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Suppressive Effects of Histamine Skin Reactivity by a Nonsedating Antihistamine-Mequitazine

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SUMMARY **The suppressive activity of mequitazine (MQZ) on histamine skin reactivity was evaluated in 29 healthy subjects (age 22-25 years) in a single-blind study. Fifteen subjects received MQZ, at a dosage of 5 mg BID, for 7 days while 14 served as controls. A prick skin test with saline or histamine hydrochloride (1 mg/ml and 10 mg/ml) was performed in duplicate, on both forearms, starting from the baseline day and continuing for 4 days after medication had been discontinued (total of 11 days). The skin-test subject and the reader was unaware of the randomization process. Mean diameters of wheal and flare as well as the skin index scores (after Voorhost) were used in the analysis. Maximal flare suppression (as compared to the baseline values) was observed on day 6 (97% suppression for 1 mg/ml and 54% suppression for 10 mg/ml, $p < 0.01$). Suppression of wheal size was significant (19% for 1 mg/ml and 28% for 10 mg/ml) but was not clinically relevant. Suppression of skin index scores was maximal on day 6 (71% for 1 mg/ml and 43% for 10 mg/ml, $p < 0.01$). After MQZ had been discontinued, all measurements gradually returned to baseline values and were not different therefrom within 3 days. However, final measurements of wheal and flare were smaller than baseline values (60-94% of baselines). We conclude that MQZ, at the manufacturers's recommended dose of 5 mg BID, significantly suppressed flare size of histamine skin tests and recommend that MQZ be discontinued for at least 3 days prior to performing allergy skin tests.**

Mequitazine (10-3 quinuclidinylmethyl phenothiazine-MQZ, trade name-Primalan, Pharmuka Laboratory, France) is a new nonsedating H-1 specific antihistamine, widely used in Europe for treating a variety of allergic conditions. MQZ has been commercially available in Thailand since 1986. The lack of central nervous system (CNS) side effects has been well documented. [1] Besides its antihistaminic effect, MQZ was also found to possess activities antagonistic to several steps in the process of mast cell mediator release. [2] Clinically, MQZ has been shown to be as effective as conventional antihistamines such as brompheniramine in alleviating allergic symptoms of allergic rhinitis. [3] As compared to other nonsedating antihistamines, MQZ was also found to be as effective as terfenadine [4] and loratidine [5] in its antihistaminic effects.

Despite its accessibility and the knowledge of its pharmacokinetics, [6] few data exist in regard to the pharmacodynamics of MQZ. The primary purpose of this investigation was to determine the length of the interval between the discontinuation of a short term use of MQZ and the time point when one can perform a diagnostic prick skin testing without histamine suppressive effect from MQZ. Data on its pharmacodynamics in healthy volunteers were also presented.

MATERIALS AND METHODS

Subjects

Twenty nine healthy adult volunteers (age range = 22-25 years) from the Faculty of Medicine, Siriraj Hospital were recruited into the study (18 males and 10 females). The protocol was reviewed and approved by the Human Rights Committee of the hospital and a written informed consent was obtained. All subjects were interviewed, were found to be in healthy condition and were not taking any other medications. Fifteen

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subjects (11 males and 4 females, mean age 20.9 years) were randomized to the MQZ group and 14 (8 males and 6 females, mean age 21.8 years) were allocated to serve as controls.

Medications

Mequitazine (Primalan, 5 mg/tablet) was administered to the MQZ group at the manufacturer's recommended dosage of 5 mg BID for 7 days while the control group received no medication during the same period. The skin-test subject and the reader (SJ) were blinded to the randomization process; the study was thus considered a single blind study.

Skin test

Prick skin testing with 1 and 10 mg/ml of histamine hydrochloride solution (prepared from dry powder of histamine hydrochloride, Sigma Laboratory, St. Louis, MO) and saline control solution were carried out in duplicate on both forearms of each subject, daily, between 7 to 8 a.m. each day (to minimize circadian variation in skin reactivity) for a total duration of eleven days (starting from the baseline day, just before the administration of the first dose until 72 hours after the discontinuation of the last dose) as shown in **Fig. 1.** Skin tests were performed with a straight surgical needle size #27 with skin test site placed 5 centimeters apart using a template. All skin tests were read at approximately ten minutes after the prick with a transparent tape technique. In brief, the wheals and flares were outlined with a ball-point pen; these outlines were then transferred to permanent records with transpore tape (3M-Riker, St Paul MN). The largest diameters and their orthogonal diameters (in mm) of wheal and flare were measured and were used in the comparisons. Composite values of wheal and flare or skin index score were computed using formula as described by Voorhost.[7]

Skin index score = ½ [(L + W) wheal + 3.7 + 11.5 log (L + W) flare]

where L (length) and W (width) represent the two diameters measured. Percent suppression of skin test size was defined as the difference between the size measured on a particular day and the baseline size expressed in percentage of the baseline.

Statistics

The comparisons of wheal and flare sizes as well as of skin indices from various days, were made using an analysis of variance with repeated measures (Fisher's exact test) using the StatView 512 + program package (Brain Power, Calabacas, CA) on a MacIntosh-SE computer (Apple Co., Cupertino, California).

RESULTS

The mean diameters of histamine wheals from the MQZ group are shown in **Fig. 2.** Suppression of wheal sizes by MQZ (striped and solid bars) was minimal and was not clinically apparent for 1 mg/ml of

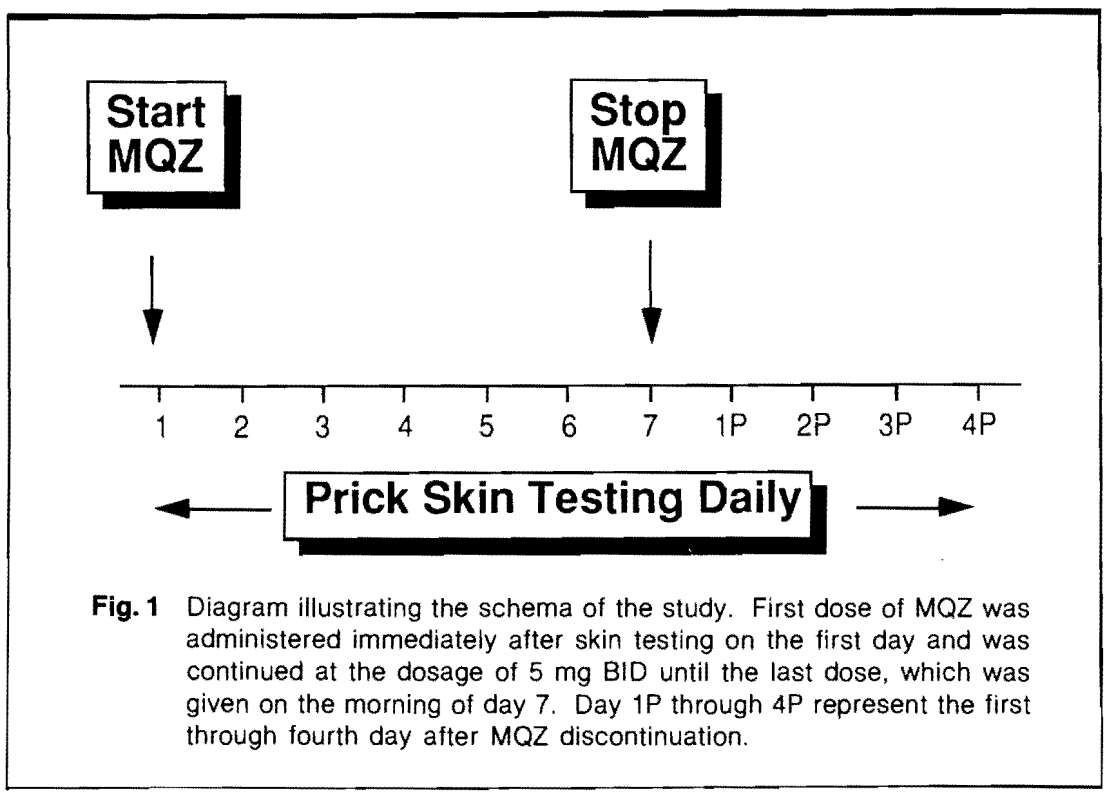

Fig. 1 Diagram illustrating the schema of the study. First dose of MQZ was administered immediately after skin testing on the first day and was continued at the dosage of 5 mg BID until the last dose, which was given on the morning of day 7. Day 1P through 4P represent the first through fourth day after MQZ discontinuation.

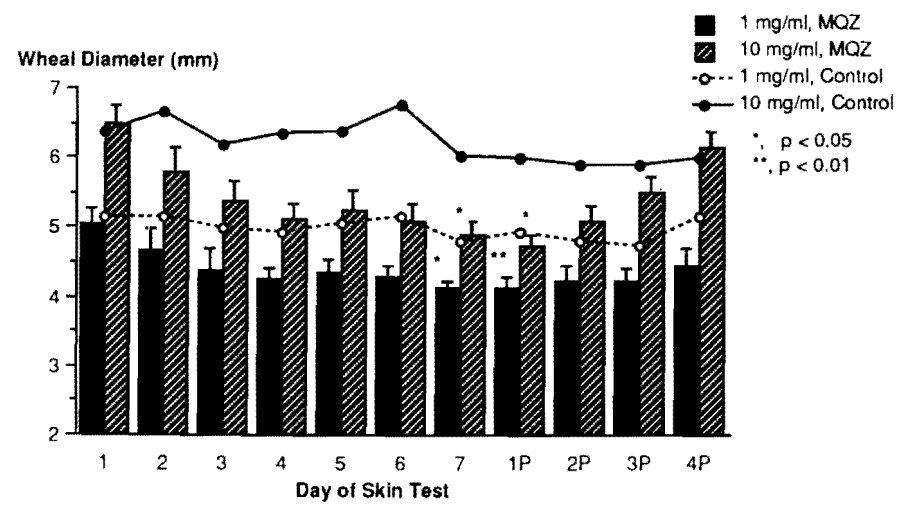

Fig. 2 Suppression of histamine wheal diameters. Measurement of histamine wheals (in mm) from the MQZ group (filled and striped bars) and the control group (solid and broken lines) tested with 1 mg/ml and 10 mg/ml of histamine hydrochloride is shown. Standard error of the means, in the control group, has been omitted for clarity of the illustration. Significance denotes difference from the baseline measurement.

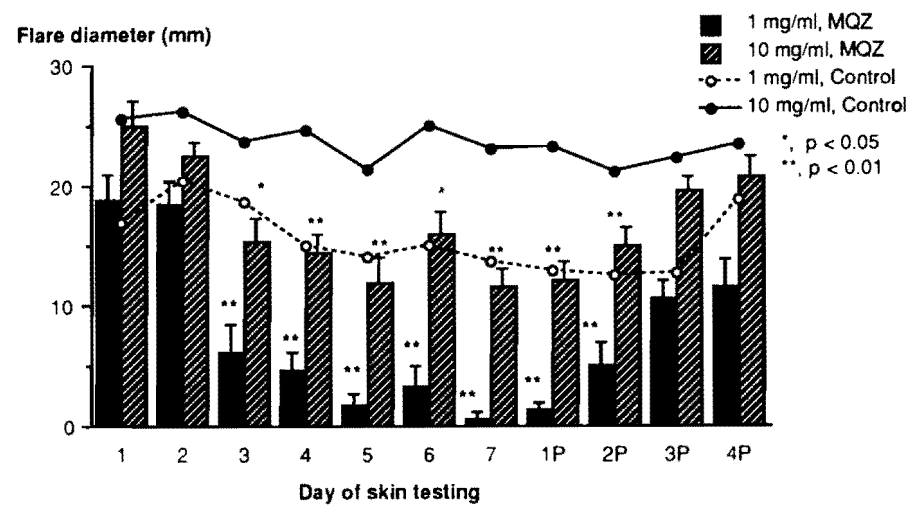

Fig. 3 Suppression of histamine flare diameters. Measurement of histamine flares (in mm) from the MQZ group and the control group tested with 1 mg/ml and 10 mg/ml is shown. Significance denotes difference from the baseline measurements. As in Fig. 2, standard errors of controls are omitted for the purpose of clarity; annotations used are the same as in Fig. 2

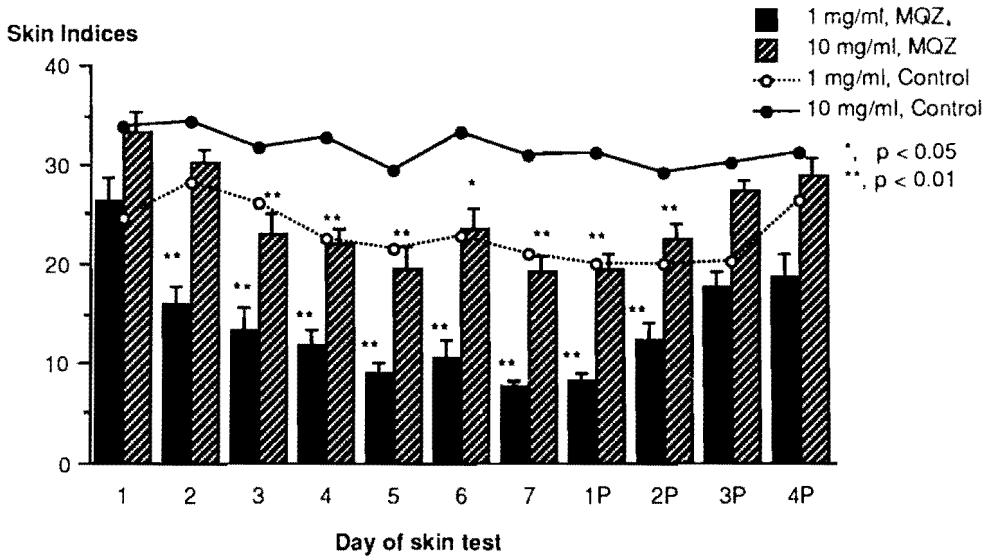

Fig. 4 Skin indices in the MQZ group and the control group. Annotations used are the same as in previous figures. See text for details.

histamine; the differences were just barely appreciable for 10 mg/ml solution. Nevertheless, the differences became statistically significant on day 7 of the medications and for one more day after MQZ had been discontinued. The maximal suppression of wheals observed was 19% and 28% for 1 (day 7) and 10 mg/ml (day 1P) of histamine hydrochloride, respectively. Histamine wheal sizes gradually returned to the baseline values and became insignificant from the baselines on the day 2 after the discontinuation of MQZ. It is to be noted that the final wheal sizes were smaller than the baseline sizes (88% and 94% of baseline for 1 and 10 mg/ml of histamine, respectively). No significant suppression of histamine wheal diameters within the control group was observed. In contrast to wheal measurements, the suppression of histamine flares by MQZ was clearly very perceptible, especially with the 1 mg/ml solution (**Fig. 3**). This suppression occurred gradually over the first three days of MQZ administration and reached the maximum on day 7 for both 1 mg/ml (97% suppression) and 10 mg/ml (54% suppression). After discontinuation of MQZ, flare sizes gradually returned to baseline and became statistically similar to the baseline on the day 3 after stopping the drug ($p > 0.05$). As with histamine wheals, the final sizes of histamine flare (as measured on day 4 after the discontinuation of MQZ) were also smaller than their baseline values (60% and 80% of baseline for 1 mg/ml and 10 mg/ml, respectively). However, these differences were not statistically significant ($p > 0.05$). In the control group, as with wheals, no significant suppression of flares was noted.

The skin indices, representing the composite values for wheal and flare measurements, are shown in **Fig. 4.** Suppression of histamine reactivity gradually occurred during the first three days of MQZ administration and reached the minimum by day 7 (71% and 43% of baseline for 1 mg/ml and 10 mg/ml, respectively). After the discontinuation of MQZ, the skin indices became insignificantly different from the baseline by day 3 ($p > 0.05$) with the final indices being smaller than baseline (70% and 80% of baseline for 1 mg/ml and 10 mg/ml, respectively).

DISCUSSION

MQZ, a nonsedating anti H-1 antihistamine, is a derivative of phenothiazine (10-3 quinuclidinylmethyl phenothiazine). Despite its phenothiazine structure, MQZ has been found to possess low central nervous system (CNS) side effects due to its low affinity with the CNS H-1 receptor rather than poor penetrability of the compound into cerebral tissue.[8] Clinical studies have indicated that the use of MQZ at the recommended dose is not associated with an impairment of visual-motor coordination, nor with digit symbol substitution or dynamic visual activity.[9] Moreover, MQZ has been found to lack anticholinergic effects.[10]

However, it has recently been shown that MQZ could induce EEG changes typical of a subconvulsive state in laboratory animals while loratidine and astemizole lack such

effect.[11] Thus, MQZ is perhaps not completely devoid of CNS effects but, rather, bears a higher therapeutic index in this regard than classic anti-H1 antihistamines. Clinical efficacy of MQZ has been demonstrated in various allergic states such as in perennial rhinitis,[4] seasonal rhinitis[12] as well as in urticarial therapy.[13,14] Hence, MQZ can be considered as an alternative for those who could not tolerate the sedative effects of the classic first generation antihistamines such as chlorpheramine, hydroxyzine, diphenhydramine and the like. In addition, MQZ was found to be equally effective to, if not, more than the more popular nonsedating antihistamine-terfenadine.[4,15] Moreover, repeated administration of MQZ to laboratory animals did not produce drug-induced tolerance as with the chlorpromazine parent compound.[16]

MQZ has been shown to possess anti-allergic properties such as an antagonistic effect to LTD4 on the contraction of isolated lung tissues, an inhibition of histamine release by phospholipase A2, calcium ionophore and an inhibition of cyclic AMP-dependent phosphodiesterase activity.[2] These antagonistic effects of MQZ have been demonstrated in situations such as in the blocking of agonist induced-bronchospasm (histamine, acetylcholine, LTC4) as well as in the blocking of allergen induced-bronchospasm both *in vivo* and *in vitro,*[17] thus, making MQZ very attractive to clinicians who are treating chronic allergic conditions, currently believed to encompass inflammatory mediators as playing central roles in its pathogenesis. LG 30465, a derivative of MQZ, is perhaps an even more interesting compound since its bronchodilator effect was found to be 500 times as effective as MQZ and it is poorly absorbed from the lung when delivered by an aerosol route.[18]

Among the new non-sedating antihistamines, astemizole is taken up by the liver and is released from lysozymes as an active metabolite. Its onset of action is therefore slow and because it is only slowly dissociated from H1 receptor, it also has a prolonged duration of action.[19] Similar to astemizole, it is apparent that suppression of histamine skin reactivity by MQZ gradually occurred over the first three days of therapy and by the end of the study period (day 11) histamine skin reactivity had not returned to the baseline values indicating that MQZ may have high affinity to peripheral H1 receptor and may require several days for its complete dissociation from H1 receptor to occur. Recently, data reported by Ylitalo *et al*[6] have indicated that the elimination half-life of MQZ is exceedingly long (45 ± 26 hours) confirming our contention in this regard. Notwithstanding, at the end of day 3 after the discontinuation MQZ, histamine skin indices were not statistically different from the baseline (although the actual values were smaller); thus, it was considered adequate to delay diagnostic prick skin testing for at least 3 days after discontinuation MQZ. It is possible that with its anti-mediator effects, the suppressive effect of MQZ on antigen-induced wheals and flares could even be more pronounced than on histamine-induced ones. Nonetheless, patterns of suppression of skin reactions from allergen, codeine and histamine by other antiallergic antihistamines were found to be similar for both the time course and the magnitude of suppression.[20,21] At the time of our investigation, reagents which induce mast cell mediator release such as compound 48/80 and codeine phosphae were not available to us. Therefore, this hypothesis was not scrutinized in this investigation but is being investigated in our ongoing research. Our findings that histamine skin suppression by MQZ at 5 mg/kg dose was only 60% of the baseline is similar to that of Malet *et al.*[22] Nevertheless, these findings can not be generalized to other nonsedating anti-H1 agents such as to loratidine and cetirazine since their different metabolic pathways may be responsible to the difference in their onset and duration of action.[5,23-25]

It is to be noted that most of the studies in this field have utilized intradermal skin test techniques rather than prick skin tests as used in our study. The finding that anti-H1 antihistamine suppresses wheals to a lesser degree than flares is intriguing to us. This finding has been previously observed but has never been emphasized with prick techniques[24] or with intradermal techniques.[26] This phenomenon is of clinical importance since several atopic patients, such as those with atopic dermatitis, react to prick skin tests in this manner (residual wheal with no flare). Nonetheless, taken into account with both flares and wheals, delaying the time of skin test performance for at least three or more days after the stopping of MQZ would be adequate not to interfere with the interpretation of the histamine skin reactivity.

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