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EFFECTS OF RANITIDINE ALONE AND IN COMBINATION WITH CHLORPHENIRAMINE ON HISTAMINE-INDUCED WHEAL AND FLARE AND PSYCHOMOTOR PERFORMANCE

P. P. KHOSLA, N. SAHA, A. KOUL*, A. CHAKRABARTI, A. SANKARANARAYANAN** AND P. L. SHARMA

Departments of Pharmacology and Biophysics, Postgraduate Institute of Medical Education & Research, Chandigarh - 160 012*

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Abstract : Some reports suggest that addition of an H_2 antagonist increases the efficacy of H_1 antagonist but the influence on the side effect profile of antihistamines are largely unknown. The effects of ranitidine, chlorpheniramine, their combination and placebo on histamine induced wheal and flare, psychomotor performance and subjective symptoms were studied in 6 healthy male volunteers in a double blind randomized and cross-over (Latin square) study. Ranitidine significantly reduced the histamine induced wheal at 4 hrs ($P<0.05$). Chlorpheniramine and the combination significantly reduced both histamine induced wheal and flare at 2 hrs and at 4 hrs ($P<0.05$). Addition of ranitidine reduced the feeling of sleepiness produced by chlorpheniramine, though other subjective symptoms were not affected. None of the treatment schedules produced any consistent change in the psychomotor performance of the volunteers.

Key words : chlorpheniramine ranitidine histamine induced wheal and flare psychomotor performance

INTRODUCTION

H_1 antagonists have been used in various allergic conditions. There is also a high rate of non-responsiveness which may be due to non-compliance of the patients, because of drowsiness (1) and impairment of psychomotor performance (2, 3).

The effect of H_2 antagonists on immediate skin reaction to allergens and histamine is controversial (4, 5) though a combination of H_1 and H_2 antagonists have been shown to be superior to either drug in chronic idiopathic urticaria (1), symptomatic dermographism, allergic rhinitis and conjuctivitis (6).

The effect of a combination of H_1 and H_2 antagonists on the psychomotor performance in man has not been reported. The present study was therefore, undertaken to assess the effect of chlorpheniramine (H_1 antagonist) or ranitidine (H_2 antagonist) and in combination on psychomotor function and histamine induced wheal and flare responses in human volunteers.

METHODS

Six male healthy volunteers (age 25-40 years weight 55-70 kgs) were enrolled in the study after a written informed consent. No one was taking any other drug one week prior and during the study. The volunteers with skin disease, anxiety-neurosis, depression and a score of more than ten on PGI Health Questionnaire N_1 were excluded. The study was randomized (with a Latin square) double blind, double dummy, placebo controlled with a wash-out period of 3-4 days between treatments. Volunteers had overnight fast and abstained from tobacco, tea, coffee or caffeine containing beverages on the day of study. The subjects reported at 7.00 a.m. Their visual analogue scale (VAS) for subjective symptoms of tiredness, sleepiness, concentration, dryness of mouth and mental

**Corresponding Author

relaxation (7), histamine induced wheal and flare test (8) digit symbol substitution test (DSST) (9) two digit cancellation test (DCT) (14), Card sorting test (CST) (10) and critical flicker fusion (11) test were recorded at 0 hr (baseline), and at 2 hr and 4 hr after drug.

The treatment schedule was as follows : placebo plus placebo, placebo plus Chlorpheniramine 16 mg, Chlorpheniramine 16 mg plus ranitidine 300 mg and ranitidine 300 mg plus placebo in random order.

For skin test a sterile solution of histamine phosphate 2 µg in 0.1 ml of 0.9% w/v sodium chloride solution was administered intradermally on the flexor aspect of forearm with 26 G hypodermic needle. Twenty minutes after the injection, the wheal and flare size was marked with a fiber tipped pen and was copied on to a transparent tracing paper and then to a graph paper. The total wheal area was determined by planimetry (12).

The data have been presented as mean (±s.e.m.) percentage change from zero hour score at two and four hours. Statistical analysis was done by analysis of variance followed by method of least significant difference. P values less than 0.05 was taken to be statistically significant.

RESULTS

Chlorpheniramine significantly reduced the histamine induced wheal and flare area at 2 and 4 hr as compared to that of the placebo and its response was greater at 2 hr than at 4 hr. Ranitidine caused only a decrease in histamine induced wheal at 4 hrs. The combination of chlorpheniramine and ranitidine produced a significant decrease in the wheal and flare area at 2 hr and 4 hr (Table I).

TABLE I: Mean % change (±s.e.m.) from base line histamine induced wheal and flare response, psychomotor tests, and subjective symptoms, 2 and 4 hr after administration of placebo, ranitidine, chlorpheniramine and a combination of chlorpheniramine and ranitidine.

Hours after drug admn.	*Placebo*		*Ranitidine*		*Chlorpheniramine*		*Chlorpheniramine + Ranitidine*	
	2	4	2	4	2	4	2	4
Wheal area	−13.92 ± 5.76	−17.19 ± 6.63	−25.59 ± 4.18	−40.89a ± 4.57	−54.94* ± 1.86	−39.30a ± 10.14	−46.36* ± 10.14	−44.57a ± 8.78
Flare area	−6.83 ± 6.71	−19.38 ± 5.88	−26.07 ± 7.69	−36.23 ± 11.39	−58.84* ± 7.7	−43.65a ± 7.89	−66.42* ± 8.45	−57.85a ± 6.36
CFF	0.65 ± 1.91	0.74 ± 1.19	−2.05 ± 0.91	−1.26 ± 2.33	−5.05 ± 1.11	−4.35 ± 1.6	−2.47 ± 1.93	−1.29 ± 2.20
DCT	11.60 ± 7.26	3.28 ± 6.69	1.22 ± 2.29	−4.10 ± 5.99	−6.24 ± 7.97	−12.11 ± 5.12	−5.36 ± 9.17	−6.37 ± 4.21
DSST	3.58 ± 2.84	4.07 ± 5.63	1.73 ± 1.62	−2.90 ± 2.77	−4.20 ± 5.66	−4.87 ± 5.20	−6.24 ± 3.30	−6.60 ± 2.94
CST	2.08 ± 2.43	1.75 ± 4.06	2.39 ± 1.94	5.43 ± 2.53	1.19 ± 1.81	4.51 ± 5.35	6.49 ± 2.94	3.51 ± 2.80
Sleepiness	8.67 ± 3.54	14.17 ± 12.28	22.33 ± 12.28	29.17 ± 11.20	63.67* ± 7.84	43.66 ± 17.20	30.17** ± 10.28	22.67 ± 9.83
Tiredness	6.83 ± 2.78	10.14 ± 2.40	23.17 ± 6.18	25.83 ± 11.65	58.33* ± 11.92	48.17 ± 14.82	34.83 ± 10.28	32.50 ± 9.83
Concentration	7.0 ± 4.22	8.5 ± 5.30	25.0 ± 9.56	19.17 ± 6.41	46.17 ± 12.15	35.70 ± 14.94	24.33 ± 15.84	14.83 ± 11.90
Relaxed	−5.33 ± 3.52	−13.17 ± 6.35	−4.00 ± 5.44	−7.00 ± 5.12	−8.17 ± 6.85	−6.00 ± 4.27	−14.83 ± 9.15	−1.00 ± 2.78
Dry Mouth	−4.50 ± 2.31	−4.83 ± 0.76	13.50 ± 7.80	6.50 ± 10.57	32.67 ± 12.45	17.17 ± 15.54	12.67 ± 8.59	11.17 ± 6.65

*P < 0.05 in comparison to placebo 2 hr value
**P < 0.05 in comparison to chlorpheniramine 2 hr value.
•P < 0.05 in comparison to placebo 4 hr value.

The effect of ranitidine on psychomotor tests was not different from the group treated with placebo. Chlorpheniramine was found to impair the psychomotor performance as measured by CFF, DCT and DSST when compared to the baseline performance. Combining ranitidine with chlorpheniramine tended to conter the suppressive effect of chlorpheniramine alone observed in CFF and DCT though the change did not attain statistical significance (Table I).

Chlorpheniramine treatment caused significantly more sleepiness and tiredness and tended to exaggerate inability to concentrate and dryness of mouth compared to placebo at 2 hr. Combining ranitidine with chlorpheniramine, resulted in a notable attenuation of chlorpheniramine induced sleepiness, tiredness inability to concentrate and dryness of mouth, although statistically significant difference was found for the sleepiness parameter (Table I).

DISCUSSION

In the present study, chlorpheniramine significantly inhibited the histamine induced wheal and flare response as reported earlier for other H_1 antagonists (12, 13). Ranitidine produced an inhibition of wheal response to histamine at 4 hrs which is in contrast to the result of earlier studies employing cimetidine and ranitidine (4, 5, 14). This might in part reflect the influence of different dosage schedule employed. The finding that a combination of chlorpheniramine and ranitidine had a tendency to increase the inhibition of histamine induced cutaneous response over chlorpheniramine indicates that though H_1 and H_2 receptors are involved in the cutaneous response H_1 receptors probably play a dominant role in volunteers. Our findings that ranitidine diminished the central nervous system adverse effects of chlorpheniramine is of considerable clinical relevance. Animal experimental studies do suggest the same (15, 16) though no reports are available in humans. Considering the wide inter-individual variability in response to anti-histamines it would be prudent to conduct similar studies on a larger number of allergic subjects to elucidate the exact mechanism.

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