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EFFECT OF THE ANTIHISTAMINES, BROMPHENIRAMINE MALEATE AND TRIPROLIDINE HYDROCHLORIDE, ON PERFORMANCE IN MAN

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1 Effects of brompheniramine maleate (4 and 12 mg) and triprolidine hydrochloride (2.5 and 10 mg) on visuo-motor coordination, and on subjective assessments of performance, well-being and sleep were each studied in six subjects at 0.5, 1.5, 3.0, 5.0 and 7.0 h after ingestion. The doses refer to immediate and sustained release preparations respectively.

2 Triprolidine hydrochloride (2.5 mg) had an immediate effect on performance which persisted to 3.0 h, and the sustained release preparation (10 mg) impaired performance from 1.5 to 5.0 h. Brompheniramine maleate (4 mg) impaired performance from 1.5 to 3.0 h, and the sustained release preparation (12 mg) impaired performanc at 1.5 h. There were no consistent changes in the subjective assessments of performance, or of well-being and sleep.

3 The studies emphasize the variable effects of antihistamines on performance, and suggest that effects on performance of sustained release preparations may be similar to those of the usual form. Sustained release preparations may provide an advantage in clinical practice if the antihistaminic activity is prolonged.

Introduction

Impaired central nervous function is the usual sequel of the use of antihistamines in man. However, time of appearance and severity may vary between drugs and between subjects, and, although the decrement when present is usually obvious, it may be of limited duration compared with that of the hypnotics. It would appear that adverse effects of antihistaminic activity may be minimized by time of ingestion or even avoided by choice of drug, and it is in this context that we have extended our previous studies (Clarke & Nicholson, 1978) on the effects of several antihistamines to brompheniramine maleate and triprolidine hydrochloride. Each drug is available in a sustained release form, and the possibility arises that persistent antihistaminic activity may not be accompanied by impaired performance.

Methods

Six healthy female subjects were used. Their ages ranged from 19–32 (mean 22) years, and their weights ranged from 48–70 (mean 57) kg. None of the subjects had used antihistamines previously except in experimental studies. Instructions were given to avoid alcohol within 24 h of the experiment, and the subjects were not involved in any other form of therapy except possibly the use of oral contraceptives. They were required to avoid beverages which may have contained stimulants from 18.00 h the day preceding the experiment, and to refrain from smoking during 0.5 h preceding each performance measurement. Decaffeinated coffee was provided during the day of the experiment. Subjects retired to bed at their normal times the night before, and on the day of the experiment had their usual breakfast. Transport was provided for all subjects to and from their homes.

Performance was measured with a visuo-motor coordination task (Borland & Nicholson, 1974). The task required the subject to position a spot inside a randomly moving circle displayed on an oscilloscope, and the movement of the spot was controlled by a hand-held stick. An error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the spot and circle, and so the radial error signal, were recorded. Subjects were trained on the task until they reached steady performance. Each tracking run lasted 10 min, and subjects reached plateau performance within 100 s from the beginning of each run. The mean amplitude of the task over the final 500 s of the run was the performance measure.

Two drugs (Figure 1) were studied, brompheniramine maleate (4 mg) and triprolidine hydrochloride (2.5 mg), and each was available in a sustained release form (brompheniramine maleate 12 mg: triprolidine

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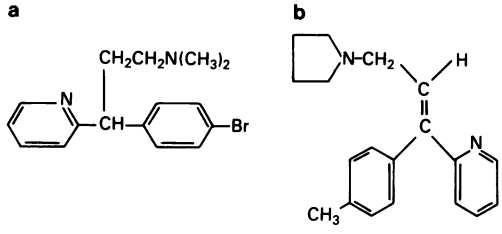

Figure 1 Structural formulae of a) brompheniramine (γ-(4-bromophenyl)-*N, N*-dimethyl-2-pyridinepropanamine) and b) triprolidine ((E)-2-[1-(4-methylphenyl-3-(1-pyrrolidinyl)-1-propenyl] pyridine).

hydrochloride 10 mg). Brompheniramine maleate (12 mg) had one-third of its active ingredients in a coating for immediate release and two-thirds in a delayed release core, and triprolidine hydrochloride (10 mg) was in three layers to give a rapid onset of action followed by a sustained release. The corresponding preparations were believed to be of similar therapeutic activity. Chlorpheniramine (4 mg) was included as an active control, and each subject received on each occasion an active tablet and a placebo for each of the other four drugs. The placebo ingestion involved placebos of each drug.

Evaluation of the effect of each ingestion of a drug involved five measurements of performance. The placebo or drug was ingested between 08.30 and 09.00 h, and performance was measured exactly 0.5, 1.5, 3.0, 5.0 and 7.0 h later. Each subject received the five drugs and placebo, and the order of drugs and placebo ensured equal distribution throughout the study. Performance after each drug was compared with performance at the same time of day after ingestion of placebo. The data were analysed by a split plot analysis of variance with time being treated as the sub-plot. Subjective assessments of well-being, sleep and performance were obtained by the methods used in a previous study (Clarke & Nicholson, 1978), and were analysed in the same way. Experiments were separated by at least 1 week, and performance studies were avoided within 2 days, before and after, the onset of menstruation. The trial was double-blind.

Results

In the assessments of well-being, sleep and performance there were no consistent changes with drugs compared with placebo. Changes in visuo-motor performance are summarized in Table 1. Triprolidine (2.5 mg) had an immediate effect on performance ($P<0.001$) which persisted to 3.0 h ($P<0.01$), and

Table 1 Analysis of variance for change in performance (compared with placebo) on visuomotor coordination (arbitrary units) after antihistamines (means for six subjects).

Source	*Degrees of freedom*	*Mean squares*	F	*Significance*
Subjects (S)	5	1.046038	1.71	
Drugs (D)	4	1.574696	2.57	
SxD (error a)	20	0.611840		
Time (T)	4	1.183519 (SxT)	1.86	
SxT	20	0.634734	4.21	***
TxD	16	0.242655	1.61	
SxTxD (error b)	80	0.150940		

		Time after ingestion (h)				
Drug		0.5	1.5	3.0	5.0	7.0
Chlorpheniramine	4 mg	−0.15	0.00	0.01	−0.04	0.19
Brompheniramine	4 mg	0.11	−0.31 (*)	−0.33 *	0.16	0.09
	12 mg	0.11	−0.43 **	−0.17	−0.04	−0.08
Triprolidine	2.5 mg	−0.78 ***	−1.05 ***	−0.47 **	−0.28	−0.17
	10 mg	−0.18	−0.81 ***	−0.30	−0.51 **	0.09

Least significant differences for comparison of differences between drug and placebo with zero for means of six: *=0.32; **=0.42; ***=0.54

Significance levels * 5%; ** 1%; *** 0.1%

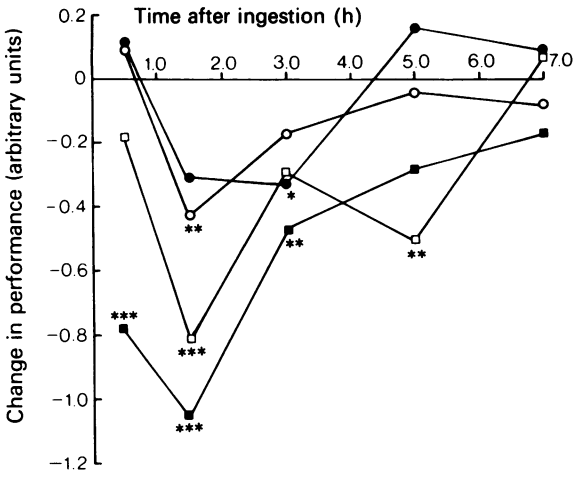

Figure 2 Change in performance on visuo-motor coordination (arbitrary units) after 2.5 mg (■) and 10.0 mg (□) triprolidine hydrochloride, and after 4.0 mg (●) and 12.0 mg (○) brompheniramine maleate. Closed symbols refer to immediate release and open symbols to modified release preparations. Significance levels *5%, ** 1% and *** 0.1%.

the sustained release preparation (10 mg) impaired performance from 1.5 h ($P<0.001$) to 5.0 h ($P<0.01$). Brompheniramine (4 mg) impaired performance at 1.5 and 3.0 h ($P<0.05$), and the sustained release form (12 mg) impaired performance at 1.5 h ($P<0.001$). Inspection of Figure 2 suggested that performance reached placebo level about 7 h after triprolidine (2.5 mg and 10 mg), and about 5 h after brompheniramine (4 mg and 12 mg).

Discussion

The present observations on triprolidine (2.5 mg) are in close agreement with the previous studies of Bye, Dewsbury & Peck (1974) and Peck, Fowle & Bye (1975). Essentially, the onset of impaired performance was rapid and recovery occurred around 7 h after ingestion, and, though it was delayed with the sustained release form of triprolidine, recovery occurred within a similar time. A similar effect was observed with brompheniramine as with both the immediate and sustained release preparations recovery occurred around 5 h after ingestion. These observations suggest a possible advantage of sustained release preparations, assuming that their antihistaminic activity persists. With triprolidine there is such evidence because both weal and flare measurements show a persistent antihistaminic effect for 24 h after ingestion (Fowle, Hughes & Knight, 1971), and with brompheniramine maleate there is pharmacokinetic evidence of maintained plasma levels (A.H. Robins & Co Ltd – Internal Report).

With all the antihistamines the question arises whether tolerance develops during the continued exposure of the nervous system to the drug. With triprolidine there is some evidence that tolerance may develop with 12 hourly ingestion (Bye, Claridge, Peck & Plowman, 1977), and the studies with the sustained release preparations suggest persistent antihistaminic activity accompanied by impaired performance for only the initial part of its time course. Triprolidine (10 mg), in the immediate release form has a duration of antihistaminic activity around 10–12 h (Fowle *et al.*, 1971), and so the duration of the activity of 2.5 mg triprolidine, used in the present study, is likely to be similar to that of its decrement in performance. It would appear that the relative duration of impaired performance and antihistaminic activity of sustained release preparations have clinical importance, and that overnight ingestion would leave a residual antihistaminic effect during the day without adverse effects.

Though with most antihistamines some impairment is likely, it is evident that its persistence and severity may be different between drugs. In a previous study (Clarke & Nicholson, 1978) impaired performance was observed with chlorpheniramine (4 mg) around 1.5 h after ingestion, though we have been unable to establish any effect in the present study, and with clemastine and promethazine from 3.0 to 5.0 h after ingestion. On the other hand terfenadine was without effects on performance, and possibly improved alertness and wakefulness. Similar results have been reported by other workers with chlorpheniramine and promethazine (Molson, Mackay, Smart & Turner, 1966; Large, Wayte & Turner, 1971), with clemastine (Peck *et al.*, 1975) and with terfenadine (Kulshrestha, Gupta, Turner & Wadsworth, 1978), and, though Hedges, Hills, Mackay, Newman-Taylor & Turner (1971) did not report depression of critical flicker fusion with clemastine, there was a significant trend toward 6 h after ingestion.

It is also clear from the present studies that impaired performance may not be detected by subjective assessments, and may not be accompanied by a change in well-being. There was little subjective evidence of drug effects even when they were exerting maximum effects on performance, and so subjective data alone are unlikely to be useful in the evaluation of the central effects of antihistamines. Further, the variable nature of performance deficits with antihistamines lends some support to the suggestion (Peck *et al.*, 1975) that effects on the nervous system may not be mediated by antagonism of endogenous brain histamine. Previous studies with terfenadine (Kulshrestha *et al.*, 1978; Clarke & Nicholson, 1978), and the present studies with sustained release

preparations show that impaired performance is not an inevitable accompaniment of antihistaminic activity.

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