reported under the combination treatments in relation to the reports under alcohol alone. There was no suggestion of any change in vital sings thought the course of the study. Furthermore, laboratory assessments prior to and following treatment revealed no trends which could be attributed to the study medications.

In summary, the data presented here suggest that rupatadine 10 mg taken together with alcohol is safe because the objective impairment observed after alcohol alone does not increase. However, higher doses of the drug in combination with alcohol may induce psychomotor impairment, so patients should be

informed about the possibility that concomitant use of alcohol and high doses of rupatadine could result in increased disruptive effects on cognitive and psychomotor functioning.

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