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A Study on CNS-Side Effects of Mequitazine, An H_1-Specific Antihistamine in Healthy Thai Volunteers

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SUMMARY **Mequitazine is a potent, non-sedative, long-acting H_1-specific antihistamine proven to be a better therapeutic drug than other conventional antihistamines. It is also reported by many authors that the drug produces less sedative or other depressive actions on the central nervous system than other antihistamines.**

In order to evaluate the advantage of this drug in Asian people, an assessment of side effects of mequitazine, in comparison with chlorpheniramine, on the central nervous system was done in 20 healthy Thai volunteers, 10 males and 10 females 23-39 years of age, using a double blind crossover placebo controlled trial. Various subjective tests: alertness scale rating, visual analogue scale rating as well as objective tests: card sorting, glassbead picking and estimation of reaction time, were performed. There were no significant differences in side effects on the central nervous system between mequitazine and the placebo, whereas chlorpheniramine did produce side effects.

Mequitazine, 10-(3-quinuclidinylmethyl) phenothiazine is a potent, non-sedative long-acting antihistamine. The antihistaminic efficacy of this drug both in experimental animals and in man has been reported by many authors.[1-4] Conventional H_1-receptor antagonists such as diphenhydramine, promethazine and chlorpheniramine are known to possess side effects on the central nervous system.[5-7] Mequitazine, which has the same basic phenothiazine structure as promethazine, was reported to produce weak central side effects.[8,9] These studies have been done mainly on Caucasians, primarily in European countries. The purpose of this study was to investigate the side effects of mequitazine on the central nervous system, after the first oral therapeutic dose as well as after chronic administration, in Asian people.

MATERIALS AND METHODS

Subjects

The subjects consisted of 20 healthy Thai volunteers, 10 males and 10 females aged 23-39 years and weighing 42-73 kg. None had any history of acute or chronic disease, especially allergic disease. They did not take any drugs for at least 48 hours prior to testing or during the experiment. Alcohol and other stimulant beverages such as coffee and tea were also avoided for a 24-hour period before testing and during the test.

The experimental design was a double-blind cross-over trial. Mequitazine (5 mg), chlorpheniramine (4 mg), and placebo tablets, all identical in appearance, were given twice a day during a period of 7 days. One group of volunteers received mequitazine first, the other two groups received chlorpheniramine and placebo first respectively. Between each treatment period there was a washout time of 7 days. All tests were performed immediately before, and 1, 2 and 3 hours after intake of the first and the last dose (i.e. the second dose of the seventh day) of the drugs and placebo.

Test methods

The tests carried out in study were divided into two groups as follows:

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(a) Subjective tests

(i) *Visual analogue rating scale*

Each subject estimated his own mood, emotions, and well-being on a 10-cm-long visual analogue scale (Fig. 1). The extremes of the scale were denoted "high" to which a score of 3^+ was assigned, and "low" to which a score of 0 was assigned.

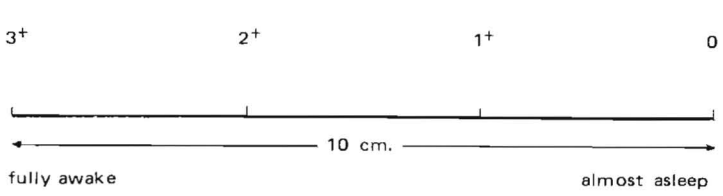

Fig. 1 Visual analogue scale.

(ii) *Alertness rating scale*

Each subject estimated his alertness and his ability to perform normal tasks by crossing the appropriate box with one of four possible scores, as shown in Fig. 2.

□ I am quite alert	3^+
□ I am less alert than usual but I can work without any difficulty.	2^+
□ I am markedly less alert than usual and I work with difficulty.	1^+
□ I am quite sleepy.	0

Fig. 2 Alertness rating scale.

(b) Objective tests

(i) *Card sorting test*

The objective of this test was to record the time required to match 100 cards with ten different symbols and to insert the cards, one at a time, into the appropriate slot, in front of the subject (Fig. 3). The average time of three repeated trials was recorded.

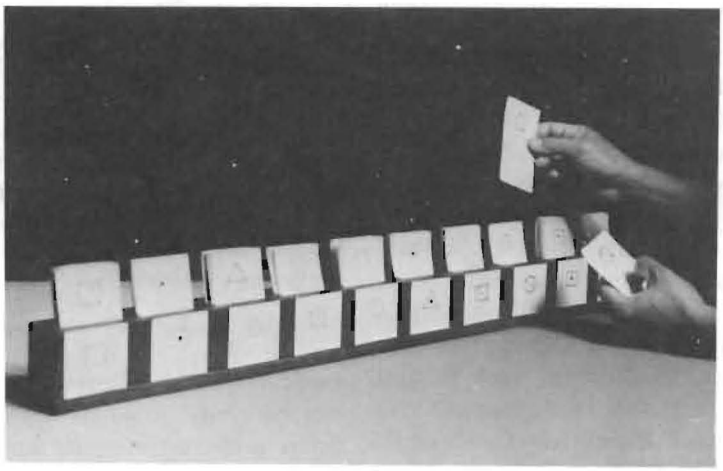

Fig. 3

(ii) *Glassbead picking test*

In this test, the time was recorded that was needed to pick up small glassbeads, one at a time, with a blunt pair of forceps and to fill up a 15-cm-high glass tube of which the inner diameter was slightly larger than that of the glassbead (Fig. 4). Again, the average time of the three repeated trials was used.

(iii) *Reaction time test*

The instrument used for this purpose was an electronic time recorder (Fig. 5). It was designed to work in the same way as a traffic light. The observer randomly pressed the yellow, red, or green light button. The subject responded every time he saw the red light by pressing a switch-off button. The instrument recorded the time in msec between on and off. Again, the time recorded was the average of three repeated trials.

Each time, before participating in a test, the subject was allowed to practice in repeated trials until his performances became stable. Statistical analysis for testing of significant differences was carried out by the Mann-Whitney U test.

RESULTS

The overall results obtained from five methods of testing, two subjective, and three objective tests are shown in Table 1.

Subjective tests

(i) *Visual analogue rating scale:* There was no significant score change at 1, 2 and 3 hours after oral administration of either placebo or mequitazine compared with the control values on the first and seventh day (Fig. 6). While chlorpheniramine caused a significant change ($p<0.05$) in the score at all periods of testing when compared with control values. No significant score changes were found between mequitazine and placebo in comparable test periods on either the first or seventh day. Chlorpheniramine caused significant

Table 1. Effect of Mequitazine on Psychomotor Performances in Healthy Thai Volunteers.

Test	Drug	Day 1				Day 7			
		Just prior to adm.	1 hr. after adm.	2 hr. after adm.	3 hr. after adm.	Just prior to adm.	1 hr. after adm.	2 hr. after adm.	3 hr. after adm.
Visual analogue scale ratings	Placebo	2.9	2.85	2.9	2.9	3	3	3	2.8
	Mequitazine	3	3	2.85	2.7	2.8	2.8	2.8	2.9
	Chlorpheniramine	3	2.55	2.15	2.1	2.75	2.35	2.35	2.2
Alertness scale ratings	Placebo	2.9	2.9	2.9	2.95	3	2.95	2.95	2.95
	Mequitazine	3	2.95	2.9	2.8	2.85	2.7	2.75	2.8
	Chlorpheniramine	2.95	2.5	2.2	1.95	2.8	2.45	2.3	2.25
Card sorting (mean in sec. ± SEM)	Placebo	129.56 ± 4.48	128.68 ± 4.14	127.85 ± 3.95	125.35 ± 3.87	128.72 ± 4.08	124.33 ± 3.68	126.32 ± 3.80	123.29 ± 3.57
	Mequitazine	133.63 ± 4.41	130.25 ± 3.91	130.87 ± 4.41	129.37 ± 4.38	127.23 ± 3.95	126.37 ± 4.11	125.0 ± 4.67	122.8 ± 3.99
		129.65 ± 3.98	129.3 ± 3.85	130.23 ± 4.51	128.75 ± 3.73	126.03 ± 4.34	125.63 ± 4.03	126.24 ± 4.68	124.37 ± 4.23
Glass bead picking (mean in sec. ± SEM)	Placebo	66.37 ± 2.14	64.88 ± 1.97	65.07 ± 2.37	64.00 ± 1.70	65.15 ± 2.21	63.95 ± 1.98	64.15 ± 1.68	62.68 ± 2.02
	Mequitazine	68.33 ± 2.21	66.03 ± 1.93	63.97 ± 1.81	64.83 ± 1.98	66.48 ± 1.53	65.45 ± 1.75	63.93 ± 1.93	64.23 ± 2.06
	Chlorpheniramine	66.9 ± 2.86	64.18 ± 2.77	66.4 ± 2.54	66.73 ± 2.46	67.5 ± 2.77	67.55 ± 2.40	70.38 ± 3.23	67.73 ± 2.43
Reaction mine (mean in sec. ± SEM)	Placebo	.257 ± .007	.251 ± .008	.248 ± .007	.245 ± .007	.247 ± .009	.238 ± .007	.240 ± .007	.240 ± .009
	Mequitazine	.243 ± .008	.243 ± .002	.242 ± .004	.241 ± .006	.231 ± .007	.238 ± .006	.238 ± .006	.237 ± .005
	Chlorpheniramine	.248 ± .008	.257 ± .009	.258 ± .010	.260 ± .008	.241 ± .006	.245 ± .009	.252 ± .009	.256 ± .012

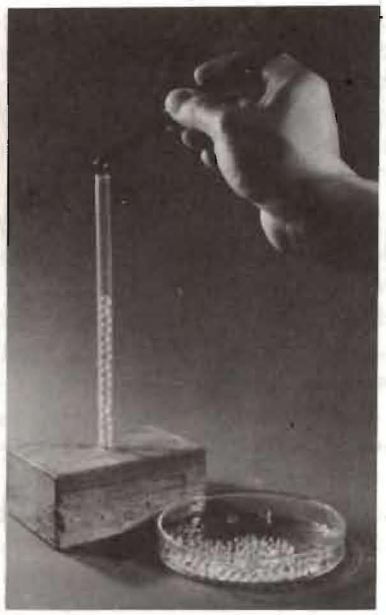

Fig. 4

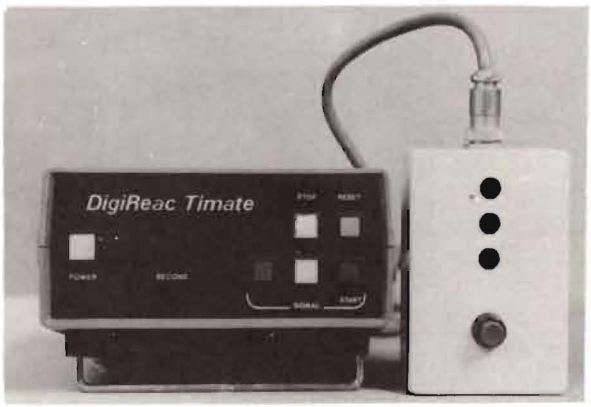

Fig. 5

score changes at 2 and 3 hours and at 1, 2 and 3 hours after oral administration when compared with placebo and mequitazine, respectively.

(ii) *Alertness rating scale:* There was no significant score change at 1, 2 or 3 hours after either placebo or mequitazine administration compared with control values on either the first or the seventh day (Fig. 7).

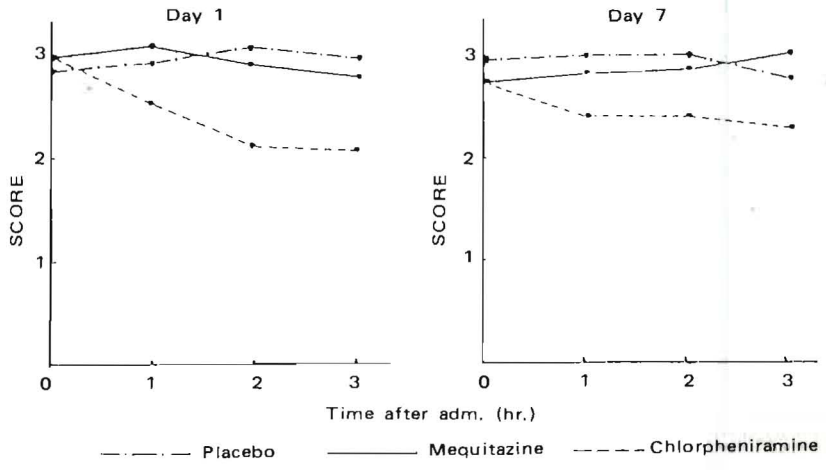

Fig. 6. Effects on the visual analogue scale. (mean)

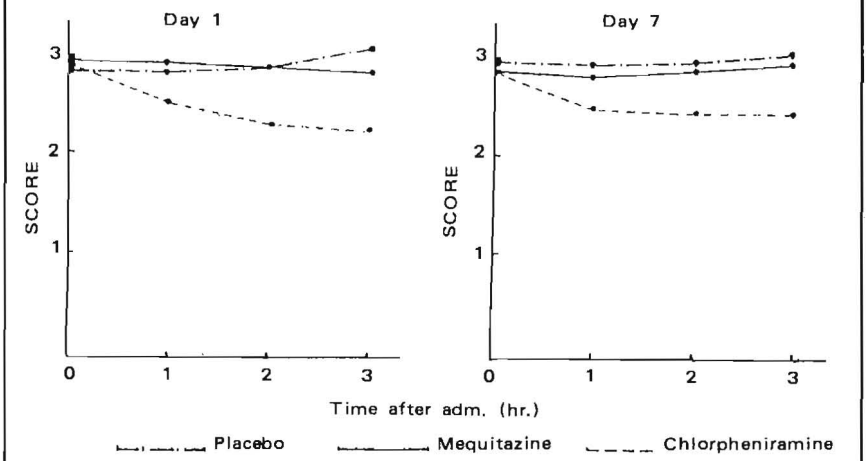

Fig. 7 Effects on the alertness rating scale. (mean)

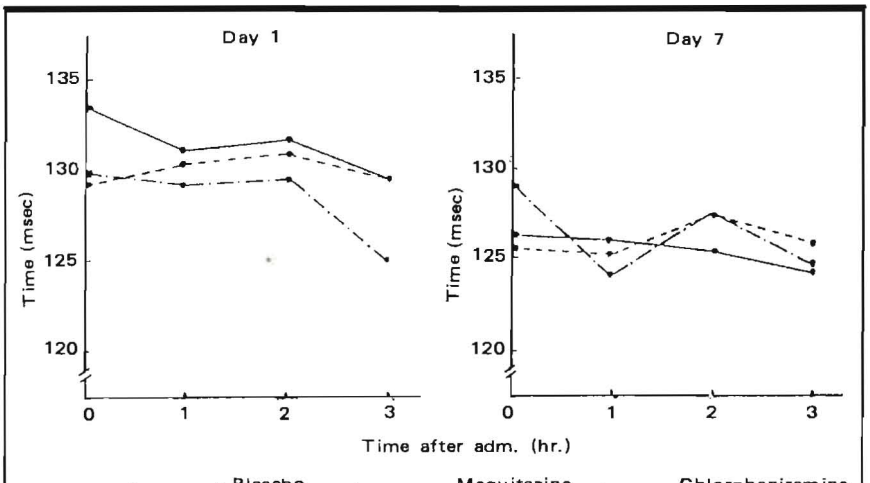

Fig. 8 Effects on the card sorting test. (mean)

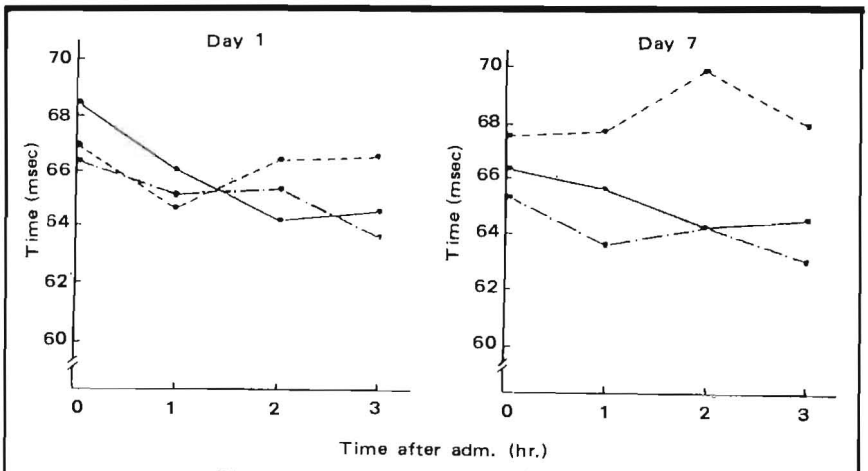

Fig. 9 Effects on the glassbad picking test. (mean)

Significant differences between chlorpheniramine and control scores began to occur at 1 hour after oral administration and persisted up to 3 hours both on the first and seventh days.

There was no significant difference between scores for mequitazine and placebo at 1, 2 and 3 hours on day 1 or day 7. Compared with the placebo, chlorpheniramine caused significant score changes at 2 and 3 hours on day 1; and 1, 2 and 3 hours on day 7. Significant differences between chlorpheniramine and mequitazine were observed at 2 and 3 hours on day 1.

Objective tests

(i) *Card sorting test:* After intake of the placebo, mequitazine and chlorpheniramine on both the first and the seventh day, the time required to sort the cards remained unchanged relative to the control period or when comparing between the drugs and placebo at any period of testing (Fig. 8).

(ii) *Glassbead picking test:* On the first day of drug administration, the times required to perform the test after placebo, mequitazine and chlorpheniramine showed no significant different between each other (Fig. 9). On the seventh day, the same results were obtained after placebo and mequitazine but chlorpheniramine significantly increased the time required in the test at 2 and 3 hours after drug administration.

(iii) *Reaction time test:* Mequitazine did not prolong reaction time relative either to the control period or to the placebo (Fig. 10). Chlorpheniramine, on the other hand, significantly prolonged the reaction time both on day 1 and day 7 in all test periods as compared with both placebo and mequitazine.

DISCUSSION

The results of the two subjective tests used can give only a broad idea of subjects' alertness and wakefulness. One should bear in mind that psy-

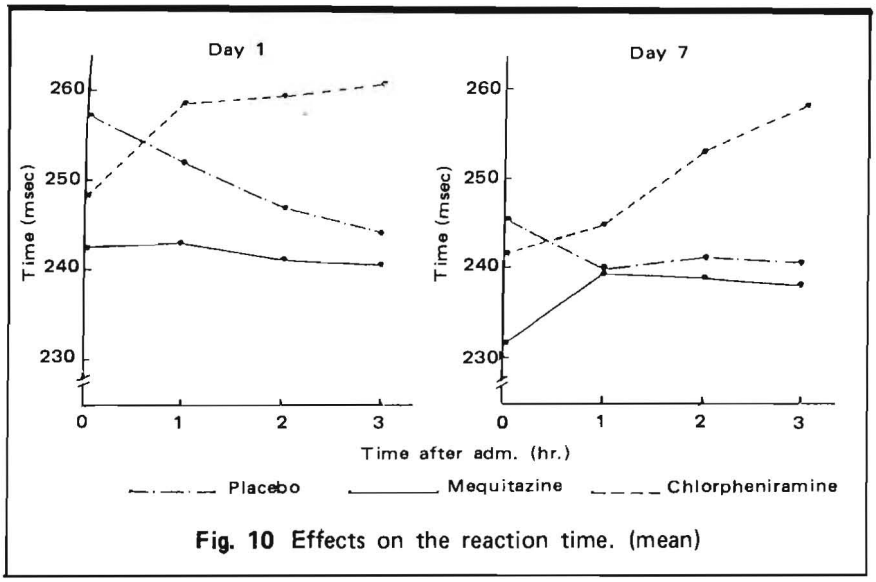

Fig. 10 Effects on the reaction time. (mean)

chological factors can significantly influence these kinds of testing. Therefore more than one method of subjective test is generally employed in order to confirm the result. The visual analogue scale rating seemed to give more accurate and detailed result when compared with the alertness scale rating. These two types of testing were also used to check the results in the same individual. The data indicate that mequitazine did not diminish mental alertness but chlorpheniramine markedly did.

Among the objective tests, the card sorting test assesses the ability of the central nervous system to solve problems and order task elements at the same time. Such performances require both judgement and coordination. A decrease in time at all test periods after drug and placebo intake compared with the control period would be due to a learning effect.

The glassbead picking test constitutes an index of the ability of the central nervous system to concentrate on fine perceptivomotor tasks that require the coordination of sight and touch. On the first day of drug administration the time used for the test after placebo and chlorpheniramine were in fact not significantly shorter than that of the control period. The result could be due to a learning effect on the subjects. After mequitazine administration the time required in this test at 1, 2 and 3 hours was significantly shorter than in the control period. It is possible that mequitazine caused less psychomotor depression than chlorpheniramine or even the placebo.

Responses to external stimuli such as traffic lights are very important for an individual who takes antihistamines. Response delays can cause accidents. The results showed that mequitazine did not prolong the reaction time on either the first day or after the seventh day of drug administration. Mequitazine therefore might be an antihistamine of choice for ambulatory patients who have to perform the tasks such as driving a car or controlling a machine.

Concerning the mechanism underlying the observed sedation with antihistamines, three relevant drug characteristics should be considered: anticholinergic activity, affinity for peripheral versus central receptors, and whether or not it readily crosses the blood-brain barrier. [10] Mequitazine causes less sedative side effects because it hardly crosses the blood-brain barrier and it possess a greater affinity for peripheral receptors. [11]

The results of this study confirmed the findings reported by Nicholson in 1983 that the central effects of antihistamines may vary between drugs, between patients, or within a patient between days. [12]

It can be concluded on the basis of the results of both subjective and objective tests that mequitazine, in an oral therapeutic dose of 5 mg twice a day, did not interfere with the psychomotor performance of healthy Thai volunteers either at the beginning or after a chronic period of treatment for seven days. Chlorpheniramine significant depressed the central nervous system in comparison with both the placebo and mequitazine.

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