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Mequitazine and dexchlorpheniramine in perennial rhinitis. A double-blind cross-over placebo-controlled study

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SUMMARY

The therapeutic effect and adverse reactions of two antihistamines, mequitazine and dexchlorpheniramine were double-blindly compared both to placebo, to each other and to the pre-treatment status in 29 adult patients suffering from perennial rhinitis. Dexchlorpheniramine relieved the rhinitis symptoms significantly ($p < 0.01$) better compared to placebo while mequitazine did not differ from placebo. 20 out of 29 patients chose dexchlorpheniramine as their favourite drug. Dexchlorpheniramine reduced all the separate symptoms studied (obstruction, rhinorrhoea, sneezing) significantly, mequitazine relieving merely rhinorrhoea. In anterior rhinoscopy mucosal congestion was reduced both by dexhlorpheniramine ($p < 0.01$) and by mequitazine ($p < 0.05$) but secretion or lividity showed no difference between the active drugs and placebo. The occurrence of side-effects was not significantly different between the drugs. In controlling perennial rhinitis symptoms mequitazine was markedly inferior to dexchlorpheniramine and only slightly better than placebo.

INTRODUCTION

Antihistamine compounds have been a widely used remedy in controlling the symptoms of allergic and vasomotor rhinitis for decades. The main drawback of the conventional H_1 antagonistic drugs has been the central effects especially drowsiness. Therefore increasing efforts have been focused on the developing of antihistamines without sedation. One of these novel compounds is mequitazine ((quinuclidinyl-3-methyl)-10-phenothiazine). The absence of the central effects

of these drugs has been explained by their difficulty in crossing the blood-brain barrier and by the greater affinity for peripheral than for central H_1-receptors (Nicholson, 1979).

The aim of this study was to compare the efficacy of mequitazine and dexchlorpheniramine against placebo in controlling the symptoms of patients with perennial rhinitis.

MATERIAL AND METHODS

The study population consisted of 29 patients (13 males and 16 females) suffering from perennial rhinitis, seen in the Out-Patient Department of Otolaryngology at the Tampere University Central Hospital, Tampere, Finland in 1984–1986. The enrollment of the patients based primarily on anamnestic and clinical criteria of rhinitis, but also skin-prick tests were performed on 22 patients; 19 showed positive reactions, house dust being the most common allergen (Table 1). The age of the patients ranged from 17 to 54 years, the mean age being 30.1 years. The patients were allowed to have no prostatahypertrophy, arrhythmias, endocrinological diseases, glaucoma or psychiatric diseases neither to be gravid. Those who used corticosteroids, asthma medicines, cromoglycate or other medication for rhinitis were also excluded.

The setting of the study was double-blind cross-over, the patients acting as their own controls. The patients were given mequitazine 5 mg (Mircol®), dexchlor-

Table 1. Results of skin-prick tests of 19 patients.

allergen	number of patients with positive reactions
house dust	13
feather mix	1
sheep wool	1
horse	1
cow	2
dog	1
cat	1
birch	2
alder	3
willow	2
dandelion	1
chrysanthemum	4
mugwort	5
timothy	5
alopecurus	2
kentucky blue	2
meadow fescue	2
candida albicans	2
aspergillus	1

pheniramine prolongatum 6 mg (Polaramine®) or placebo distributed by Pharmacal Ltd. twice daily each for a 4-week period. The patients seen in the Out-Patient Department were enrolled into the study in consecutive order, the drugs were coded and the sequence of them was randomized in advance by a computer. The patients visited the study clinic every fourth week when the drugs were changed, according to the randomization list. The total study period was 12 weeks. Though the drugs were commercial tablets, the appearance of the non-transparent bottles were identical so neither the patient nor the study personnel knew which one of the three coded compounds the patient received in the beginning of each treatment period. The patients recorded the efficacy of the drug on their nasal symptoms (obstruction, rhinorrhoea, sneezing) by the daily diary cards over the last week of each treatment period using scores 0–4 (0 = no effect, 1 = slight effect, 2 = moderate effect, 4 = completely symptom free). During the follow-up visits the diary card symptom scores of the previous week were discussed and gone through by the study doctor and this confirmed symptom status was the basis for the subjective efficacy analysis. Anterior rhinoscopy was performed by an ENT specialist at every visit evaluating nasal secretion, mucosal swelling and lividity by 0–3 scale (0 = no, 1 = mild, 2 = moderate, 3 = severe).

The possible adverse reactions with special emphasis put on drowsiness were checked from the diary cards and confirmed by the study doctor in discussion with the patient in each follow-up visit. For safety control the blood tests including routine haematology, common liver enzymes, serum electrolytes and creatinine as well as urine sugar and albumin were carried out every time. During the last visit the drug code was broken, but before that the patients were asked to choose their overall favourite of these drugs in controlling of rhinitis symptoms and the occurrence of the side effects.

The crude statistical analyses of the efficacy of the drugs were made by using the Kruskal-Wallis one way analysis of variance by ranks applied to four groups (pretreatment - mequitazine - dexchlorpheniramine - placebo) or three groups (mequitazine - dexchlorpheniramine - placebo). The pairwise comparison was made using the Wilcoxon rank sum test.

RESULTS

Overall efficiency

The patients' opinions of the overall efficacy of the drugs in controlling their symptoms are shown in Table 2. Comparisons between the two antihistamines and placebo showed that dexchlorpheniramine was more effective compared to placebo ($p < 0.01$) and also better than mequitazine ($p < 0.05$). No difference was found between the mequitazine and placebo in controlling the rhinitis symptoms. 20 out of 29 patients chose dexchlorpheniramine as their favourite drug ($p < 0.01$) (Table 3).

Table 2. The patients' opinions of the overall efficacy of different treatments.

	number of patients				
	no effect	slight effect	moderate effect	good effect	completely symptom free
mequitazine	9	8	6	1	5
dexchlorpheniramine	5	5	5	5	9
placebo	8	9	9	3	0

Table 3. The patients' favourite ranking of the different treatment in controlling their symptoms.

mequitazine	5	
dexchlorpheniramine	20	$p<0.01$
placebo	3	
no opinion	1	

Nasal symptoms

The degree of separate symptoms (obstruction of the nose, rhinorrhoea and sneezing bouts) were compared after every 4-week-treatment period (the last week's scores in the diary card). No significant difference in any symptom scores between mequitazine and the pre-treatment visit neither between placebo and pre-treatment scores were found. On the contrary dexchlorpheniramine reduced obstruction ($p<0.05$) and sneezing ($p<0.05$) compared to the pre-treatment status (Table 4). Both the antihistamines reduced rhinorrhoea, dexchlorpheniramine however more effectively ($p<0.01$) than mequitazine ($p<0.05$), compared to placebo. Furthermore dexchlorpheniramine relieved sneezing ($p<0.01$) and blockage of the nose ($p<0.05$) compared to placebo, mequitazine showing no difference from placebo.

Anterior rhinoscopy

No difference in the amount of nasal secretion or in the lividity of the turbinates between the drugs compared to each other or to placebo was shown. Both the active drugs decreased the mucosal swelling compared to placebo: dexchlorpheniramine more effectively ($p<0.01$) than mequitazine ($p<0.05$) (Table 5).

Adverse reactions

In regard to the occurrence of drowsiness the two active drugs were very similar: approximately 50% of the patients did not suffer from drowsiness while using either mequitazine or dexchlorpheniramine (Table 6). Because of drowsiness two patients had to discontinue mequitazine and one dexchlorpheniramine

Table 4. Nasal symptoms during the different treatments.

symptom	number of patients according to severity of symptom			
	no	mild	moderate	severe
obstruction				
pretreatment visit	1	10	13	5
mequitazine	5	7	14	3
dexchlorpheniramine	11	6	9	3
placebo	3	10	11	5
rhinorrhoea				
pretreatment	7	13	5	4
mequitazine	11	11	4	3
dexchlorpheniramine	12	9	7	1
placebo	6	8	11	4
sneezing				
pretreatment	12	7	6	4
mequitazine	15	7	5	2
dexchlorpheniramine	20	7	1	1
placebo	10	11	7	1

Table 5. Anterior rhinoscopy observations during the different visits

	number of patients according to degree of disorder															
	no				mild				moderate				severe			
	pre	mq	dx	pl	pre	mq	dx	pl	pre	mq	dx	pl	pre	mq	dx	pl
secretion:																
- watery	10	11	11	8	11	9	11	9	5	5	5	8	2	2	1	2
- purulent	26	25	24	23			1	2			1	4				
obstruction	1	7	6	6	14	14	18	10	10	3	4	11	3	4	1	1
lividity of mucous membranes	11	11	17	15	13	11	5	9	4	4	5	4			1	
swollenness of mucous membranes	4	7	8	4	9	8	9	9	10	9	10	13	5	3	1	11

pre = before treatments
mq = after mequitazine treatment
dx = after dexchlorpheniramine treatment
pl = after placebo treatment

Table 6. Diurnal drowsiness during the different treatment periods.

degree of drowsiness	mequitazine	dexchlorpheniramine	placebo
none	14	15	21
slight	8	9	5
moderate	4	2	3
severe	1	2	0
requiring cessation of the treatment	2	1	0

treatment. On the other hand 27% of the patients experienced more or less drowsiness also when receiving placebo, but it did not cause any cessations. No individual patient suffered from noticeable drowsiness during all of these three treatment periods. Other adverse reactions were much more infrequent, accounting 37% for mequitazine and 24% for dexchlorpheniramine. The most common complaints were dryness of the mouth, gastrointestinal disorders and dizziness (Table 7). There were, however, no significant differences between the drugs in the occurrence of these adverse reactions.

No significant changes were found in blood or urine laboratory test results after the use of active drugs or placebo compared to those of the pre-treatment visit.

Table 7. Other adverse reactions during the different treatment periods.

adverse reaction	mequitazine	dexchlorpheniramine	placebo
dryness of the mouth	4	4	0
dizziness	0	1	1
nausea	1	0	2
diarrhoea	1	0	1
other	5	2	0

DISCUSSION

Antihistamines are one of the most important and probably the most commonly used group of drugs in controlling various allergic symptoms. Untoward side effects especially drowsiness of most oral H_1 antagonists have indicated the searching and developing of new compounds with anti-allergic properties. The best known and widely used compounds in the category of newer non-sedating antihistamines are terfenadine and astemizole. Mequitazine is one alternative among these new non-sedative antihistamines. The pharmacodynamic properties of mequitazine looked fairly promising. It is absorbed reasonably quickly after oral ingestion and its half-life time, 38–45 hours (Nicholson, 1983; Ylitalo et al., 1989) goes between terfenadine and astemizole being long enough, however, to allow twice-daily dosage (Blamoutier 1978; Ylitalo et al., 1989), but the elimination of the drug is not dangerously slow in the case of severe adverse reactions (Nicholson, 1983). In this respect the novel compound looks theoretically acceptable. The antihistaminic drugs are known to have a greater effect on sneezing and rhinorrhoea than on nasal obstruction, which is the main symptom of perennial rhinitis due to vasomotor imbalance. These points might compromise the suitability of H_1 receptor antagonists in the treatment of perennial rhinitis. The number of patients suffering from this disorder, however, is great and no superior remedy exists for the moment. That is why we regarded relevant to study the effect of a new antihistamine also in perennial rhinitis. Furthermore, the seasonal symptoms are much more studied concerning any anti-allergic drug.

There are some clinical reports suggesting mequitazine to have a fairly good H_1 antagonistic effect compared to conventional antihistamines, and the side effects especially diurnal drowsiness not significantly differing from those of placebo (Gervais et al., 1975; Blamoutier, 1978; Laugier and Orusco, 1978). The result of the present study differed strikingly from the previous reports with the same dose of 10 mg mequitazine per day indicating only a modest therapeutic effect with adverse reactions similar to dexchlorpheniramine, the "classic" H_1 antagonist we used as a reference drug. One reason for this poor therapeutic effect might be that though mequitazine is absorbed reasonably well from the gastrointestinal tract, relatively low concentration of effective unconjugated drug is found in serum, but the most of drug seems to be deactivated by the extrarenal route (Ylitalo et al., 1989).

Clinical trials are subjected to many biasing factors and various aspects might affect the results. As far as we know the present study is the only published one in which a cross-over technique is used thus eliminating the possible bias from the patient selection between the different treatment groups. Our trial lasted for over two years and the drugs were changed in randomized order so we think the bias originating from the alteration in the atmospheric pollen levels is very small. In the cross-over technique the carry-over effect of the previous drug must be taken into account. We tried to avoid this bias by assessing the symptom scores only during the last week of each 4-week treatment periods thus allowing a three-week wash-out period for the previous drug. Furthermore, the active treatment in most of the previous published trials have lasted for not longer than a few weeks which might be a rather short time to give a real picture about the clinical efficacy of a drug (Gervais et al., 1975; Laugier and Orusco, 1978; Muler and Blum 1978). The more unfavourable effect of mequitazine in the present study can partly be explained by the differences in the patient selection. Our patients suffered mainly from merely rhinitis as the only symptom (only 25% of them had other atopic manifestations) while most of the previous studies – though possessing a double-blind setting – had mixed all the allergic symptoms (rhinitis/sinusitis, asthma, eczema, urticara) together (Blamoutier, 1978; Muler and Blum, 1978; Dry et al., 1980; Vialatte and Paupe, 1982).

One might claim that antihistamines in general act the better the more evident the allergic origin of the disorder. Perennial rhinitis symptoms are also caused by vasomotoric, autonomic and other non-allergic phenomena. In our patients dexchlorpheniramine, however, worked as expected relieving the symptoms compared both to the pre-treatment situation as well as to placebo. The majority of our patients chose dexchlorpheniramine as their favourite drug, while mequitazine was not better than placebo in this respect. Though this was patients' subjective opinion and though rhinoscopy could not find distinct differences between the drugs it seems quite obvious that at least with these dosages mequitazine does not offer major benefits in the treatment of perennial rhinitis compared to dexchlorpheniramine.

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