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SINGLE AND REPEATED DOSE COMPARISON OF THREE ANTIHISTAMINES AND PHENYLPROPANOLAMINE: PSYCHOMOTOR PERFORMANCE AND SUBJECTIVE APPRAISALS OF SLEEP

T. SEPPÄLÄ, E. NUOTTO & K. KORTTILA

Department of Pharmacology, University of Helsinki, Helsinki, Finland

1 In a double-blind cross-over study, nine healthy male students received placebo, brompheniramine 12 mg), carbinoxamine (12 mg), clemastine (1 mg), and phenylpropanolamine (50 mg) orally. Three doses of each drug were given: at 08.30 h and 21.00 h on the first day of treatment and at 08.30 h on the following day.

2 Psychomotor skills and subjective feelings were recorded before and 2, 6 and 12 h after the first dose on day 1 as well as before and 2 and 6 h after the third dose on day 2. Subjective appraisals of sleep were requested on the morning of day 2.

3 All antihistamines tended to cause subjective drowsiness on the first day of treatment. Drowsiness was felt for a maximum of 2 h after carbinoxamine, 6 h after brompheniramine, and 12 h after clemastine. In contrast to antihistamines, phenylpropanolamine made subjects more alert and quick witted. Tolerance to the antihistamine-induced drowsiness developed on the second day.

4 Divided attention, tracking, speed anticipation and sleep were not affected by any drug. Carbinoxamine slowed reactions 2 h after the first dose, but no impairment was measured in objective tests after brompheniramine or clemastine.

5 Phenylpropanolamine improved reaction speed and reaction accuracy and enhanced flicker recognition throughout the study. Phenylpropanolamine plasma levels and improvement in flicker fusion test results correlated with each other on day 2.

6 The results suggest that phenylpropanolamine and the antihistamines studied are comparatively harmless to psychomotor performance and driving skills.

Introduction

Antihistaminic compounds are extensively used against allergic rhinitis and travel sickness. Due to their well-known sedative side effects most antihistamines are conventionally regarded as detrimental to drivers (Wagner, 1962) and in many countries warning labels are attached to the packages of antihistamines to inform patients of their possible harmful effects on people driving in traffic. A recent epidemiological study (Skegg, Richards & Doll, 1979) suggests an association between antihistamines and motorcycle accidents, but only a small number of accidents involving antihistamine users were available for the study and it was not possible to discriminate the effects of individual antihistamines. According to Meyers (1978) there is no epidemiological evidence that antihistamines are detrimental to driving skills, and laboratory studies have confirmed rather than opposed this statement. Common therapeutic doses of promethazine and triprolidine have significantly impaired psychomotor skills and CNS-function tests (Hedges *et al.*, 1971; Peck, Fowle & Bye, 1975; Clarke & Nicholson, 1978) while chlorpheniramine has impaired performance in some studies (Clarke & Nicholson, 1978), but not in every study (Kulshrestha *et al.*, 1978; Hindmarch & Parrot, 1978). However, the effects on performance of most antihistamines studied, including diphenhydramine, mebhydrolin, clemizole, phenindamine, tripelennamine, terfenadine, ketotifen and cyproheptadine have been estimated as negligible (Wagner, 1962; Hughes & Forney, 1964; Landauer & Milner, 1971; Linnoila 1973a; Kulshrestha *et al.*, 1978; Hindmarch & Parrot, 1978). However, shortcomings in trial design, duration of observation period or relevance of test battery prevent the drawing of definite conclusions in many studies.

The present study was conducted to obtain a deeper understanding of the effects of antihistamines on performance. Clinical doses of carbinoxamine, brompheniramine and clemastine were chosen for the study. Carbinoxamine has not been studied earlier in this respect, single doses of brompheniramine

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mine (4 mg) have impaired visuo-motor coordination from 1.5 h to 3 h (Nicholson, 1979) after administration and clemastine (1 or 2 mg) has impaired auditory vigilance from 6 to 7 h and reactions from 2.5 to 5 h (Peck *et al.*, 1975) after administration. However, clemastine did not impair psychomotor performance in four earlier studies using single or repeated doses (Landauer & Milner, 1971; Linnoila, 1973a; Hindmarch, 1976; Hindmarch & Parrot, 1978), but the skills were only measured up to 1–3 h after either a single or the final dose.

In addition to antihistamines, we deemed it appropriate to include phenylpropanolamine in the study, because sympathomimetic drugs are often combined with antihistamines to enhance symptomatic relief in vasomotor and allergic rhinitis. Phenylpropanolamine has proved beneficial for these indications, even when administered alone (Weisberg & Breslow, 1966). Since both antihistamines and phenylpropanolamine may affect sleep (Reinberg *et al.*, 1978), and since this could be related to altered early morning performance, the effects of the drugs on subjective appraisals of sleep were also studied. Because antihistamines are generally used periodically both acute and subacute effects were studied.

Methods

Subjects

Nine male medical students of normal weight and between the ages of 20 and 25 years served as paid volunteers. All of them were in good physical and mental health, with no history of either psychiatric or organic disorders. On the days of the study the subjects ate standard meals at noon and at 16.00 h. Subjects were told not to take alcohol or other drugs during the course of the experiment. Tea, coffee and cola were not allowed during the test period. Informed consent was obtained from each subject.

Experimental design

Each subject underwent each of the five experimental conditions. Each condition consisted of two consecutive days followed by a constant drug-free period of five days. During each condition three repeated doses of lactose placebo (Pl); brompheniramine maleate, 12 mg; carbinoxamine maleate, 12 mg; clemastine, 1 mg; or phenylpropanolamine HCl, 50 mg (Figure 1) were administered. The sequence of drug conditions was random, (balanced according to two 5 × 5 Latin squares with one subject failing to participate), and drugs were given under supervision, double-blind in identical soft gelatin capsules. During each experimental condition, the subjects adhered to the following schedule of drug intake and tests:

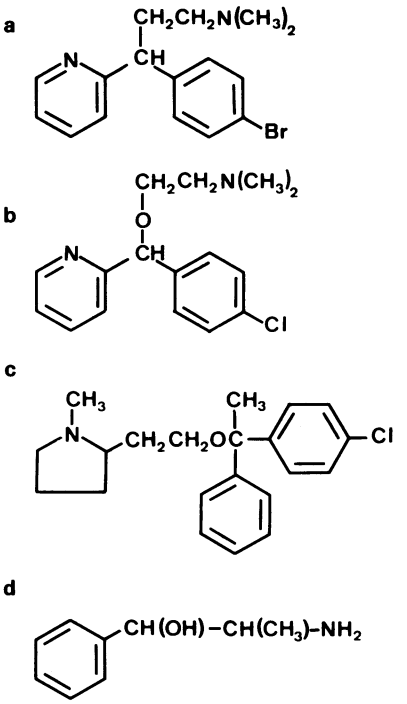

Figure 1 Structural formulae of a) brompheniramine, b) carbinoxamine, c) clemastine and d) phenylpropanolamine.

Day 1

08.00 h	Psychomotor tests (pre-drug performance)
	Subjective assessments
08.30 h	Drug intake (first dose)
10.30 h	Psychomotor tests
	Subjective assessments
	Blood sample
14.30 h	Psychomotor tests
	Subjective assessments
	Blood sample
20.30 h	Psychomotor tests
	Subjective assessments
21.00 h	Drug intake (second dose)

Day 2

08.00 h	Sleep appraisals
	Psychomotor tests (early morning performance)
	Subjective assessments
08.30 h	Drug intake (third dose)
10.30 h	Psychomotor tests
	Subjective assessments
	Blood sample
14.30 h	Psychomotor tests
	Subjective assessments
	Blood sample

On test days and the days preceding them the subjects were told to be active from 07.00 h to 23.00 h and to sleep from 23.00 h to 07.00 h in order to stabilize their circadian rhythms. Before starting the study, the subjects were carefully trained to carry out the tests in order to eliminate the learning effect on the results.

Psychomotor tests

The test facilities are described elsewhere in greater detail (Linnoila & Mattila, 1973; Linnoila, 1973b; Seppälä *et al.*, 1976; Seppälä *et al.*, 1980). The main features of individual tests were as follows:

(a) *The divided attention test* consisted of four dials (two in the middle and two in the periphery of the subject's field of vision) with revolving pointers. For a period of 5 min, the subject had to push one of the four buttons in front of him every time the pointer in any dial passed a sign (3 to 4/dial). The total number of stimuli was 420 (300 in the central dials and 120 in the peripheral dials). The total number of responses and the number of correct responses to both central and peripheral dials were recorded.

(b) *A tracking task* (Wiener Koordinationsgerät, J.C. Pöhlman, Munich) was used to measure hand-eye coordination. The subjects tried to keep a black dot superimposed on a moving track by turning a steering wheel. Each run lasted 30s. The number of mistakes and mistake percentage (100 × cumulative length of mistakes/total track length) were scored.

(c) In a complex visual and auditory *choice reaction test* (Test d'attention diffusée, PPII, Ets Pierre Dufour, Paris) subjects pushed an appropriate combination of foot pedals in response to three light stimuli and pressed a button by hand in response to presentation of a masked target tone. Cumulative reaction time and the number of errors to 32 successive stimuli (spaced at an interval of 1.5 s) were recorded.

(d) *A flicker fusion test* was used to determine the critical flicker frequency (CFF). The rate of flickering of a red light (ϕ 3 mm), induced by a light emitting diode, was gradually increased in steps until it appeared to become steady. During the procedure, the subjects wore artificial pupil constrictors. Results were recorded in arbitrary units.

(e) In *the speed anticipation test* (Takei & Company Ltd, Tokyo) the subject had to estimate the time taken by a round light (ϕ 12 mm), gliding at a constant speed along a horizontal depression in a grey screen, to pass behind a black wall (35 cm) if it had continued at the same speed. The subject expressed his estimate by pressing a key at the instant he expected the light to reappear from behind the black wall. The time was measured with a digital chronometer with an accurary of 1 ms. The correct time was 2080 ms. Ten successive measurements were made and the mean, standard deviation, range, and coefficient of variation of 10 serial estimations were recorded.

Subjective assessments

Subjective assessments were made by filling in a questionnaire sheet including the following sections:

(a) *Subjective feeling of performance* was rated by using a 5-point scale (very good, good, normal, bad, very bad).

(b) *The nature of the treatment* was estimated to be either stimulant, tranquillizer or placebo.

(c) In the *side effect list*, the subjects graded the feeling of fatigue, dryness of the mouth, difficulties in concentration, dizziness or unsteady gait, headache, restlessness, nausea, tremor, tinnitus and palpitation from 0 to 2.

(d) *Visual analogue scales* were used to give a rough idea of some psychological effects of the drugs. Subjects were required to mark the point which represented their current state on 100 mm linear vertical scales. The extremes of the scales were: Quick witted—Mentally slow, Alert—Drowsy, Calm—Excited, Amicable—Antagonistic and Happy—Unhappy.

No access to previous assessments was permitted when filling in the rating scales.

Sleep estimations

On the morning of day 2 the subjects filled in a sleep evaluation questionnaire (SEQ), modified according to Sunshine (1975) and Lahtinen & Pekkola (1978). The SEQ comprised the following factors, graded by the subjects on 3 to 5 point scales: quality of sleep, quality of falling asleep, rapidity of falling asleep, total length of sleep, soundness of sleep, interruption of sleep, amount of dreaming, recall of dreaming, feeling upon awakening and main problems concerning sleep.

Drug serum concentrations

Venous blood samples were centrifuged immediately after drawing and the separated serum stored at −22°C for 1 month prior to the determination. Gas-chromatographic methods were applied for assays of plasma brompheniramine, carbinoxamine and phenylpropanolamine, while clemastine was assayed with a mass fragmentographic method (Simonyi *et al.*, 1975; Neelakantan & Kostenbauder, 1976; Ghanekar & Das Gupta, 1978).

Statistics

Parametric data (objective measurements and visual

analogue scales) showed a Gaussian distribution. The overall drug effect, effect of test time and drug versus drug analysis were first checked by two-way analysis of variance (ANOVA). Thereafter, a posteriori comparison between the treatments at individual test times was made by Tukey's hsd-procedure (Winer, 1971). Linear correlation co-efficients were calculated with a standard programme provided by the Computer Centre of the University of Helsinki.

The non-parametric data (SEQ and subjective assessments) were treated using the Wilcoxon-Mann-Whitney test or Fisher's exact probability test. $P = 0.05$ was considered the limit of significance.

Results

Psychomotor performance

The results were computed as changes from pre-drug values. The mean pre-drug scores of different treatment conditions did not deviate significantly in respect of any parameter measured. No significant drug effects were seen on divided attention, tracking or on the speed anticipation test (Table 1).

Reaction time (Figure 2) Generally, the subjects' reaction times quickened during the study (effect of test time, $P < 0.01$, ANOVA). The reactions of the subjects were slower ($P < 0.05$ *v* placebo, Tukey) 2 h after the first dose of carbinoxamine on day 1 (at 10.30 h), but reactions returned to normal thereafter. Individual variation in the subjects' responses was seen in the large s.d. at the time of impairment. This obviously reduced the statistical significance of the observation. Phenylpropanolamine improved reaction times ($P < 0.05$, ANOVA), in comparison with placebo, carbinoxamine and brompheniramine. The results shown in Figure 2 suggest that brompheniramine tends to slow down reactions after the third dose (at 10.30 h on day 2), but this effect was not significant and the large s.d. indicates that slower reactions were again measured in only a few subjects.

Reaction mistakes (Figure 3) Clemastine and brompheniramine slightly decreased and phenylpropanolamine significantly decreased ($P < 0.001$, ANOVA) reaction mistakes when compared with placebo. Carbinoxamine impaired reaction accuracy at 2 and 6 h after the first dose, but this effect was not significant at either test time.

CFF (Figure 4) On both treatment days, phenylpropanolamine enhanced the ability to distinguish between two discrete flashes of light. The effect was significant in comparison with placebo, carbinoxamine and brompheniramine ($P < 0.01$, ANOVA).

Drug plasma levels

The mean + s.d. drug serum levels are shown in Table 2. The drug recoveries from plasma were 100% for brompheniramine, carbinoxamine and phenylpropanolamine and 85% for clemastine.

Correlations between plasma levels and objective recordings

Drug serum levels and recorded parameters were correlated by processing the data from days 1 and 2

Table 1 *F* values in psychomotor tests for overall drug effect and effect of test time according to two-way analysis of variance (270 measurements).

Test and parameter	*Drug (DF=4)*	*Test time (DF=5)*
	F	*F*
Tracking test		
Number of mistakes	0.96	1.94
Mistake percentage	1.65	1.24
Choice reaction test		
Reaction time	4.07**	3.71**
Number of mistakes	7.62***	0.40
Divided attention test		
Total number of responses	1.99	2.12
Number of correct responses	1.58	0.93
Flicker fusion test		
CFF	3.07*	2.11
Speed anticipation test		
mean	1.16	0.48
s.d.	1.02	0.54
Coefficient of variation	0.93	0.50
Range	0.93	0.64

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

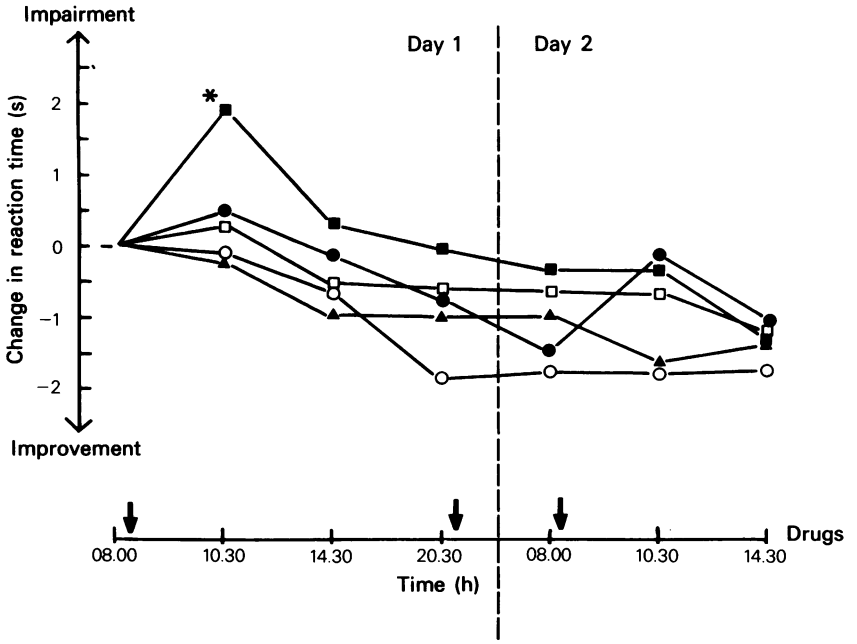

Figure 2 Drug effects on cumulative choice reaction times. Median changes from pre-drug values (range: 23.4 to 24.5 s). □ = placebo; ● = brompheniramine (12 mg); ■ carbinoxamine (12 mg); ▲ = clemastine (1 mg) ○ = phenylpropanolamine (50 mg). Drug *v* drug analysis: ANOVA: phenylpropanolamine *v* placebo, brompheniramine or carbinoxamine, $P < 0.05$; Tukey: * = $P < 0.05$ *v* placebo.

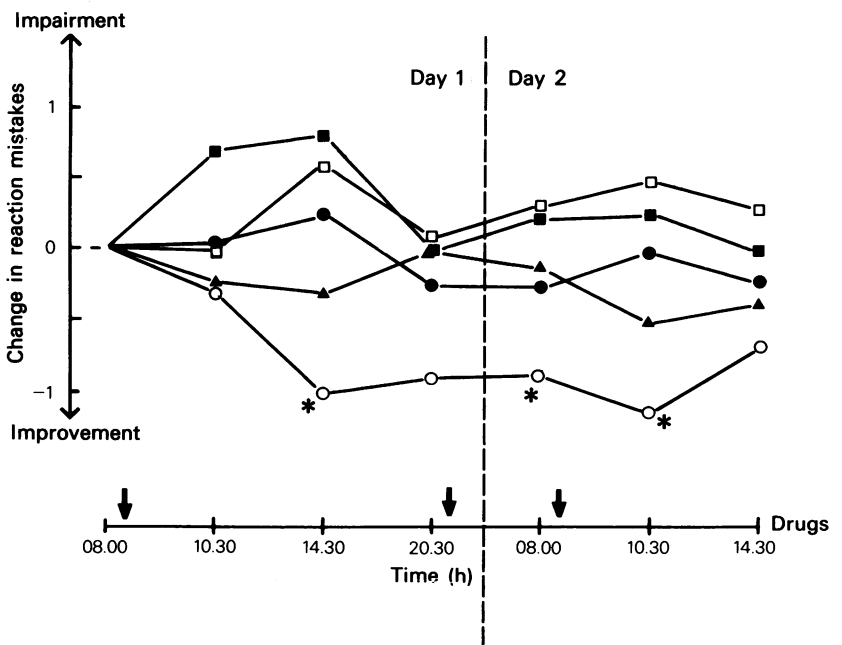

Figure 3 Drug effects on reaction mistakes. Median changes from predrug values (range: 0.8 to 1.4). □ = placebo; ● = brompheniramine (12 mg); ■ = carbinoxamine (12 mg); ▲ = clemastine (1 mg); ○= phenylpropanolamine (50 mg). Drug *v* drug analysis: ANOVA: phenylpropanolamine *v* placebo or carbinoxamine, $P < 0.001$; phenylpropanolamine *v* brompheniramine or clemastine, $P < 0.01$; Turkey: * = $P < 0.05$ *v* placebo.

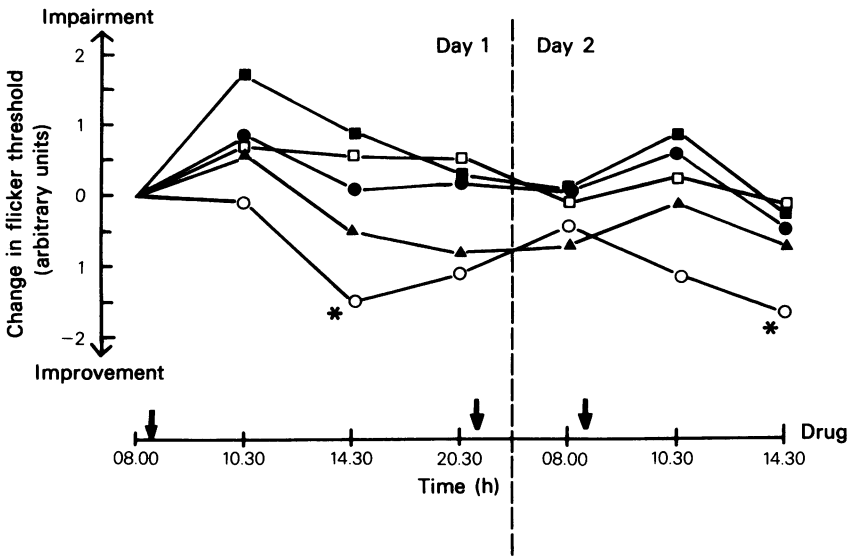

Figure 4 Drug effects on flicker recognition. Median changes from pre-drug values (range 43.9 to 44.9). □ = placebo; ● = brompheniramine (12 mg) ■ = carbinoxamine (12 mg); ▲ = clemastine (1 mg); ○ = phenylpropanolamine (50 mg). Drug *v* drug analysis: ANOVA: phenylpropanolamine *v* placebo, brompheniramine or carbinoxamine, $P < 0.01$; Tukey: * = $P < 0.05$ *v* placebo.

Table 2 Drug plasma levels (mean ± s.d.)

Drug	*Day 1*		*Day 2*	
	10.30 h	*14.30 h*	*10.30 h*	*14.30 h*
Brompheniramine (ng/ml)	8.04 ± 4.01	9.36 ± 2.8	18.7 ± 3.9	19.5 ± 5.1
Carbinoxamine (ng/ml)	16.4 ± 6.6	16.8 ± 2.2	32.6 ± 6.7	28.7 ± 6.2
Clemastine (pg/ml)	147.8 ± 124.3	192.2 ± 122.1	238.9 ± 179.4	343.3 ± 212.2
Phenylpropanolamine (ng/ml)	63.0 ± 16.5	63.0 ± 12.4	90.8 ± 12.1	74.6 ± 15.4

separately. No significant correlations were seen on the first day. On day 2, the carbinoxamine plasma levels correlated with a reduced ability to recognize flicker ($r = 0.48$, $n = 18$, $P < 0.05$), while phenylpropanolamine serum concentrations related highly significantly to the improvement of flicker discrimination ($r = 0.74$, $n = 18$, $P < 0.001$) (Figure 5). No other significant correlations were seen between plasma levels and scores recorded.

Subjective assessments

No treatment significantly affected the subjective feeling of performance. On the first day of treatment antihistamines were estimated to be a tranquillizer more often than placebo, but only clemastine differed significantly from placebo ($P < 0.05$, Fisher).

On day 2, no active treatment essentially differed in nature from placebo. Fatigue was the most common complaint and was felt mainly on the first day (Table 3). Other side effects were reported infrequently.

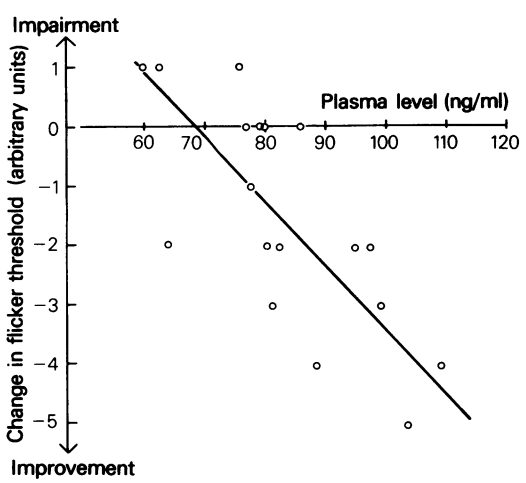

Figure 5 Correlation between phenylpropanolamine plasma level and response to flicker fusion test ($r = 0.74$, $n = 18$, $P < 0.001$).

Table 3 The number of subjects out of the total of 9 who reported fatigue on the questionnaire before and after the drug intake on days 1 and 2.

Treatment	*Day 1*		*Day 2*	
	Before drug	*After drug*	*Before drug*	*After drug*
Placebo	3	5	3	5
Brompheniramine	2	7*	2	5
Carbinoxamine	5	9*	2	3
Clemastine	3	7*	2	3
Phenylpropanolamine	2	3	3	4

*$P < 0.05$ *v* before drug (Fisher's exact probability test)

Visual analogue scales Diurnal variation in the alertness-drowsiness scale was seen during placebo administration (Figure 6). Antihistamines tended to cause drowsiness, carbinoxamine was the most rapid in this respect and produced its maximum effect at 10.30 h (NS, Tukey). Significant differences from placebo towards drowsiness were seen 6 h after the intake of brompheniramine and 12 h after the intake of clemastine. Drowsiness was felt only on the first day of antihistamine treatment. Phenylpropanolamine increased alertness, especially at 10.30 h and 14.30 h on the second day. Drug plasma levels did not correlate with the change in the alertness-drowsiness scale on either test day.

During every treatment, the scale 'quick witted-mentally slow' became modified in accordance with the alertness scale, so that when alertness was increased the subjects felt themselves to be more quick witted, and accordingly when drowsiness was increased they felt themselves to be mentally slow (correlation between the scales: $r = 0.542$, $n = 270$, $P < 0.001$). The other visual analogue scales were not modified by any treatment.

Increased drowsiness on the visual analogue scale correlated positively with reduction in reaction time ($r = 0.247$, $n = 270$, $P < 0.01$), increased number of reaction mistakes ($r = 0.195$, $n = 270$, $P < 0.05$) and reduced ability to recognize flicker ($r = 0.194$, $n = 270$, $P < 0.05$) when all records were computed together.

SEQ No parameter investigated in the SEQ was

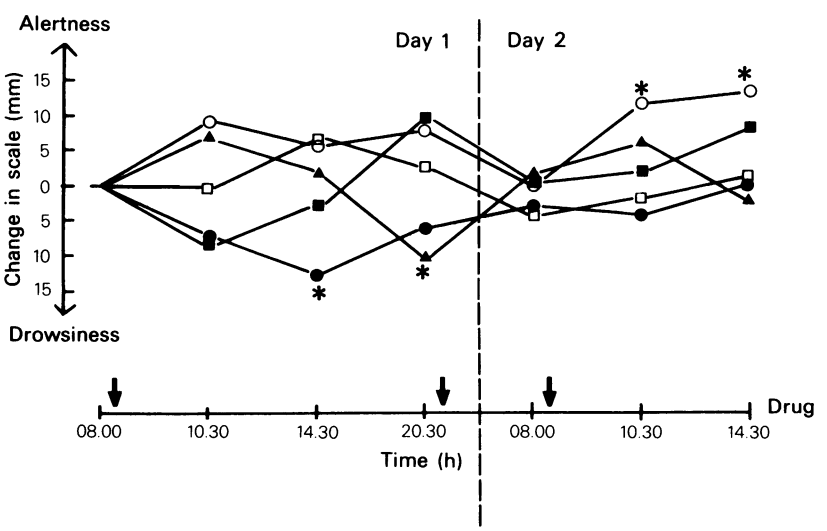

Figure 6 Drug effects on rating scale for alertness-drowsiness. Median changes from pre-drug values (range 66.0–70.8 mm). □ = placebo; ● = brompheniramine (12 mg); ■ = carbinoxamine (12 mg); ▲ = clemastine (1 mg); ○ = phenylpropanolamine (50 mg). Drug versus drug analysis: ANOVA: phenylpropanolamine *v* brompheniramine $P < .01$; Tukey: * = $P < .05$ *v* placebo.

modified from the placebo level by active treatments. Generally, the subjects slept well.

Discussion

Although the tests used in this study were relatively short lasting the test battery attained the level required for performance studies and has been reliable in predicting the accident liability in real driving in a 20-year follow-up study (Häkkinen, 1958; Häkkinen, 1976). However, when the results are applied in real life it should be remembered that in performance studies like this the practical importance is evident only when alterations in performance are seen concurrently and in a large number of tests (Häkkinen, 1958). In this study, brompheniramine and carbinoxamine were the only drugs which tended to impair skills, but only reaction accuracy was impaired at certain time points and neither drug impaired a variety of the tests. Therefore, the main conclusion is that the antihistamines examined and phenylpropanolamine with the doses used are obviously not detrimental to driving competence or operation of machinery. This statement seems legitimate in spite of the fact that brompheniramine and clemastine have earlier been reported as impairing skills (Peck *et al.*, 1975; Clarke & Nicholson, 1978; Nicholson, 1979), because the tests having the highest correlations with real driving performance (divided attention, coordination, speed anticipation) (Häkkinen, 1958; Maruyama & Kitamura, 1961) remained unaffected in our study and the validity of tests used in earlier studies is not stated. The visuo-motor test, which requires the subject to manually keep a spot inside a circle moving randomly on an oscilloscope, used in a study concerning brompheniramine (Nicholson, 1979) is probably too sensitive to produce valid results concerning the effects of drugs on real driving behaviour, and is better suited to other purposes. With clemastine, impaired skills have mostly been measured after higher doses or after more frequent administration, which may lead to accumulation (Reinberg *et al.*, 1978; Biehl, 1969).

Antihistamines generally cause drowsiness, as did all antihistamines of the present study. The time of maximum drowsiness varied, occurring soonest after carbinoxamine (2 h after the first dose), while brompheniramine exerted its maximum depressant effect on alertness 6 h after the intake of the drug. Clemastine, which is known to have a slow absorption rate, exerted this effect only in the evening 12 h after the morning intake of the drug. Notwithstanding the higher plasma levels on day 2 drowsiness was not felt then anymore indicating that during prolonged exposure to CNS tolerance develops to the sedative effects of antihistamines, as it does during advanced treatment with many psychotropic drugs (cf. Seppälä, Linnoila & Mattila, 1979). Evidence of tolerance to central effects of an antihistamine (triprolidine) has been given earlier by Bye *et al.* (1977).

When psychomotor skills are impaired due to CNS active drugs, sedation is often assumed to be the source of impairment. Accordingly, sedation and impaired skills have been measured simultaneously during treatment with benzodiazepines, neuroleptics and antidepressants (cf. Seppälä *et al.*, 1979) as well as after antihistamines (Peck *et al.*, 1975). However, in the present study all antihistamines induced sedation, although this was not followed by impaired performance. Brompheniramine tended to slow down reactions on day 2 at the time when drowsiness had already disappeared, and clemastine did not impair performance, even at the time of maximum drowsiness. Slow reactions were recorded at the same time as the subjects felt drowsiness in the carbinoxamine group only. In any case, a loose correlation between drowsiness and slow reactions was found only when all measurements were computed together. The effect of phenylpropanolamine, which made subjects more alert and enhanced reactions, may have had a decisive effect on the increase in the capacity of correlation analysis to detect such an association. Moreover, in an earlier study by Moser *et al.* (1978) concerning the CNS actions of terfenadine and diphenhydramine, the strikingly clear sedation was not reflected in any deterioration of psychomotor performance. It therefore seems evident that the impairment of skills cannot be predicted on the basis of known sedative properties of antihistamines, and that both sedation and impairment of skills are probably mediated through different mechanisms. The mechanism is obviously not H_1-receptor antagonism (Peck *et al.*, 1975), in fact impairment of skills and sedation are probably non-specific.

The relationships between drug plasma level and the responses to it were checked because a positive correlation is, in itself, confirmation of a drug action and may reveal something of the mechanism of action. However, only a few significant correlations were found regardless of the number of measurements. This is however not surprising for the following reasons: firstly, the drugs of the present study affected skills only very occasionally; secondly, tolerance confused the situation at least with regard to drowsiness; thirdly, steady-state kinetics (which corresponds to the pharmacokinetic phase, during which the plasma levels and responses are most likely to show correlations) was not achieved in the course of the study; and fourthly, antihistamines are the drugs to which responses show marked individual variation between subjects. Indeed, when slow reactions were recorded during treatment with carbinoxamine and brompheniramine, they were actually measured in only some of the subjects. This

supports the idea that antihistamine-induced impairment may be related more closely to the subject's individual response to a drug than to pharmacokinetics. Furthermore, those subjects whose reactions were slowed down neither showed higher plasma levels nor were more sedated than the others.

Sympathomimetic phenylpropanolamine differed clearly from antihistamines in its effects. The fact that phenylpropanolamine has a hydroxyl substituent on its β-carbon (Figure 1) makes it theoretically difficult for it to enter the CNS. However, this drug undoubtedly behaved as a mild stimulant, increasing alertness and facilitating information retrieval from the memory (seen as increased accuracy and decreased response time in the choice reaction test), and its effect on critical flicker threshold was also related to its plasma levels. Similar but still more marked improvement has been observed under laboratory conditions after administration of many CNS stimulants, e.g. amphetamines (Laties & Weiss, 1966; Turner 1968; Smith & Misiak, 1976).

Because of its mild stimulatory properties, phenylpropanolamine might be beneficial in combined preparations for allergic rhinitis by decreasing the antihistamine-induced drowsiness, though on the basis of the present study it is not possible to draw any conclusions about the combined central effects of these compounds. It is noteworthy that mood elevation, which is often inevitable after potent stimulants and which may be reflected in real road traffic as increased risk-taking behaviour (Hurst, 1962; Baumler, 1976), was not noted after phenylpropanolamine.

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