

A comparison of topical mequitazine and disodium cromoglycate in allergic conjunctivitis induced by a specific conjunctival provocation test

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PURPOSE. *Twenty-two people with a history of grass pollen allergic conjunctivitis were enrolled outside the pollen season in this study to compare the efficacy of 0.05% mequitazine eyedrops with topical 2% disodium cromoglycate.*

METHODS. *This randomized, double-blind study compared right and left eyes. Subjects received 2% disodium cromoglycate eyedrops in one eye and mequitazine vehicle in the fellow eye 4 times daily for 4 days. For the last instillation, mequitazine vehicle was replaced by one drop of 0.05% mequitazine and 15 min later a conjunctival provocation test (CPT) with grass pollen was performed.*

RESULTS. *The sum of the scores for hyperemia and itching, and total composite score were lower after 0.05% mequitazine than after 2% disodium cromoglycate ($p < 0.0001$ in each case). The allergen threshold dose which elicited a positive allergic response was higher in the mequitazine group ($p < 0.001$). Both treatments showed good tolerance upon instillation. No adverse events related to study treatment occurred.*

CONCLUSIONS. *These results demonstrate the superior efficacy of a single drop of 0.05% mequitazine 15 min before CPT compared with 2% disodium cromoglycate 4 times daily for 4 days. (Eur J Ophthalmol 2000; 10: 15-21)*

KEY WORDS: *Allergic conjunctivitis, Conjunctival provocation test (CPT), Disodium cromoglycate, Mequitazine*

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INTRODUCTION

Seasonal allergic conjunctivitis is a common ocular disease, mediated by IgE, whose typical clinical manifestations include conjunctival hyperemia, itching, tearing and eyelid edema. Histamine and H1-receptors play a central role in its pathogenesis (1).

The most widely prescribed treatments for allergic conjunctivitis are mast-cell stabilizers and antihistamines. Topical mast-cell stabilizers, such as disodi-

um cromoglycate, have been used for many years, but have the disadvantage of requiring frequent instillations throughout the day; furthermore, for maximal efficacy, they should preferably be started a few days before exposure to pollen (2,3). Oral antihistamines provide a highly effective treatment for allergic conjunctivitis, but on account of their absorption time the onset of action is slower than with topical H1-blockers (4).

Mequitazine is a widely-studied H1-selective anti-

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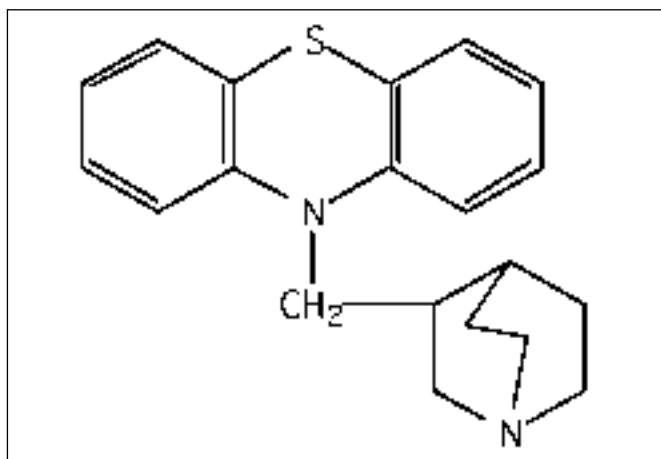


Fig. 1 - Mequitazine: chemical structure.

histamine, prescribed to both adults and children for the treatment of seasonal rhinoconjunctivitis (5). Until recently, it was only available for oral administration. The addition of 1% cyclodextrins as excipient has now enabled an ophthalmic formulation of 0.05% mequitazine to be developed (6). The first studies with the new ophthalmic formulation confirmed the pharmacological efficacy and speed of action in conjunctival provocation tests (CPT) with allergens, versus placebo (6,7). CPT using allergens provide a sensitive and reproducible means of assessing treatments in controlled conditions, in contrast to environmental studies where the allergen contact varies diurnally and from day to day. They are now the method of reference for the evaluation of anti-allergic therapies (8-10).

To assess the efficacy in CPT with grass pollen of two topical eyedrops with 0.01% benzalkonium chloride, 0.05% mequitazine and 2% disodium cromoglycate, a double-masked comparative trial was conducted outside the pollen season in allergic volunteers.

METHODS

The study was a randomized, double-masked design with intraindividual comparison (right and left eye). It was performed at a single centre during October and November, outside the grass pollen season. The protocol was approved by the Ethics Committee of Nîmes (France) and the study was conducted according to Good Clinical Practice. All subjects gave written informed consent.

PATIENTS

Volunteers of either sex, aged between 18 and 45 years, were enrolled in the study. They had to have a history of allergic conjunctivitis induced by grass pollen (at least two episodes), with a positive skin prick test to grass pollen and/or serum-specific IgE \geq class 3. In addition, a selection visit CPT (described below) done between 4 and 15 days before the study had to be positive for allergenic orchard grass concentrations <100 RI/ml, and examination of both eyes (described below) was to be normal on days D1, D4 and D8 (objective score ≤ 0.5 with hyperemia ≤ 0.5 , and subjective score = 0, with itching = 0).

The main exclusion criteria were any active ocular or systemic disease, particularly inflammation, sequelae of corneal lesions, contact lens use in the seven days preceding or during the trial, and history of allergy or intolerance to the study products. The following drugs were prohibited: desensitization started within the three months before the study; astemizole less than one and a half months before the study; antidepressants, antihistamines, ketotifen and oral anti-inflammatory medication within the 15 days before the study; and topical eye preparations in the seven days before inclusion and during the study. Oral treatments, except anti-inflammatory, anti-allergic and anti-cholinergic drugs, were authorised during the trial if necessary.

After the selection visit, at which a CPT was performed in order to determine the reactivity threshold, three further visits were scheduled during the study: on days D1, D4 and D8.

On D1, a baseline examination was done comprising an interview (medical history and concomitant treatment), and an ophthalmic examination to check the selection criteria prior to inclusion. A bilateral CPT was then performed, starting with the concentration corresponding to the reactivity threshold defined at the selection CPT. The aim was to establish the reference concentration to be used on D8, at the end of the period of treatment. The CPT method is described below. Subjective and objective ophthalmic scores were assessed 5 min after the CPT.

On D4, the subjective and objective ophthalmic scores were evaluated to ensure the absence of ocular inflammation before allocation to double-masked treatment. Subjects then instilled one drop of 2% di-sodium cromoglycate in one eye and one drop of

mequitazine vehicle in the other eye as follows: D4: one drop in the evening; D5-D7: one drop four times daily; D8: one drop at 8:00 am and 12 noon. The eye which received 0.05% mequitazine (or vehicle) and 2% disodium cromoglycate was defined by prior randomisation. Subjects had been taught how to instil the eye-drops before the first dose of study treatment.

On D8, after checking the absence of ocular inflammation by evaluating the subjective and objective scores, the sixteenth and final drop was administered by a physician. One drop of 2% disodium cromoglycate was instilled in the pre-treated eye and one drop of 0.05% mequitazine in the eye having received the vehicle. Fifteen minutes later the CPT was carried out and the subjective and objective ophthalmic scores were assessed 5 min later. In the absence of a positive reaction in one eye, characterised by hyperemia or itching <2, the next higher allergen concentration was instilled in the less reactive eye; the positive threshold for each eye could thus be specified.

Ophthalmic scores

Ophthalmic examination was done on D1 before and 5 min after the CPT, on D4 before treatment allocation, and on D8 before and 5 min after the CPT. Four subjective symptoms (stinging, burning, itching and photophobia) were assessed by interview, and four objective signs (conjunctival hyperemia, conjunctival edema, eyelid edema and tearing) by slit-lamp examination. Each sign or symptom was graded as follows: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Intermediate grading was allowed. The composite score of Abelson was defined as the sum of the scores for hyperemia, itching, tearing and conjunctival edema.

Conjunctival provocation test

The CPT method used was based on that of Möller (9) with the modifications described by Abelson et al (10). A standardised extract of freeze-dried grass pollen (orchard grass) was reconstituted at the time of the test (Stallergènes SA, Fresnes, France). Seven concentrations were prepared by serial dilution 1:3 and expressed in terms of Reactivity Index (0.10, 0.33, 1, 3.3, 10, 33, and 100 RI/ml). On D1, the CPT was conducted starting with the concentration corresponding to the reactivity limit defined during the selection

CPT. Allergenic solution (20 µl) was instilled using a micropipette into the right and left lower conjunctival cul-de-sac. Ophthalmological parameters, hyperemia and itching, were recorded 5 min after instillation. The D1 CPT threshold concentration was achieved when hyperemia affected 50% or more (or grade 2) of the conjunctival surface, and at least moderate itching was observed. In the absence of reactivity after 10 min, the next highest concentration was instilled. The concentration threshold was obtained after instillation of increasing concentrations every 10 min.

Assessment of safety

All adverse events were recorded. Local tolerance was assessed on D8, immediately after the last instillation, and measured using a 100-mm long horizontal Visual Analogue Scale (VAS). Subjects drew a vertical line between the two extremes of "very well tolerated" (0 mm) and "very poorly tolerated" (100 mm), according to the sensation experienced. The type of discomfort and its duration were specified during the interview.

Statistical methods

Subjective and objective scores in the two groups at baseline (after the CPT on D1), efficacy criteria and subjective tolerability (VAS) were analysed using a non-parametric test on paired series (Wilcoxon). The software was SAS version 6.12 on IBM PC.

RESULTS

Demography and baseline characteristics

Of the 24 subjects screened for the study, 22 were randomized and completed the study, 14 males and 8 females, their mean age was 27.7 years (20-42). An investigation on allergy had been carried out and was positive in all subjects (Tab. I): all had a positive prick test to orchard grass, so specific IgE assay was not justified. No concomitant medication was being taken at inclusion, apart from oral contraception by four. The selection CPT 8 to 15 days before the inclusion visit was positive for all subjects. No subjective symptoms (stinging, burning, itching or photophobia) were

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TABLE I - MAIN DETAILS OF ALLERGIES

Duration of allergic conjunctivitis (years)	
Mean \pm SD	15.4 \pm 6.8
Range	3 - 29
<i>Other associated allergic diseases</i>	<i>% of patients</i>
Rhinitis	100.0
Asthma	36.4
Eczema	13.6
<i>Allergic exploration</i>	<i>% of patients</i>
Positive prick test	100.0

TABLE II - ABELSON SCORE AT D1 AFTER CPT

	Eye receiving 2% disodium cromoglycate	Eye receiving 0.05% mequitazine
No.	22	22
Mean	6.66	6.66
SD	0.99	1.04
Median	6.75	6.50
Range	5-8.5	5-8.5

observed at the inclusion visit (D1) before the CPT. Very mild bilateral hyperemia (grade 0.5) was reported by five subjects. For both eyes, a punctate intake of fluorescein of less than five points was observed. The distance visual acuity was 10/10 e (Monoyer scale) for 91%. The baseline ocular examination was thus in the normal range for all subjects.

A bilateral CPT was performed at the D1 visit to establish the threshold allergen concentration to be used for the CPT on D8. All subjects gave a response to the CPT, with hyperemia ≥ 2 and itching ≥ 2 (Tab. II). There was no difference between the two treatment groups in the subjective and objective ophthalmic scores 5 min after the CPT on D1. In both groups, the median (range) subjective score was 5.5 (2.0-8.0), and the median (range) objective score was 5.5 (3.0-7.0).

The subjective and objective ophthalmic scores on D4, before the first instillation of study treatment, were 0 in all subjects except one. This volunteer had an objective score of 0.5, due to very mild conjunctival hyperemia of grade 0.5 in both eyes.

After four days of treatment, just before the CPT on D8, the subjective score was 0 for all subjects. The objective score was 0 for all except five subjects, who presented very mild bilateral conjunctival hyperemia, grade 0.5. The comparability of the two treatment groups before the CPT was therefore satisfactory.

Compliance to treatment during the study was good, with no instillations omitted.

Efficacy

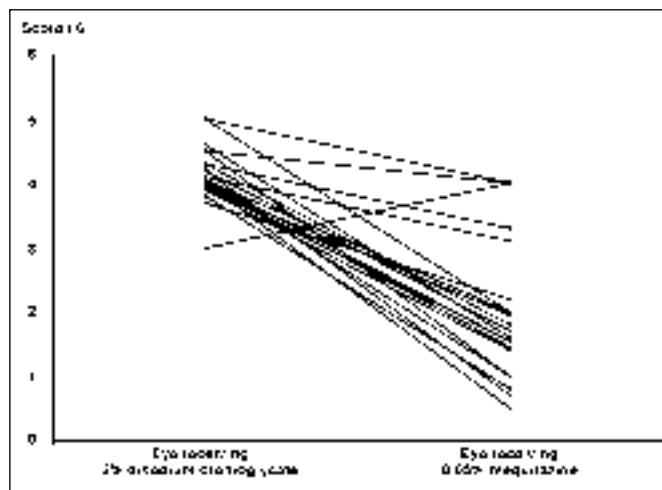
Efficacy was evaluated on D8 using the sum of the conjunctival hyperemia and itching scores, and Abelson's composite score after CPT (using the allergen concentration which induced a positive reaction at the inclusion visit).

The sum of the conjunctival hyperemia and itching scores for each subject at CPT is described in Figure 2. Even at the highest allergen concentration (100 RI/ml), one subject did not give a positive reaction (hyperemia ≥ 2) in either eye, and was therefore not taken into account in analysis of the score of signs and symptoms. The median (range) score was 4.0 (3.0-5.0) in the disodium cromoglycate group and 1.5 (0.5-4.0) in the mequitazine group. There was a significant difference between groups ($p < 0.0001$).

The composite score of Abelson (the sum of the scores for conjunctival hyperemia, itching, tearing and conjunctival edema) is shown in Figure 3. The median (range) composite score was 5.5 (4.5-8.5) in the disodium cromoglycate group and 2.5 (0.5-6.5) in the mequitazine group. This score was also significantly higher in the disodium cromoglycate group ($p < 0.0001$).

The median (range) overall subjective score at the positive CPT was significantly higher ($p < 0.0001$) in the disodium cromoglycate group (5.0, range 2.5-8.0) than in the mequitazine group (2.0, range 0.0-5.0). In terms of individual subjective symptoms, stinging, burning and itching were all significantly more marked in the disodium cromoglycate group than in the mequitazine group ($p < 0.0001$ for stinging and itching; $p < 0.002$ for burning). Photophobia was absent or mild in the majority of subjects, with no noteworthy difference between treatments.

The median (range) overall objective score at the positive CPT was 4.0 (2.5-6.5) in the disodium cromoglycate group and 2.5 (0.5-4.5) in the mequitazine



p<0.0001	2% disodium cromoglycate	0.05% mequitazine
Mean	4.12	1.95
SD	0.41	1.08
Median	4.0	1.5

Fig. 2 - Sum of hyperemia and itching scores per patient after CPT.

group. Hyperemia, conjunctival edema and eyelid edema, and the overall objective score, were significantly more marked in the disodium cromoglycate group than in the mequitazine group ($p < 0.0001$, $p < 0.0004$, $p < 0.002$ and $p < 0.0001$ respectively). There was no difference in tearing.

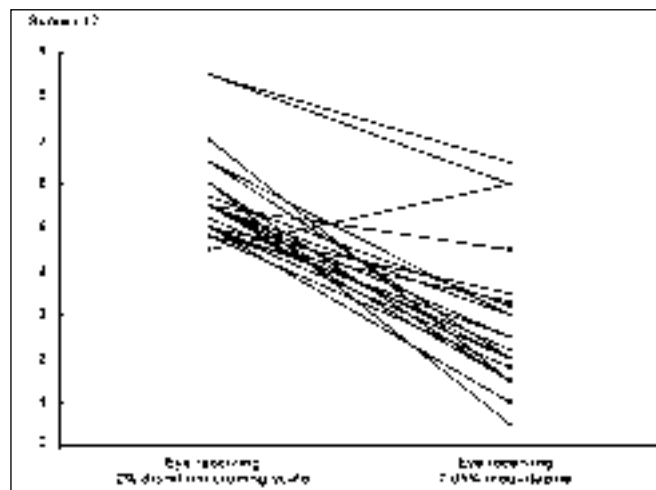
Threshold allergen concentration

In the absence of a positive reaction in one eye, the next higher allergen concentration was instilled in the same eye to measure the threshold concentration for this treatment group. The threshold allergen concentration was not available for six eyes (four after mequitazine and one after both mequitazine and disodium cromoglycate) because no positive reaction was observed even at the highest concentration of the CPT (100 RI/ml).

The threshold of the positive CPT was significantly higher in the mequitazine group than the disodium cromoglycate group ($p < 0.001$) (Fig. 4).

Safety

The local tolerability on instillation, evaluated using a 100-mm VAS, was good for both treatments. The



p<0.0001	2% disodium cromoglycate	0.05% mequitazine
Mean	5.78	2.86
SD	1.09	1.66
Median	5.5	2.5

Fig. 3 - Abelson's composite score per patient after CPT.

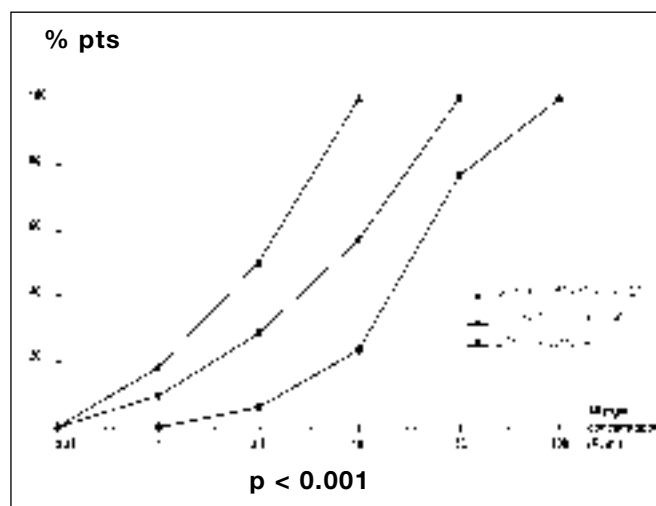


Fig. 4 - Threshold concentrations. Cumulative percentage of patients responding to increasing allergen concentrations.

median score was 5.5 for 2% disodium cromoglycate and 7.5 for 0.05% mequitazine, with no difference between the two groups.

Mild discomfort was felt by 50% of the subjects, similar in the two groups; this was essentially mild burning or a foreign body sensation, and resolved within an average of one minute.

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No serious adverse events were reported. Four subjects experienced one minor adverse event but the relationship to the test treatments was excluded.

DISCUSSION

The specific CPT used in this study is a widely-used method that reproduces, in controlled conditions, a clinical picture similar to that provoked by natural exposure to an allergen.

For maximal efficacy, the reference drug, 2% disodium cromoglycate, should be administered several times a day (10). In the present study, the 2% disodium cromoglycate eyedrops were therefore instilled four times daily for four days before testing. Therefore, a single drop of mequitazine was significantly more effective in reducing signs and symptoms than repeated instillations of 2% disodium cromoglycate.

The use of the fellow eye as control was justified by the fact that bilateral ocular challenges with the same dose of allergen induce a symmetrical allergic reaction during selection CPT (11,12). Although the possibility of systemic passage of each drug into the contralateral eye could not be excluded, its effect would have been to reduce the difference between the two treatments.

The sum of the scores for hyperemia and itching, and the composite score after the first positive CPT were significantly lower in the eyes treated with 0.05% mequitazine ($p < 0.0001$). In addition, the allergen threshold concentration was significantly higher after 0.05% mequitazine than after 2% disodium cromoglycate. These data confirm previous results showing the superiority of one drop of an H1-receptor antagonist over disodium cromoglycate, administered for 14 days before the provocation test (13).

Mequitazine is a potent and selective histamine H1-antagonist with no sedative effect in humans. It is a phenonazine derivative with a saturated heterocyclic ring in its side chain which almost prevents its metabolism. This chemical structure explains the prolonged anti-histaminic action and the lack of neurological side effects.

It has also been reported as having a direct action on mast cells (14). A comparison with cromolyn sodium was conducted in a pharmacological experiment, assessing histamine release from mast cells and in-

tracellular C^{2+} release induced by bradykinin which were inhibited by antiallergic drugs, similar to the effects of substance P and compound 48/80.

Mequitazine caused potent inhibition of both responses, whereas cromolyn sodium was weaker. The clinical data reported are in accordance with this difference. Moreover, mequitazine has a long duration of action similar to levocabastine (15).

Apart from a little transient ocular discomfort after instillation, similar in both groups, no serious adverse events were reported. Local irritation after instillation was evaluated using a 100-mm VAS. The median score was 5.5 for disodium cromoglycate and 7.5 for mequitazine, which suggest that both drugs are well tolerated. As reported for levocabastine (13), mequitazine not only controls itching, but also hyperemia, which could be due to a collateral mechanism effecting mast cells.

In conclusion, 0.05% mequitazine eyedrops were well tolerated, with rapid onset of action and significantly superior efficacy to topical 2% disodium cromoglycate. Mequitazine eyedrops therefore appear to offer a useful alternative to topical mast cell stabilizers in the treatment of allergic conjunctivitis.

This protocol was accepted by the French Ethics Committee (CCPPRB) in Nimes, on 15 September 1997.

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