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A Comparison of Triprolidine and Clemastine on Histamine Antagonism and Performance Tests in Man: Implications for the Mechanism of Drug Induced Drowsiness

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Summary. The effects of triprolidine hydrochloride 1.25, 2.5 and 5 mg, clemastine 1 and 2 mg and lactose dummy administered orally, in a balanced order, at weekly intervals to 12 healthy volunteers, on the flare and weal responses to intradermal histamine injection, and also on both subjective effects and objective psychomotor tests were examined. The histamine response was significantly larger at 09.00 h falling through the day but increasing by late afternoon. Triprolidine produced a dose-related antagonism of both flare and weal response maximal at 3 h and wearing off after the lower doses at 8 h. Clemastine by contrast produced poor antagonism of histamine at 3 h but a marked effect at 5.5 and 8 h. Auditory vigilance was significantly ($p<0.05$) impaired by all doses of triprolidine 1 to 2 h after administration, but no change followed clemastine at this time. When tested 6 to 7 h after administration significant impairment followed both doses of clemastine but only the 5 mg dose of triprolidine. Both drugs prolonged reaction time in a dose-related manner at 2.5 and 5.0 h but the effects had worn off at 7 h. Digit symbol substitution was impaired by the top doses of both antihistamines but short term memory was unaffected. Subjective effects measured using analogue lines reflected the effects in the vigilance test, in that drowsiness and mental impairment were noted early after triprolidine, while clemastine produced maximal effects at 5 h. Subjects were ranked in order of magnitude of inhibition of both flare and weal, and impairment of vigilance, prolongation of reaction time and subjective drowsiness score. There was no indication of a significant correlation, using Spearman's test, between antagonism of histamine and effects on the central nervous system.

Key words: histamine antagonists, triprolidine, clemastine, skin responses, circadian rhythm, psychomotor tests, subjective effects.

No antihistamine drug has so far lacked the unwanted effect of drowsiness despite claims to the contrary during early usage of many. Animal experiments fail to predict the occurrence of drowsiness in man following antihistamines, while the relationship between most tests of human central nervous system function and drowsiness is uncertain. Clemastine (Tavegil), a new antihistamine, did not impair tests of central nervous system function in studies by Hedges, Hills, Maclay, Newman-Taylor and Turner (1971); Day, Jones, Stewart-Jones and Turner (1972), or Landauer and Milner (1971). It could be inferred from these studies either that clemastine would not cause drowsiness, or that the tests used were of a type unlikely to detect changes in the nervous system related to drowsiness. Antihistamine drugs are widely used and introduction of a drug which does not produce drowsiness would be an important therapeutic advance. Conversely, use of a new compound believed erroneously to lack this effect and therefore prescribed extensively and without safeguards is undesirable.

Bye, Dewsbury and Peck (1974) showed that drowsiness, measured by using the analogue line technique, together with objective impairment in auditory vigilance followed administration of the antihistamine triprolidine in clinically used dosages. Triprolidine has a potency similar to clemastine and it was decided to design an experiment to compare the effects of both established and newly introduced drugs on the nervous system using these tests. However, when comparing the central nervous system effect of a new histamine antagonist with an established drug, it is desirable that histamine antagonism is

also measured simultaneously in the same group of subjects, and this was achieved in the investigation reported here by measuring the effects of the treatments on the response to intradermal histamine.

The experimental design provides relative data for two antihistamines concerning antagonistic potency for intradermal histamine, effects on performance of psychomotor tests and subjective drowsiness ratings by means of a group of healthy subjects. Additionally it provides comparisons of the potency and duration of the central nervous and cutaneous effects of a histamine antagonist for individuals. This might offer insight into a possible relationship (or lack of it) between brain histamine and drowsiness.

Methods

Subjects

Twelve healthy male volunteers aged 25 to 46 years (mean 34) were studied. They were transported to and from the laboratory and were paid. Subjects fasted overnight before receiving treatments and were not allowed any tea, coffee or cigarettes through the day of testing and spent the whole day in the department. None had received any drug treatment during the month preceding the study. Subjects were studied in the same groups of 4 on Tuesdays, Wednesdays, and Thursdays.

Daily Schedule of Tests

From 8.40 h and at 2 min intervals subjects were given intradermal histamine injections into the back and flare and weal responses were measured 20 min later as described by Fowle, Hughes and Knight (1971), to establish a pretreatment baseline response. Subjective effects were recorded using the analogue line technique of Norris (1971). Treatments were then given orally at 9.00 h followed by a light breakfast at 9.45 h. At 10.00 h a 2 h schedule of tests began consisting of:

1. Auditory vigilance test lasting 1 h described by Wilkinson (1968) in which the subject listened through headphones to tones lasting 0.5 s occurring every 2 s. Randomly occurring through the hour but with 10 every 15 min were shorter tones 0.4 s in duration and on hearing these signals the subject recorded his recognition by pressing buttons which also indicated his level of confidence, high, medium or low in the detection. The number of signals detected and false alarms made were recorded.
2. Short term memory test lasting 15 min in which 90 series of 8 digits were recorded by the subject and the number of individual errors and the number of lines containing an error were counted.
3. A digit symbol substitution test lasting 90 s (Wechsler, 1955).
4. Auditory reaction time test lasting 15 min in which the subject pressed a microswitch as rapidly as possible on hearing short tones which occurred with a mean interval of 7 s and which varied from 5 to 9 s.
5. Subjective effects were then measured using analogue lines.
6. Four intradermal histamine injections were then made and the response measured 20 min later.

The complete 2 h schedule was repeated at 12.30 h after a light lunch and again at 15.00 h after another light meal.

Assessment of Response to Histamine

At each time, pretreatment, 3, 5.5, and 8 h post treatment, four intradermal injections of histamine (as acid phosphate) were made into the back: 0.1, 0.4, 1.6 and 6.4 µg all in 0.05 ml isotonic saline. After 20 min the longest and narrowest axes, at 90° to one another were measured for each flare and weal, using a plastic ruler, and the areas calculated assuming an elliptical shape. All injections and measurements were made by the same investigator. (On 3 of the 1152 occasions there was obvious leakage of the syringe and the Fisher missing plot technique was used to insert values for analysis of variance but avoid bias in analysis of results).

In order to reduce the effects of possible variation in response resulting from differences in site over the back the injections were sited according to a graeco-latin square design. The same graeco-latin square was used for all subjects on all occasions and ensured that a given dose at any particular time was always sited in the same

Table 1. The graeco-latin square design used to determine allocation of histamine dose, site and time. The four doses of histamine given intradermally, 0.1, 0.4, 1.6 and 6.4 µg are the lower figures. Measurement of resultant flares and weals at 9.00 (0 h), 12.00 (3 h), 14.30 (5.5 h) and 17.00 (8 h)

Upper

Left	Left Lateral	Left Medial	Right Medial	Right Lateral	Right
	8 h 0.4	0 h 0.1	5.5 h 6.4	3 h 1.6	
	0 h 1.6	8 h 6.4	3 h 0.1	5.5 h 0.4	
	5.5 h 0.1	3 h 0.4	8 h 1.6	0 h 6.4	
	3 h 6.4	5.5 h 1.6	0 h 0.4	8 h 0.1	

area of back. It also ensured that at any particular time each of the 4 i.d. injections was placed in a different horizontal and vertical column of the 4 x 4 square. (Table 1).

Drugs

Each subject received each of the following 6 treatments at weekly intervals: triprolidine hydrochloride 1.25, 2.5 and 5 mg; clemastine hydrogen fumarate, 1.34 and 2.68 mg, (equivalent to 1 and 2 mg clemastine base); and a lactose dummy. All treatments were prepared in identical soft gelatin capsules and the order of administration was based on 2 six sided latin squares. Neither subjects nor investigators knew the nature of treatments on any occasion until after completion of the study.

Analysis of Results

The significance of differences following different treatments was evaluated by the method of analysis of variance accepting a probability of less than 5% as significant. Scores derived from the analogue lines indicating subjective effects were first submitted to arc-sine transformation.

Relative potency of different treatments at different times was calculated as the ratio of dose of histamine producing a given flare or weal area after active treatment with that producing the same area after lactose dummy at the same time, as shown in Table 4. Regressions of mean responses of the 12 subjects on log dose of histamine after all 6 treatments at the 3 post-treatment times were calculated. The slopes did not differ significantly at any one time, or between times and were assumed to be parallel. The common slope was estimated and the horizontal displacement of the lines following active drug treatments from that after lactose dummy was determined from the set of lines with a common slope.

Results

The Histamine Response

By incorporating a dummy lactose treatment the experimental design enabled variations in the flare and weal size throughout the day to be measured. Table 2 shows the dose response relationship for flares and weals at the four times. Weal areas were significantly larger at 09.00 than later in the day. Flare areas were also larger at 09.00 than at 14.30 but increased again later in the afternoon.

Use of the graeco-latin square design to determine the siting of four different doses of histamine given at any one time enabled differences in response ascribable to position on the skin to be evaluated. The 4 doses at any one time were always on different vertical and horizontal rows of the 4 x 4 square. Flares were significantly larger on the right lateral side of the back. Weal areas were significantly smaller in the two medial columns. No significant differences in either flare or weal area occurred between different horizontal rows of squares across the back.

Antihistamine Effects

The effects of different treatments on the size of flares and weals produced by the four intradermal doses of histamine at different times are given in Tables 3 and 4 together with the statistical significance of the differences. The main difference between triprolidine and clemastine is illustrated in Fig. 1 which shows the pattern of antihistamine activity assessed by effects on the size of flare at 3 and 8 h after treatment.

As expected no significant differences occurred between the six groups before administration of treatments. Mean values for the 12 individual responses to each of the 4 doses of histamine are given in Table 3, which shows that at 3 h significant inhibition of flare and weal responses followed administration of all doses of triprolidine at all histamine doses except for

Table 2. Differences in flare and weal area associated with site on back and time of day after lactose dummy. Mean values for responses after all 4 doses of histamine in 12 subjects after lactose are shown. Columns are the vertical rows of 4 squares labelled from left to right; left lateral, left medial, right medial, right lateral. Values are ranked in ascending order, and those underlined by a common bar do not differ significantly. Values not underlined by a common bar differ significantly ($p<0.05$)

	Mean flare area (mm^2)			
Time	14.30	12.00	17.00	09.00
	1414	1484	1576	1648
Column	Lf med	Lf lat	Rt med	Rt lat
	1463	1483	1503	1672
	Mean weal area (mm^2)			
Time	14.30	17.00	12.00	09.00
	134	134	137	156
Column	Rt med	Lf med	Lf lat	Rt lat
	126	132	148	154

the response to 6.4 µg histamine after triprolidine 1.25 mg. The response was in general related to dose of triprolidine. The effect of clemastine at 3 h on both flare (illustrated in Fig. 1) and weal was much less and differed significantly from lactose only after clemastine 2 mg against 0.4 and 1.6 µg histamine on flares and 0.1 and 6.4 µg histamine on weals.

At 5.5 h the pattern had changed and this persisted to 8 h. Clemastine 2 mg then produced the maximum antihistamine effect on both flare and weal size, though this rarely differed significantly from the effect of tripolidine 5 mg. By 5.5 h all the lower doses of both drugs produced significant inhibition of flare size but not of weal size. The effect of clemastine 1 mg generally fell between the response following triprolidine 1.25 mg and 2.5 mg. Both drugs were therefore effective histamine antagonists, but the onset of action of triprolidine was quicker.

The relative potency of the different doses of the two drugs at different times is shown in Table 4 as the ratio of dose of histamine required to produce a given response after drug to the dose required for the same response after lactose. The potency of all doses of triprolidine in inhibiting the flare was maximum at 3 h and subsequently declined after all doses. Inhibition of weal after triprolidine 5 mg was maximum at 5.5 h however. Maximum potency of clemastine on both variables usually occurred at 5.5 h but was still well maintained at 8 h.

Vigilance Test

Performance in this test is shown in Table 5. During the first test, 1 to 2 hours post-treatment there was a significant reduction in the number of signals detected after all doses of triprolidine compared with values after lactose. The largest reduction followed triprolidine 5 mg.

Table 3. Responses to histamine following different treatments. The values shown are for the mean areas of flares and weals measured in 12 subjects after different treatments and at different times. Means are ranked in ascending order and those underlined by a common bar do not differ significantly ($p>0.05$). Means not underlined by a common bar differ significantly ($p<0.05$). Abbreviations used are: triprolidine 1.25, 2.5 and 5 mg, T1.25, T2.5 and T5; clemastine 1 and 2 mg, C1 and C2; and lactose dummy, L

Histamine dose (µg)	Mean flare areas (mm^2) Hours after drug 3						5.5						8					
0.1	T5	T2.5	T1.25	C2	L	C1	T5	C2	T2.5	C1	T1.25	L	C2	T5	T2.5	C1	T1.25	L
	449	626	646	798	955	975	422	479	557	593	643	818	570	633	764	766	864	1074
0.4	T5	T2.5	T1.25	C2	C1	L	C2	T5	T2.5	T1.25	C1	L	C2	T5	T2.5	C1	T1.25	L
	553	736	811	874	1005	1132	611	620	716	800	824	1083	824	942	1005	1032	1234	1371
1.6	T5	T2.5	C2	T1.25	C1	L	C2	T5	C1	T2.5	T1.25	L	C2	T5	T2.5	C1	T1.2	L
	1108	1285	1428	1443	1556	1726	1105	1187	1236	1370	1446	1685	1180	1298	1511	1517	1684	1786
6.4	T2.5	T5	T1.25	C2	C1	L	C2	T5	T2.5	C1	T1.25	L	C2	T2.5	T5	C1	L	T1.25
	1565	1694	1873	1967	2070	2123	1383	1598	1720	1733	1752	2068	1559	1806	1832	1998	2071	2082
	Mean weal areas (mm^2)																	
0.1	T5	T2.5	C2	T1.25	C1	L	T5	C2	T2.5	C1	T1.25	L	C2	T5	C1	T1.25	T2.5	L
	51.9	60.1	60.6	63.3	70.3	77.8	58.5	63.3	69.8	72.4	81.2	96.4	63.0	74.6	79.8	81.8	84.7	90.4
0.4	T5	T2.5	T1.25	C2	C1	L	C2	T5	T2.5	C1	T1.25	L	C2	T5	T2.5	C1	T1.25	L
	58.1	75.9	78.3	84.7	91.6	95.7	64.8	70.8	81.7	89.2	90.1	104.5	76.2	81.5	83.8	85.4	94.2	113.5
1.6	T5	T2.5	T1.25	C1	C2	L	C2	T5	C1	T2.5	T1.25	L	C2	T5	T2.5	C1	T1.25	L
	85.9	104.6	115.3	123.8	139.2	159.2	88.9	96.3	117.7	127.3	130.0	156.8	83.3	106.6	112.6	112.7	128.0	134.3
6.4	T5	T2.5	C2	T1.25	L	C1	C2	T5	C1	T2.5	T1.25	L	C2	T5	C1	T1.25	T2.5	L
	141.2	156.8	176.0	184.1	214.4	217.0	113.7	119.3	148.8	159.4	168.9	177.3	124.1	141.4	158.5	179.9	186.5	198.2

Table 4. Antihistamine potency of different treatments.
The relative potency after different treatments was calculated by dividing the dose of histamine required to produce a flare or weal of given area after any of the 5 active treatments, by the dose required to produce a response of the same size after lactose at that time

Treatment (mg)	Time after Treatment (h)	Potency Flare	Potency Weal
Triprolidine 5	3	6.4	6.4
	5.5	5.0	12.8
	8	4.4	5.1
Triprolidine 2.5	3	4.5	3.7
	5.5	3.1	3.7
	8	3.1	2.3
Triprolidine 1.25	3	2.7	2.5
	5.5	2.4	2.4
	8	1.5	1.9
Clemastine 2	3	2.1	2.1
	5.5	6.2	15.4
	8	7.4	10.4
Clemastine 1	3	1.3	1.5
	5.5	3.1	4.2
	8	2.5	3.4

After clemastine performance did not differ significantly from that after lactose. During the third test, between 6 and 7 h post-treatment, performance after both doses of clemastine was significantly lower than after lactose. Only the highest dose of triprolidine produced significant impairment, the effect of the two lower doses having worn off. The second vigilance test, between 3.5 and 4.5 h post treatment failed to show significant differences in performance following different treatments. However, the trend seen in the last test was apparent at this time in that maximum impairment following triprolidine 5 mg but clemastine 2 mg and 1 mg were ranked next in order. No changes occurred in false detections ascribable to drug treatments.

Auditory Reaction Time

Reaction time results are shown in Table 6. Values for separate 5 min periods of the test are shown because in previous work it was seen that significant drug induced differences only appeared in the later parts of the test or when the full 15 min was analysed. Reaction time tended to lengthen both through the 15 min period and through the day. In this study most significant increases ascribable to drug treatment would have been seen in the first 5 min period of the test. The reaction time was prolonged by all doses of both antihistamines 2.5 h after treatment and was dose related. At 5 h post treatment only the two highest doses of both drugs gave significant prolongation, and by 7.5 h all effects had disappeared.

Table 5. Vigilance test. The mean number of correct detections for 12 subjects, out of 10 per quarter hour or 40 per total test are shown. Values following different treatments are ranked in ascending order and those underlined by a common bar do not differ significantly ($p>0.05$) while those not underlined by a common bar differ significantly ($p<0.05$). Abbreviations used are: triprolidine 1.25, 2.5 and 5 mg - T1.25, T2.5 and T5 respectively; clemastine 1 and 2 mg - C1 and C2; and lactose dummy L

	Mean number of correct detections																	
	1-2 h						3.5-4.5 h						6-7 h					
1st 15 min	T1.25 5.5	T5 5.8	L 6.7	T2.5 6.7	C2 7.0	C1 7.4	T5 4.8	L 5.8	C2 5.9	T2.5 6.0	C1 6.2	T1.25 6.7	C2 4.2	T1.25 4.4	T5 5.0	C1 5.4	T2.5 6.1	L 6.4
2nd 15 min	T5 2.9	T2.5 3.5	C1 4.6	T1.25 4.6	C2 5.0	L 5.6	C2 3.3	T2.5 3.8	C1 3.9	T5 4.1	T1.25 4.3	L 4.8	T5 3.7	C1 4.2	C2 4.3	T1.25 4.7	T2.5 4.9	L 5.2
3rd 15 min	T5 2.2	T1.25 2.6	T2.5 3.0	C2 3.3	C1 4.2	L 4.3	C2 3.0	C1 3.2	T5 3.3	T1.25 3.4	L 3.8	T2.5 4.3	T5 3.3	C1 3.3	C2 3.4	T2.5 4.2	L 4.6	T1.25 4.8
4th 15 min	T5 2.3	C2 3.5	T2.5 3.9	T1.25 4.0	L 4.3	C1 4.8	C2 3.3	T5 3.3	C1 3.8	T1.25 3.8	T2.5 3.9	L 4.8	C2 3.8	T5 3.8	T2.5 3.8	T1.25 4.0	C1 4.2	L 4.8
Total hour	T5 13.2	T1.25 16.7	T2.5 17.1	C2 18.8	L 20.8	C1 20.9	T5 15.5	C2 15.6	C1 17.0	T2.5 18.0	T1.25 18.3	L 19.1	C2 15.7	T5 15.8	C1 17.0	T1.25 17.9	T2.5 19.0	L 20.9

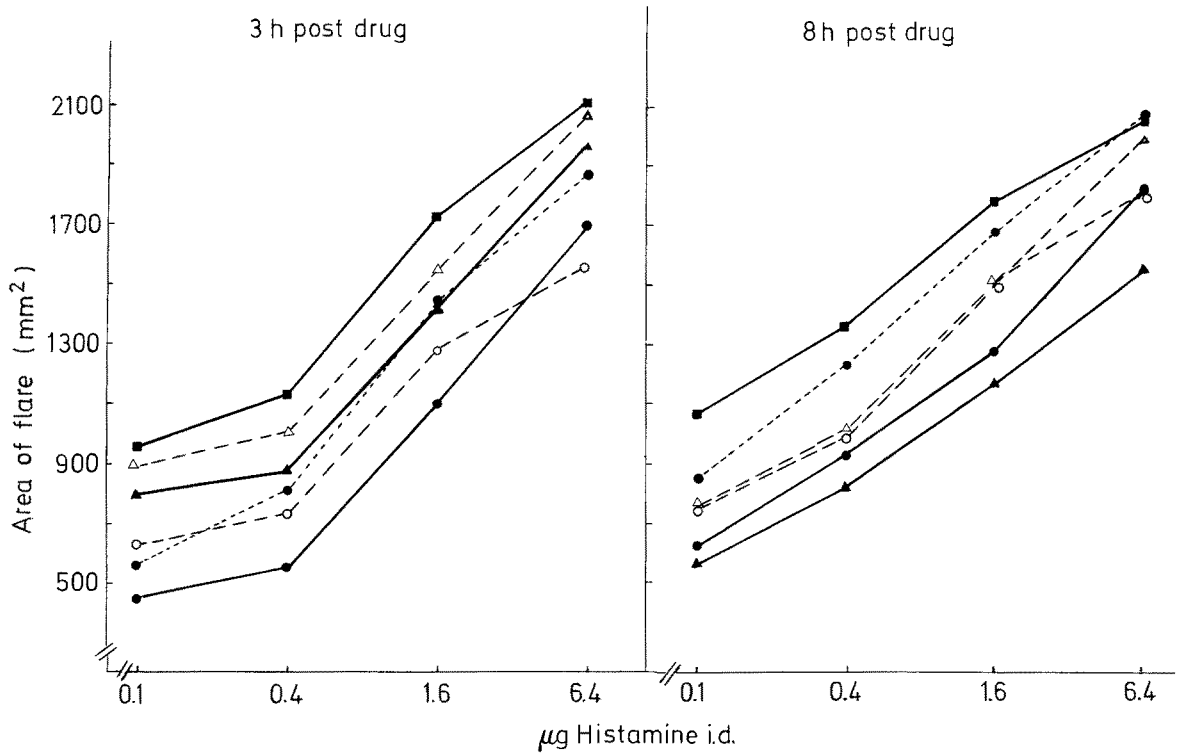

Fig. 1. Mean flare areas for 12 subjects produced by 4 doses of histamine acid phosphate 3 and 8 h after 6 different systemic treatments: Lactose dummy ■——; triprolidine hydrochloride 5 mg ●——, 2.5 mg ○·····, 1.25 mg ●-----, clemastine base 2 mg ▲——, 1 mg △-----

Table 6. Auditory reaction time (msec). Mean values for reaction time and digit symbol substitutions for 12 subjects are shown. Mean values after active drugs which differ significantly from those after lactose are indicated by [a] where $p<0.05$ and [b] where $p<0.01$

Test time post treatment (h)	Lactose Dummy	Triprolidine 5 mg	Triprolidine 2.5 mg	Triprolidine 1.25 mg	Clemastine 2 mg	Clemastine 1 mg
2.5						
1st 5 min	214	240[b]	231[a]	228	237[b]	235[b]
2nd 5 min	223	261[b]	247[a]	249[a]	265[b]	252[b]
3rd 5 min	239	276[a]	270[a]	261[a]	274[a]	264[a]
Whole test	225	258[b]	249[b]	246[b]	259[b]	250[b]
5						
1st 5 min	223	254[a]	238	233	260[b]	244
2nd 5 min	229	307[b]	252	250	275	245
3rd 5 min	243	271[a]	271[a]	253	285[b]	261
Whole test	232	278[b]	254	245	274[b]	250
7.5						
1st 5 min	227	238	228	234	233	240
2nd 5 min	236	250	243	239	249	243
3rd 5 min	243	251	255	245	251	244
Whole test	236	246	242	239	244	243
Digit Symbol Substitution Test (No substitution/90s)						
2.25	73.2	67.8[b]	69.9	72.3	69.1[a]	72.4
4.75	74.3	69.5[a]	72.0	72.3	70.1[a]	70.3[a]
7.25	74.8	67.7	71.9	73.4	68.7	71.8

Table 7. Subjective effects.
Scores were measured from the 100 mm lines indicating 18 dimensions. After arc-sine transformation, the scores were submitted to analysis of variance. Mean scores for the 12 subjects after different treatments at different times were ranked in ascending order. In the table score values have been omitted but where scores failed to differ significantly ($p>0.05$) treatments have been underlined by a common bar. Any treatments not underlined by a common bar gave scores which were different ($p<0.05$). Only dimensions where significant differences occurred are shown. Abbreviations used are: triprolidine 1.25, 2.5 and 5 mg, T1.25, T2.5 and T5; clemastine 1 and 2 mg, C1 and C2; and lactose dummy, L

Dimension						
2h 40 min post treatment						
Alert-Drowsy	L	C1	T2.5	T1.25	C2	T5
Clear Headed-Muzzy	L	C1	T1.25	T5	T2.5	C2
Well Co-ordinated-Clumsy	C1	L	T1.25	C2	T5	T2.5
Energetic-Lethargic	L	C1	T1.25	T2.5	C2	T5
Quick Witted-Mentally Slow	C1	L	T2.5	T1.25	C2	T5
5h 10 min post treatment						
Alert-Drowsy	L	C1	T2.5	T5	T1.25	C2
Energetic-Lethargic	L	C1	T1.25	T5	T2.5	C2
Excited-Calm	T1.25	L	C1	T2.5	C2	T5
7h 40 min post treatment						
Contented-Discontented	T5	C2	T2.5	T1.25	C1	L
Amicable-Antagonistic	C2	L	T2.5	T5	T1.25	C1

Digit Symbol Substitution

The number of substitutions completed in this test were significantly reduced by triprolidine 5 mg and clemastine 2 mg at 2 h 15 min and 4 h 45 min. The lower doses failed to affect performance, except for clemastine 1 mg at 4 h 45 min.

Short Term Memory

No significant changes ascribable to drugs occurred in the number of errors made in this test.

Subjective Effects

Variation in feelings of the group of volunteers after different treatments was obtained by the analysis of the visual analogue lines illustrated in Table 7. At 2 h 40 min, subjects indicated the greatest mental impairment after the triprolidine 5 mg, with clemastine 2 mg rated very similar. Clemastine 1 mg rarely differed from the effects of lactose. By 5 h 10 min, few differences ascribable to drugs were seen but clemastine 2 mg was now rated highest on scores of drowsiness and lethargy, whereas earlier effects of triprolidine 5 mg were wearing off. By 7 h 40 min all significant measures of mental impairment had disappeared.

Relationship between Antagonism of Histamine and Effects on the Central Nervous System

The possibility that antagonism of histamine in the skin, and effects on the central nervous system were related was examined by ranking the subjects in order of magnitude of change ascribable to the 5 different active treatments. Correlation between the rank order of antihistamine effect assessed on both flare and weal, and change in reaction time, vigilance, and subjective score on the alert-drowsy dimension was examined using Spearman's test. The total number of comparisons made was 90 (5 treatments; at 3 times of day against 3 tests, for both flare and weal measures). Significant positive correlation between peripheral antihistamine effect and impairment of central nervous system function occurred on 8 occasions shown in Table 8.

Discussion

The complete balance in the order of administration of the 6 treatments to all subjects, together with the balanced graeco-latin square design used to decide the site of different doses of histamine at different times, allowed a simpler statistical analysis than that employed by Fowle, Hughes and Knight (1971). The present

Table 8. Significant ($p<0.05$) correlations between CNS effect and histamine antagonism. Twelve subjects were ranked in order of reduction of flare and weal size after treatment compared with size after lactose dummy, and also ranked in order of size of change in subjective drowsiness score, impairment of vigilance and prolongation of reaction time. Ranks were compared using Spearman's test, and out of the 90 comparisons the 8 positive correlations and 4 negative correlations are shown

Treatment	Time Post Drug (h)	Skin Measure	CNS Measure
Positive Correlations			
Triprolidine 5 mg	8	Reduction of flare	Subjective drowsiness
Clemastine 1 mg	5.5	"	"
Clemastine 2 mg	8	"	Impaired vigilance
Triprolidine 2.5 mg	5.5	"	"
Triprolidine 1.25 mg	8	"	Prolongation of reaction time
Triprolidine 5 mg	8	Reduction of weal	Subjective drowsiness
Triprolidine 1.25 mg	8	"	"
Triprolidine 1.25 mg	8	"	Impaired vigilance
Negative Correlations			
Triprolidine 5 mg	5.5	Reduction of flare	Impaired vigilance
Clemastine 2 mg	3	"	Prolonged reaction time
Triprolidine 5 mg	3	Reduction of weal	Impaired vigilance
Clemastine 1 mg	5.5	"	Prolonged reaction time

analysis, in which antagonism of histamine was obtained from the dose response relationship for histamine after antihistamine, compared with the relationship after lactose dummy measured at the same time, enabled measurement of the variation in response following dummy through the 8 h period of the experiment. This data extends that of Reinberg, Sidi and Ghata (1965), who measured responses to repeated, fixed (10 μg) doses of histamine into the flexor forearm skin through the 24 h period. Their figures indicate that significant differences in weal or flare size do not occur through the 07.00 h to 19.00 h period, though responses were considerably larger at 23.00 h. From the data presented here both weal and flare size were larger at 09.00 h than later in the day and this could confuse experiments of this type.

Variations in response due to site of the histamine in the back showed that flares were larger in the right lateral column and weals larger on both medial and lateral columns on the right. This is likely to be due to technique; the experimenter was right handed.

Both triprolidine and clemastine were effective antagonists of histamine when assessed by either flare or weal area. However, their duration of action differed considerably. Triprolidine produced a significant dose related effect maximal at 3 h when the response to clemastine was rarely significant and then only after the highest dose. By 5.5 h the effect of clemastine was significant at both dose levels and the effect of triprolidine 5 mg and clemastine 2 mg failed to differ significantly, as did the 2.5 and 1 mg doses of the drugs. The effects of both drugs were still present 8 h after administration but the effects of lower doses were beginning to wear off.

Impairment by triprolidine of central nervous system function, assessed by tests of auditory vigilance, tapping rate, and subjective scores of mental impairment derived from analogue lines has recently been reported by Bye, Dewsbury and Peck (1974). Clemastine, while only recently introduced and less extensively studied, did not cause changes in the relatively short and convenient tests used to detect depressant activity of numerous drugs which cause drowsiness. Hedges, Hills, Maclay, Newman-Taylor and Turner (1971) did not detect changes in critical flicker fusion frequency ascribable to clemastine, whereas the effect of promethazine 25 mg was readily detectable. Mean values for critical flicker fusion frequency 6 h after clemastine were lower than after dummy, and might indicate the relatively late onset of the drug measured in the present study. Tests of disc dotting and serial subtraction were unaffected by clemastine, as were tests of hand-eye co-ordination and visual function reported by Day, Jones, Stewart-Jones and Turner (1972). Landauer and Milner (1971) also found that tapping, dot tracking and pursuit rotor performance were unaffected by clemastine alone and in combination with alcohol. A complex driving simulator task lasting 8 min was also unaffected.

One feature of all the reported tests is that where the duration of task is stated it is usually brief, at the most several minutes. In addition, the driving simulator test probably greatly interests the subjects, and because of the psychological relevance to driving, increases their motivation. The present investigation deliberately used prolonged and monotonous tests and the motivation of the subjects was further reduced by withholding information on their test results until the investigation was completed, thus preventing them competing with each other, or attempting to improve their performance with time.

The rapid onset of triprolidine in antagonising intradermal histamine was associated with the rapid and dose related impairment in vigilance 1 to 2 h after drug administration. The lack of effect of clemastine on vigilance at this time is consistent with the relatively poor antagonism of histamine even up to 3 h after administration. Both drugs prolonged reaction time and impaired digit symbol substitution at 2.5 and 5 h, indicating that clemastine was having an effect on the central nervous system at these times. By 6-7 h after administration clemastine was producing the maximum impairment in vigilance though onset of this effect was apparent from the trend during the 3.5 - 4.5 h period. The relatively late onset of the subjective effects of clemastine is consistent with the objective measurements. Antagonism of the histamine skin response, and impairment of central nervous system function, therefore, follow a similar time course for both drugs.

Although the two drugs affected the central nervous system in a dose related manner, and with an approximately similar time course to their effects on histamine skin response, the conclusion cannot be drawn that the effects on the nervous system are mediated by antagonism of endogenous brain histamine. While studies of this type inevitably suffer from the necessity to average the data from a group of subjects, information relevant to the mechanism of the nervous system effect can be obtained from the available data. If the central nervous effect were mediated by antagonism of histamine, then those subjects who showed the greatest antagonism of histamine skin response following administration of an antihistamine, might also be expected to show maximal nervous system impairment and vice versa. In order to examine this postulate, subjects were ranked in order of % reduction in skin response after each active drug, relative to size after lactose and also ranked in order of % change of vigilance, prolongation of reaction time, and subjective rating of drowsiness. Comparison of the rank orders was made and showed a positive correlation ($p<0.05$) on only 8 out of 90 occasions. These 8 positive correlations were often surprising pharmacologically, not usually occurring after the highest drug doses, or at times of maximal action, and it seemed likely that they were due to chance resulting from multiple comparisons. This is supported by the

fact that 4 negative correlations also occurred, suggesting that subjects who showed the least effect of the active drug on the skin response suffered the greatest impairment in nervous function, a conclusion which would be untenable. These data, therefore, do not suggest that these two compounds exert their effects on the nervous system through action on histamine receptors.

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