PERFORMANCE STUDIES WITH ANTIHISTAMINES

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1 Effect of four antihistamines, chlorpheniramine (4 mg), clemastine (1 mg), promethazine (10 mg) and terfenadine (60 mg), on visuo-motor coordination and on subjective assessments of performance and well-being were compared with placebo in six healthy females from 0.5–7.0 h after morning ingestion of each drug. The study was double-blind, and the doses used were believed to be equally potent in their antihistaminic activity.

2 There was impaired performance 1.5 h ($P < 0.01$) after chlorpheniramine, 3.0 h ($P < 0.05$) and 5.0 h ($P < 0.01$) after clemastine, and 3.0 h ($P < 0.01$) and 5.0 h ($P < 0.001$) after promethazine. It was not possible to establish effects on performance after ingestion of terfenadine. Subjective assessments of performance were not altered.

3 The subjects as a group reported improved alertness ($P < 0.05$) and improved wakefulness ($P < 0.05$) 0.5 h and 3.5 h respectively after ingestion of terfenadine, and were less energetic ($P < 0.05$) 7.0 h after ingestion of chlorpheniramine. There were no other consistent changes in assessments of well-being.

Introduction

Most, if not all antihistamines lead to some impairment of central nervous function, but the question arises whether unacceptable impairment of performance is an inevitable sequel of such drugs. In previous studies we have been concerned with the effect of benzodiazepines on human performance. Some benzodiazepines, commonly used as hypnotics, have persistent residual sequelae, and would be unacceptable if impaired performance the next day was to be avoided (Borland & Nicholson, 1975). However, impaired performance with other benzodiazepines, which nevertheless possess useful hypnotic activity (Nicholson & Stone, 1976; Nicholson, Stone & Clarke, 1976), may be limited to the sleep period (Clarke & Nicholson, 1978), and so would be appropriate for persons involved in skilled activity. Such studies suggest that unacceptable impairment of performance may not be an inevitable sequel of drugs which have central effects, and it is in this context that we have studied several antihistamines.

Methods

Six healthy female subjects were used. The study was carried out within the months of March and April. Only one subject had used antihistamines previously, and during the study none of the subjects needed such

medication. Their ages ranged from 19–32 (mean 22) years, and their weights ranged from 48–70 (mean 57) kg. 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 steroids. They were required to avoid beverages which may have contained stimulants from 18.00 h of the preceding day, and to refrain from smoking during the 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.

Evaluation of the effect of placebo or a drug involved five measurements of performance. The placebo or drug was ingested at 08.30, and performance was measured at 09.00, 10.00, 11.30, 13.30 and 15.30. Experiments were separated by at least 1 week, and performance studies were avoided within 2 days, before or after, the onset of menstruation. Four drugs were studied: clemastine (1 mg), terfenadine (60 mg), promethazine (10 mg), and chlorpheniramine (4 mg) (Figure 1). A multiple dummy technique was used for the placebo studies. The subjects ingested four matching preparations for the placebo, and one drug and three matching preparations when a drug was being studied.

Figure 1 Structural formulae of a) clemastine, 2-(2-(1-(4-chlorophenyl)-1-phenylethoxy)ethyl)-1-methylpyrrolidine; b) terfenadine, α -(4-*tert*-butylphenyl)-4-(α -hydroxy- α -phenylbenzyl)-1-piperidine-butanol; c) promethazine N, N, α -trimethyl-10H-phenothiazine-10-ethanamine; and d) chlorpheniramine, γ -(4-chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine. Clemastine was ingested as the hydrogen fumarate equivalent to 1 mg clemastine base, promethazine as the hydrochloride, chlorpheniramine as the maleate, and terfenadine as base.

The preparations were ingested in random order, and the trial was double-blind.

Performance was measured using 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. The subjects reached plateau performance within 100 s of the beginning of each run, and the mean amplitude of the task over the final 500 s of the run was the performance measure.

Visual analogue scales were used for subjective assessments. In all assessments the subjects were instructed to consider the mid-point of a 100 mm scale as their normal state. Subjects assessed the quality of their sleep 0.5 h after waking on each day which involved the ingestion of placebo or drug. The assessments and the extremes of each scale were – I slept, *very poorly* – *very well*; Now I feel, *wide*

awake – *very sleepy*; I fell asleep, *never* – *immediately*; After I fell asleep I slept, *very well* – *very badly*. The subjects also completed an assessment 0.5 h before retiring to bed on the day of ingestion of placebo or drug. The assessment questions and extremes of each scale were – How did you feel during the day, *Fresh* – *Tired*, and How do you feel now, *Very Tired* – *Wide Awake*. With each performance run the subjects assessed their performance and their well-being. For performance the question and extremes of the scale were – How well did you perform? *Useless* – *Perfect*. For assessments of well-being the questions and extremes of the scale were A: I have, *no ability to concentrate* – *complete ability to concentrate*; B: I am, *very wide awake* – *extremely sleepy*; C: I am, *very lethargic* – *very energetic*; D: I am, *very alert* – *very dull*; E: I am, *very relaxed* – *very tense*; F: I am, *extremely anxious* – *absolutely calm*.

One subject did not complete the evaluation for promethazine, and so two separate analyses were carried out related to the effects of three drugs with six subjects, and four drugs with five subjects. The effect of promethazine only was obtained from the five subject analysis. Performance after each drug was compared with performance at the same time of the day after ingestion of placebo. Subjective assessments

of well-being at the time of each performance run were compared with the assessment at the same time of the day after ingestion of placebo and with the assessment 0.5 h after waking on the same day. Changes in subjective assessments were accepted only if a significant effect was obtained with both comparisons. Measurements of performance and subjective assessments were analysed by analysis of variance.

Results

There were no changes in assessments related to the sleep of the night preceding the experiment. The results of the six subject analysis with three drugs (excluding promethazine) are given in Table 1, and change in performance for individual subjects is given in Table 2. With promethazine mean performance of the five subjects was impaired at 3.0 ($P < 0.01$) and 5.0 h ($P < 0.001$) after ingestion. There were no changes in subjective assessments of performance. Improved wakefulness ($P < 0.05$) and alertness ($P < 0.05$) were observed 0.5 h and 3.5 h respectively after ingestion of terfenadine, and the subjects were less energetic ($P < 0.05$) 7.0 h after ingestion of chlorpheniramine. There were no other changes in assessments of well-being related to both placebo assessments and to assessments after waking.

Discussion

It is evident from these studies that the appearance of central effects may vary considerably between antihistamines. With most antihistamines some impairment of performance is likely, though persistence and severity of the impairment is likely to be different between drugs. With chlorpheniramine impairment was limited in duration around 1.5 h after ingestion, but with clemastine and promethazine impaired performance was observed at 3.0 and 5.0 h after ingestion. However, with terfenadine it was not possible to establish effects on performance, and the subjective assessments indicated improved alertness and wakefulness during the first 3.0 h after ingestion.

The effect of three of these antihistamines on performance has been studied previously (Molson, Mackay, Smart & Turner, 1966; Turner, 1968; Hedges, Hills Mackay, Newman-Taylor & Turner, 1971; Large, Wayte & Turner, 1971). With promethazine (25 and 30 mg) performance was markedly impaired 3.0 h after ingestion, and the time course was similar to that observed in the present studies, though we used a much lower dose. We have also observed impairments of performance after chlorpheniramine (4 mg) and clemastine (1 mg). With chlorpheniramine the effect was apparent 1.5 h after ingestion, but with clemastine the effect was delayed for several hours with a maximum effect 5.0 h after ingestion. This finding is of interest as though Hedges

Table 1 Change in performance (means for six subjects) on visuo-motor co-ordination (arbitrary units) after antihistamines compared with placebo

Source	Degrees of freedom	Mean squares	F	Significance
Subjects (S)	5	16.607853	44.51	***
Drugs (D)	3	0.53551	1.44	
S × D (Error a)	15	0.373117		
Time (T)	4	0.298009 (T × S)	2.12	
S × T	20	0.140459	2.76	**
T × D	12	0.281392	5.52	***
S × T × D (Error b)	60	0.050947		

Drug	Time after ingestion (h)				
	0.5	1.5	3.0	5.0	7.0
Terfenadine (60 mg)	-0.30	-0.24	-0.35	-0.10	-0.16
Clemastine (1 mg)	+0.10	+0.10	-0.54	-0.63	-0.36
			*	**	
Chlorpheniramine (4 mg)	-0.13	-0.66	-0.12	-0.22	-0.03
		**			

Least significant differences: * = 0.43; ** = 0.58; *** = 0.78
Significance levels * = 5% ** = 1% *** = 0.1%

et al. (1971) did not report impaired performance, there was evidence of a trend of depression of critical flicker fusion frequency with a similar time course to the impaired performance in our studies. In their published data on critical flicker fusion frequency there is a highly significant regression ($P < 0.025$) of depression of frequency from 2.0–6.0 h after ingestion. This would suggest progressive impairment, even though it was not possible to show change in flicker fusion compared with the control measure at 6.0 h. The present studies on performance follow closely the data of these workers on critical flicker fusion.

Impaired performance with clemastine may be delayed for several hours. This would be consistent with pharmacokinetic data (Sandoz–Internal Report), and the performance studies of Peck, Fowle & Bye (1975). These workers observed delayed appearance of impaired performance with clemastine using prolonged and monotonous tasks, and they suggested that such tasks may be more sensitive to the effects of antihistamines than the brief, interesting tasks which had been used previously. However, the present studies, which are in close agreement with Peck *et al.* (1975), suggest that impaired performance after drugs may be observed with tasks of limited duration which may enhance the motivation of the subjects.

The subjective assessments showed that impaired performance may not be detected by subjects, and may not be accompanied by changes in well-being. With chlorpheniramine, clemastine and promethazine, there was little evidence of impaired subjective assessments of well-being at the time when these drugs were having their maximum effect. It is difficult to be certain of the relevance of subjective assessments. In the present studies performance measures were more sensitive than the assessments of the subjects, and though the performance data suggests considerable variation between subjects and that choice of antihistamines may avoid impaired performance in some subjects, it is highly unlikely that such a choice could be made on subjective assessments alone.

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Table 2 Change in performance on visuo-motor co-ordination (arbitrary units) for each subject at individual times after ingestion of antihistamines compared with placebo

Subject	Terfenadine (60 mg)					Promethazine (10 mg)				
	Time after ingestion (h)					Time after ingestion (h)				
	0.5	1.5	3.0	5.0	7.0	0.5	1.5	3.0	5.0	7.0
1	-0.16	0.28	0.11	0.17	0.35	0.09	-0.89	-1.32	-1.76	-1.68
2	-0.34	0.27	-0.60	-0.04	-0.09	0.62	0.64	-0.22	-0.46	0.66
3	-0.62	-0.36	-0.41	-0.06	0.02	0.12	-0.14	-0.27	-0.60	-0.20
4	-0.59	-0.82	-0.35	-0.53	-0.70	-0.72	-0.67	-0.39	-0.40	-0.24
5	0.01	-0.68	-0.84	-0.46	-0.81					
6	-0.08	-0.11	0.02	0.33	0.24	0.16	-0.81	-1.13	-1.37	-0.82
Subject	Clemastine (1 mg)					Chlorpheniramine (4 mg)				
	Time after ingestion (h)					Time after ingestion (h)				
	0.5	1.5	3.0	5.0	7.0	0.5	1.5	3.0	5.0	7.0
1	-0.11	-0.13	-0.59	-0.79	-0.64	-0.39	-0.89	-0.48	-1.00	-0.62
2	0.75	0.64	-0.67	-0.49	0.38	-0.15	-0.43	-0.10	0.04	0.54
3	-0.22	0.05	-0.51	-0.62	-0.52	-0.13	-0.75	-0.08	-0.30	-0.01
4	-0.50	-0.66	-0.32	-0.81	-0.71	-0.95	-1.12	-0.16	-0.72	-0.59
5	0.36	-0.77	-1.68	-0.43	-0.92	0.60	-0.48	0.03	0.58	0.33
6	0.29	0.24	0.50	-0.65	0.23	0.24	-0.26	0.06	0.09	0.20

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