A COMPARISON OF TRIPROLIDINE AND CYCLIZINE ON HISTAMINE (H₁) ANTAGONISM, SUBJECTIVE EFFECTS AND PERFORMANCE TESTS IN MAN

MARGARET HAMILTON, MAUREEN BUSH, CAROLE BYE & A.W. PECK

Department of Clinical Pharmacology, Wellcome Research Laboratories, Beckenham, Kent

- 1 The effects of triprolidine and cyclizine on the histamine skin response, performance tests and subjective effects were examined in a controlled, double-blind study in eight healthy volunteers.
- 2 Triprolidine was considerably more potent than cyclizine in inhibiting the skin response to histamine. Significant inhibition of flare size occurred at 1, 2 and 4 h after triprolidine 2.5 mg. A smaller but significant reduction occurred at 2 and 4 h after cyclizine 100 mg but not after the 50 mg dose.
- 3 Cyclizine 100 mg produced a significant increase in reaction time at 4.5 h compared with lactose. Smaller though non significant increases followed triprolidine and cyclizine 50 mg.
- 4 Subjective effects were seen only after cyclizine 100 mg when subjects were significantly more drowsy, feeble, muzzy, lethargic and dreamy than after lactose dummy. No significant changes followed triprolidine 2.5 mg or cyclizine 50 mg.
- 5 It was concluded that while cyclizine has antihistamine properties, these are weak compared with triprolidine, and are not seen with doses sufficiently low to avoid central nervous system impairment.

Introduction

Most currently available histamine (H₁) antagonist drugs produce undesirable drowsiness. Cyclizine has been shown to be an effective histamine antagonist in animals (Norton *et al.*, 1954), and in man it does not appear to cause subjective drowsiness or impairment of vigilance or reaction time (Clubley *et al.*, 1979). Triprolidine is a potent histamine antagonist in man, but causes drowsiness and impairs reaction time and vigilance (Bye *et al.*, 1974; Peck *et al.*, 1975). The possibility exists, therefore, that cyclizine might be a useful histamine antagonist, lacking drowsiness and central nervous system impairment. This study compared triprolidine and cyclizine on histamine antagonism, subjective mental state, and performance tests in healthy men.

Methods

The subjects were eight healthy male volunteers, aged 21-50 years (mean 31) recruited from the staff of

Wellcome Research Laboratories. On the experimental day they received a light standardised breakfast before 07.30 h, but no tea, coffee, alcohol, or cigarettes were allowed until the tests had been completed. Subjects were transported to and from the laboratory.

Drug treatment

Subjects were studied on four occasions at weekly intervals in the same group of four each time. All eight subjects received all of the following four treatments:

Lactose dummy

Triprolidine hydrochloride, 2.5 mg

Cyclizine hydrochloride, 50 mg

Cyclizine hydrochloride, 100 mg

All treatments were in gelatin capsules which were identical in appearance. The order of the treatments was randomised according to two 4 × 4 Latin square designs. Drugs were administered at 09.30 h.

Assessment of feelings and performance

Subjective feelings were assessed at 08.50 h using visual analogue scales (Lader & Norris, 1969) repeated at 11.00 h, 12.00 h and 14.00 h. Side effects assessed by check list, were recorded pretreatment and at the end of the test day. The test schedule began at 09.05 h and consisted of:

- (1) Auditory reaction time test lasting 15 min, in which subjects pressed a microswitch as rapidly as possible on hearing randomly occurring short tones.
- (2) Tapping test in which subjects tapped a micro-switch for 60 s. The total number of taps was recorded.
- (3) Digit symbol substitution test lasting 90 s (Wechsler, 1955) in which the number of correct substitutions was counted.

The above three tests were repeated at 11.05 h, 12.05 h and 14.05 h.

Assessment of histamine antagonism

At 1, 2 and 4 h post-treatment, three intradermal injections of histamine 0.1, 0.4 and 1.6 μg (as acid phosphate) were made into the back, all in 0.05 ml isotonic saline, using a 1 ml syringe. After 20 min each flare and weal was measured using a plastic ruler, the longest and narrowest axes of each flare and weal at 90° to each other being recorded. Areas were calculated assuming an elliptical shape (Fowle *et al.*, 1971). Responses were also photographed on colour film using a fixed focus camera to see if this was more sensitive than the eye.

The effects of possible variations in response resulting from differences in site over the back, were reduced by siting the injections according to a graeco-latin square design.

Analysis of results

All the results were analysed as raw scores by the method of analysis of variance. Differences ascribable to treatments of $P < 0.05$ were regarded as significant.

The dose-response curves to histamine were evaluated at each time for each treatment, for the direct measurements of flares and weals separately. Lines were tested for parallelism, and all four treatment lines at each time were shown to have slopes which were not significantly different. The displacement of the mean curve after active drug treatment was compared with the curve obtained after dummy treatment, and was used to evaluate the potency ratio,

$$\text{where potency} = \frac{\text{amount of histamine required to produce a given area after drug}}{\text{amount of histamine producing the same area after dummy}}$$

Table 1 Mean flare and weal areas for eight subjects were calculated after 3 i.d. histamine injections at three times after treatment. Log dose-response curves were then plotted. From displacement of these curves potency was calculated. For the 2 h weal areas the common slope of the regression lines was barely significant and the limits for the potency ratio were imaginary.

	Displacements of the dose response curves to histamine			
	Flare		Weal	
	Potency	95% limits	Potency	95% limits
<i>1 h</i>				
C50	2.09	(0.88, 4.99)	2.44	(0.89, 10.35)
C100	1.66	(0.70, 3.95)	1.41	(0.49, 4.80)
T2.5	5.38	(2.26, 12.83)	7.08	(2.41, 54.54)
<i>2 h</i>				
C50	1.46	(0.89, 2.39)	1.06	—
C100	1.99	(1.21, 3.25)	11.86	—
T2.5	5.95	(3.65, 9.74)	14.71	—
<i>4 h</i>				
C50	1.22	(0.87, 1.69)	1.15	(0.35, 4.16)
C100	1.48	(1.06, 2.06)	1.42	(0.45, 5.53)
T2.5	3.96	(2.84, 5.51)	2.72	(0.92, 15.05)

Cyclizine HCl 50 and 100 mg, C50 and C100 respectively; triprolidine HCl 2.5 mg, T2.5

Where confidence limits do not include the value 1, the change in potency is significant

Results

Assessment of histamine antagonism

The effects of different treatments at different times on flare and weal areas are summarised in Table 1. It can be seen that at 1 h the only significant effects followed triprolidine 2.5 mg. Significant displacement of dose-response curves for both flares and weals occurred at this time after this treatment. Again at both 2 h and 4 h much the biggest displacement of flare dose response curves followed triprolidine. A smaller but significant effect occurred after cyclizine 100 mg at both times. Cyclizine 50 mg, however, failed to produce any significant displacement of dose response curve at any time.

Any effects on weals at 2 h could not be evaluated and at 4 h no significant changes were ascribable to treatments.

Photographs of the flare and weals taken at the same time and measured subsequently were compared with measurements made by eye and correlation coefficients for the two methods were calculated. This gave $r = 0.8165$ for flares and $r = 0.7909$ for weals. Unfortunately the photographic method proved relatively unsatisfactory in that 14 values for flares and 24 values for weals could not be read from the colour photograph.

Table 2 Mean values (ms) for eight subjects at different times after different treatments together with s.e. mean from the analysis of variance.

	L	Reaction time (ms)			pooled s.e. mean
		C50	C100	T2.5	
Pre-drug	219	219	216	217	3.7
After drug					
1 h 35 min	222	236	237	231	7.9
2 h 35 min	230	247	235	236	
4 h 35 min	226	247	257*	247	

Cyclizine HCl 50 and 100 mg, C50 and C100 respectively; triprolidine HCl 2.5 mg, T2.5; Lactose dummy, L.

Dunnett's test was used for comparing the treatment means with lactose. The asterisk indicates a significant difference ($P < 0.05$).

Performance tests

Reaction time Results of this test are shown in Table 2. Analysis of variance of all four test sessions together indicated a possible interaction between treatments and time ($P = 0.08$). The mean values shown appeared to indicate a trend towards pro-

Table 3 Raw scores recorded on the visual analogue scales by eight subjects were averaged after each treatment on each dimension. These were analysed by analysis of variance and ranked in ascending order. Treatments underlined by a common bar were not significantly different. Treatments not underlined by a common bar are significantly different ($P < 0.05$). Abbreviations as for Table 2. No differences occurred pretreatment or at 1 h 30 min post-treatment. Scales where no differences ascribable to treatments were seen have been omitted.

The following scales have been reversed in the table from their position on the experimental sheets for clarity; energetic/lethargic; sociable/withdrawn; outward going/self-centred; clear headed/muzzy; energetic/lethargic

Subjective effects				
<i>Time post treatment</i>				
<i>2 h 30 min</i>				
Energetic/lethargic	L	C50	<u>T2.5</u>	<u>C100</u>
Sociable/withdrawn	L	C50	<u>T2.5</u>	C100
Outwardgoing/self-centred	L	<u>T2.5</u>	<u>C50</u>	C100
<i>4 h 30 min</i>				
Alert/drowsy	L	<u>T2.5</u>	<u>C50</u>	C100
Strong/feeble	L	<u>T2.5</u>	<u>C50</u>	C100
Clearheaded/muzzy	L	C50	<u>T2.5</u>	C100
Energetic/lethargic	L	<u>T2.5</u>	<u>C50</u>	C100
Attentive/dreamy	L	C50	<u>T2.5</u>	C100
Mental sedation	<u>L</u>	C50	<u>T2.5</u>	C100
Physical sedation	L	<u>T2.5</u>	<u>C50</u>	C100

longation after all the antihistamine treatments compared with results after lactose dummy, but this was significant only 4 h 35 min after cyclizine 100 mg.

Tapping test and digit symbol substitution test No significant effects were ascribable to treatments on either of these tests.

Subjective effects

Significant differences ascribable to treatments are shown in Table 3. The only significant differences in feelings ascribable to treatments occurred after cyclizine 100 mg. Subjects were more lethargic, more withdrawn and more selfcentred 2 h 30 min after the higher dose of cyclizine. By 4 h 30 min after treatment more scales showed differences with subjects more drowsy, feeble, muzzy, lethargic and dreamy after the top dose of cyclizine. Analysing grouped lines (Norris, 1971) showed increased mental sedation and physical sedation, again after cyclizine 100 mg. Assessment of side effects added little to the data obtained from the visual analogue scales. Dry mouth occurred on occasions after all active drugs, as did headache which also occurred after placebo and might well be ascribed to the experiment itself.

Discussion

While cyclizine quite clearly has the ability to antagonise histamine in the skin it is weak relative to triprolidine. Only at the 100 mg dose was significant displacement of the dose response curve to histamine apparent, but even this effect did not appear until 2 h after administration. Triprolidine by contrast produced greater displacement which was evident at 1 h.

Evidence of impairment of central nervous function was not apparent after triprolidine in this study, though in earlier studies after even the modest 2.5 mg dose significant reduction in correct detections in an auditory vigilance test was seen and the reaction time was prolonged (Peck *et al.*, 1975). In the study reported here it was not possible to use the 1 h long vigilance test, but the simple reaction time might have been expected to show impairment. In this study, however, eight subjects only were used compared with twelve in most previous assessments.

The effects of cyclizine on performance and subjective scales were expected to be small. No changes in performance tests occurred after cyclizine 50 mg in a previous study (Clubley *et al.*, 1979) indeed doses of 100 mg failed to affect tests of vigilance, reaction time, short term memory and digit symbol substitution. Only an arithmetic test was impaired 5 h after administration. In the same study the only significant subjective effect produced by cyclizine was increased

mental sedation 6 h after the 100 mg dose. Brand *et al.* (1967) recorded sleepiness as a side effect of both hyoscine and cyclizine, but made no statistical analysis in their complicated investigation of the effects of these drugs on motion sickness. Sleepiness was reported as a side effect in a proportion of subjects receiving doses of between 15 and 100 mg cyclizine. It was also (not unexpectedly) reported after the placebo. It occurred much more frequently after the placebo in subjects who vomited than in subjects who received cyclizine between 15 and 100 mg, but who did not vomit. The authors did not attempt a statistical analysis on side effects but make the point that the placebo response in their study made analysis extremely difficult.

The results of this investigation suggest that while cyclizine may be a potent antihistamine in animal tests it is unlikely to be as effective as triprolidine in man in clinical situations. Triprolidine 2.5 mg three times a day was required to relieve the sneezing and eye irritation in hay fever sufferers, 1.25 mg not differing in effects from the placebo (Britton *et al.*, 1979). In this study triprolidine 2.5 mg produced the largest degree of histamine antagonism with no evidence of central nervous system impairment. By contrast cyclizine, even at top dose, was a relatively weak antihistamine while producing drowsiness and prolongation of reaction time.

References

- BRAND, J.J., COLQUHOUN, W.P., GOULD, A.H. & PERRY, W.L.M. (1967). (–)-Hyoscine and cyclizine as motion sickness remedies. *Br. J. Pharmac. Chemother.*, **30**, 463–469.
- BRITTON, M.G., EMPEY, D.W., JOHN, G.C., HODDER, M. & HUGHES, D.T.D. (1979). Two doses of triprolidine for treatment of allergic rhinitis. *Annals Allergy*, **42**, 330–332.
- BYE, C., DEWSBURY, D. & PECK, A.W. (1974). Effects on the human nervous system of the two isomers of ephedrine and triprolidine, and their interaction. *Br. J. clin. Pharmac.*, **1**, 71–78.
- CLUBLEY, M., BYE, C.E., HENSON, T., PECK, A.W. & RIDDINGTON, C. (1979). Effects of caffeine and cyclizine alone and in combination on human performance and subjective ratings. *Br. J. clin. Pharmac.*, **7**, 157–163.
- FOWLE, A.S.E., HUGHES, D.T.D. & KNIGHT, G.J. (1971). The evaluation of histamine antagonists in man. *Eur. J. clin. Pharmac.*, **3**, 215–220.
- LADER, M. & NORRIS, J. (1969). The effects of nitrous oxide on the human auditory evoked response. *Psychopharmacologia (Berl.)*, **16**, 115–127.
- NORRIS, H. (1971). The action of sedatives on brain stem oculomotor systems. *Neuropharmacology*, **10**, 181–191.
- NORTON, S., COLVILLE, K.I., LIGHT, A.E., WNUCK, A.L., FANELLI, R.J. & BEER, E.J. (1954). Pharmacological properties of cyclizine hydrochloride (Marzine). *J. Pharmac. exp. Ther.*, **112**, 297–305.
- PECK, A.W., FOWLE, A.S.E. & BYE, C.E. (1975). A comparison of triprolidine and clemastine on histamine antagonism and performance tests in man: implications for the mechanism of drug induced drowsiness. *Eur. J. clin. Pharmac.*, **8**, 455–463.
- WECHSLER, D. (1955). *Manual for the Wechsler adult intelligence scale*. N.Y.: Psychological Corporation. London: National Foundation for Educational Research.

(Received May 29, 1981)