

Onset and Duration of Action of Ketotifen 0.025% and Emedastine 0.05% in Seasonal Allergic Conjunctivitis

Efficacy after Repeated Pollen Challenges in the Vienna Challenge Chamber

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Abstract

Objective: To compare the efficacy, onset and duration of action, and the safety of ketotifen fumarate 0.025% ophthalmic solution and emedastine difumarate 0.05% ophthalmic solution in subjects with seasonal allergic conjunctivitis (SAC) induced by allergen exposure, using the Vienna Challenge Chamber model.

Design and setting: This was a double-masked, randomised, comparative, cross-over study conducted at an allergy outpatient clinic in Austria.

Study participants: Subjects with an allergy to grass pollen were exposed to the allergen in a pollen chamber for 4 hours, followed by a 3-hour break and then a second exposure for 3 hours.

Interventions: Study participants were randomised to a treatment sequence (ketotifen followed by emedastine or emedastine followed by ketotifen), receiving 1 drop per eye of ketotifen or emedastine 2 hours after the initial allergen exposure in the pollen chamber.

Outcomes: Individual and composite ocular, individual and composite nasal, and total (ocular + nasal) symptom complex scores were determined by repeated exposure to allergen 0–2 hours and 5–8 hours after dosing. Onset of action was defined as the time to the first observation of a 20% reduction from baseline in the composite ocular symptom score.

Results: All 37 subjects enrolled completed the study. The median time to onset of action was 15 minutes for ketotifen and 30 minutes for emedastine. This difference was significant using the generalised linear model ($p = 0.048$), but not for the log-rank test analysis. In the initial 2 hours post dose, ketotifen provided significantly greater relief of both composite ocular symptoms ($p = 0.026$) and total symptom complex ($p = 0.014$). Both medications were effective in reducing symptoms 5 to 8 hours after dosing. No adverse events were reported for either treatment.

Conclusions: In the Vienna Challenge Chamber model, ketotifen and emedastine both effectively alleviated ocular symptoms of SAC after single-dose administration. Ketotifen had a faster onset of action and provided better symptom relief than

emedastine during the first 2 hours after dosing. The rapid onset of action and symptom control make ketotifen a valuable treatment for SAC.

Allergic conjunctivitis affects approximately 5–22% of the general population,^[1] with the most common form being seasonal allergic conjunctivitis (SAC). The key ocular signs and symptoms of SAC are itching, tearing and hyperaemia, which usually occur in both eyes and are often associated with nasal or pharyngeal symptoms.^[2] Although SAC does not usually lead to visual impairment, the symptoms may adversely impact an individual's daily activities and quality of life.^[3]

Ocular symptoms associated with SAC occur when pollen dissolves in the tear film and then crosses the conjunctiva.^[4] The interaction of the pollen with IgE and the subsequent cross-linking of IgE receptors on mast cells result in mast cell degranulation and release of mediators.^[5] These mediators include histamine, which induces an inflammatory response via interaction with histamine H₁ receptors.^[5] In the late phase, eosinophils infiltrate the conjunctiva and contribute to the inflammatory process, resulting in prolonged signs and symptoms.^[2]

Ketotifen, a benzocycloheptathiophene derivative, has been used for many years in the treatment of patients with asthma. It exhibits potent histamine H₁-receptor antagonist activity,^[6] inhibits mast cell degranulation,^[6] and decreases chemotaxis, activation and degranulation of eosinophils.^[7] Ketotifen fumarate ophthalmic solution (Zaditen®/Zaditor™, Novartis Ophthalmics, Bülach, Switzerland)¹, is a treatment developed for alleviating the ocular signs and symptoms of SAC. The multiple pharmacological effects of ketotifen may contribute to its anti-allergy properties,^[6] raising the possibility that ketotifen could offer therapeutic advantages over existing treatments for SAC. Recent placebo-controlled clinical trials demonstrated that ketotifen fumarate 0.025% ophthalmic solution was efficacious and safe, providing a rapid onset and

long duration of action^[8] as well as a tolerability profile comparable to placebo.^[9]

In this study, the efficacy, onset and duration of action, and the safety of ketotifen fumarate 0.025% ophthalmic solution were compared with emedastine difumarate 0.05% ophthalmic solution (Emadine™, Alcon Laboratories, Fort Worth, TX, USA), a potent, highly selective histamine H₁-receptor antagonist,^[10] in individuals with SAC induced by grass pollen exposure, using the Vienna Challenge Chamber (VCC) model.^[11]

Study Participants and Methods

Subjects

Eligible subjects were 19–45 years of age, of either gender and any race, with a history of SAC of at least 2 years, presenting without symptoms. Subjects were required to have a positive skin-prick test to the grass pollen allergen used in the chamber; a SAC composite ocular symptom score ≥ 4 (table I) after 2 hours of pollen exposure (composite ocular score defined as the sum of the four individual ocular symptom scores), and clinical laboratory tests within normal limits. Women of childbearing potential had to have a negative urine pregnancy test and

Table I. Scoring system for ocular^a and nasal^b signs and symptoms

Grade	Description
0 = none	No sign or symptom evident
1 = mild	Sign or symptom clearly present but minimal awareness; easily tolerated
2 = moderate	Definite awareness of sign or symptom; bothersome but tolerable
3 = severe	Sign or symptom hard to tolerate; causes interference with planned activities during the challenge session
a	Ocular symptoms included itching, tearing, redness, and foreign-body sensation.
b	Nasal symptoms included runny nose, blocked nose, sneezing, and itchy nose.

1 The use of tradenames is for product identification only and does not imply endorsement.

use an acceptable method of birth control during the study period.

Exclusion criteria were: allergy to antihistamines or more than two different classes of medication (excluding antibiotics); known non-response to antiallergics; frequent sinusitis or chronic purulent postnasal drip; any ocular condition that could interfere with study evaluation (e.g. narrow-angle glaucoma, blepharitis); ocular surgery within the 2 months before the study; known history of retinal disease; active bacterial or viral ocular infection; upper or lower respiratory tract infection that required antibiotics within 4 weeks of screening; history of emotional or intellectual problems that could affect the validity of consent to participate in the study; use of any investigational drug in the 30 days before screening; hepatic insufficiency; or renal failure.

Medications prohibited before and during the trial included: corticosteroids; mast cell stabilisers; antihistamines; leukotriene antagonists; sympathomimetic bronchodilators; systemic antibiotics; immunotherapy; decongestants; herbal preparations or alternative therapies with proven efficacy in allergic rhinitis or conjunctivitis; nasal saline; ipratropium or atropine; eye washes/drops; ophthalmic non-steroidal anti-inflammatory drugs; tricyclic or tetracyclic antidepressants; and investigational medications. The washout period for these medications varied from 12 hours (for eye washes or nasal saline) to 90 days (for intramuscular or intra-articular corticosteroids).

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from each subject in advance.

Study Medications

Study medications consisted of ketotifen fumarate 0.025% ophthalmic solution (Zaditen®/Zaditor™) and emedastine difumarate 0.05% ophthalmic solution (Emadine™). All trial medication was provided in identical bottles to facilitate a double-masked study design.

The study did not include a placebo control since the recent amendment to the Declaration of Helsinki (Clause 29) recommends that medications are tested against a currently available treatment and not against a placebo control, except where there is no effective treatment available.^[11] The choice of emedastine as a control was based on the knowledge that it is one of the most potent histamine H₁-receptor antagonists available for topical ocular use.^[10,12-15]

Study Design and Procedures

This was a single-centre, double-masked, randomised, comparative, crossover study conducted out of the grass pollen season with outpatients using the VCC model.^[16] The VCC is a sealed chamber with a 12-person capacity. The VCC maintains a constant humidity, temperature and allergen load. Grass pollen grains were circulated throughout the chamber at a stable concentration of 1500 pollen grains/m³, which is consistent with that found in the Austrian countryside on a warm summer's day. The VCC provides a controlled environment where the efficacy and safety of antiallergic medications can be accurately assessed. The chamber complies with the recommendation for specific challenge rooms of the Subcommittee on Bronchoprovocation of Occupational Asthma.^[17]

The study involved three visits: a screening visit and two treatment visits (visits 1 and 2). The interval between the screening visit and visit 1 was less than 21 days. Treatment visits were separated with a washout period of at least 6 days.

Screening visit: At the screening visit, medical and medication histories and inclusion/exclusion criteria were reviewed. A brief physical examination was performed and informed consent obtained. A skin test to confirm hypersensitivity to common grass pollen (*Dactylis glomerata*) was conducted unless already performed within the prior 12 months. Prohibited medications were reviewed with the subjects and discontinued for an appropriate washout period and throughout the duration of the study. Subjects meeting the enrolment criteria were scheduled for the treatment visits.

Visit 1 – treatment visit: At visit 1, eligible subjects were randomised to one of two treatment sequences (ketotifen followed by emedastine or emedastine followed by ketotifen) according to a computer-generated randomisation list (program IDV, Gauting, Germany). A baseline slit-lamp examination was done, a digital image of both conjunctivas was recorded, and baseline symptom scores were assessed. Subjects were then exposed to grass pollen in a pollen chamber for 2 hours (a period judged long enough to reach maximal symptom level). Subjects rated the severity of their individual symptoms every 15 minutes via a personal computer connected to a data bank to provide prompt calculations of their total symptom severity scores. Following the first 2-hour exposure (just prior to dosing), a second digital image of the conjunctivas was recorded. A single topical dose (1 drop in each eye) of ketotifen fumarate 0.025% or emedastine difumarate 0.05% was then administered by the investigator. The subjects remained in the pollen chamber for another 2 hours and continued to rate the severity of their individual symptoms every 15 minutes via personal computer. Two hours post dose, i.e. after 4 hours of allergen exposure, a third digital image of the conjunctivas was recorded. Subjects were then allowed to leave the chamber for a 3-hour break. Thereafter (5 hours post dose), subjects re-entered the challenge chamber for an additional 3-hour pollen exposure in order to investigate the duration of action of the study medications. Individual symptom scores were recorded every 15 minutes via the personal computer. At the end of the pollen chamber session (8 hours post dose), a final digital image of the conjunctivas was recorded and a final slit-lamp examination was performed to evaluate conjunctival irritation and oedema. An appointment was scheduled for visit 2.

Visit 2 – treatment visit: At visit 2, medical and medication histories were reviewed. Subjects were queried regarding the presence and severity of any adverse events. Subjects then underwent challenge 2. Assessments proceeded exactly as described in visit 1 with the exception that subjects were crossed over to the other medication.

Outcome Measures

Subjects evaluated their signs and symptoms (ocular: itching, tearing, redness and foreign-body sensation; nasal: runny nose, blocked nose, sneezing and itchy nose) every 15 minutes for 10 hours from the start of the challenge (except during the 3-hour break) at visits 1 and 2. The severity of each individual sign and symptom was graded on a 4-point scale (table I).

Digital imaging was used to evaluate the conjunctival vascular reaction to pollen. The change in optical density of the red portion of the total image was used to measure the clinical response of conjunctival redness to allergen challenge. Imaging was performed at the following times: prior to entering the pollen chamber (baseline), just prior to dosing, and at 2, 5 and 8 hours post dose.

The primary efficacy variable was the time to onset of action, defined as the first time interval in which at least a 20% reduction in the baseline 'composite ocular symptom score' (defined as the sum of the four ocular symptom scores for itching, tearing, redness and foreign-body sensation) was achieved in the first 2 hours after drug instillation.

The secondary efficacy variables included the areas under the curves (AUCs) for individual symptom scores, the composite ocular and composite nasal symptom scores, and the total (ocular + nasal) symptom complex score for the intervals 0–2 hours (AUC₀₋₂) and 5–8 hours (AUC₅₋₈) after dosing. The uncorrected AUCs were calculated using the trapezoidal method for individual symptom scores. The composite ocular and nasal symptom scores were derived from the individual symptom scores, while the total symptom complex score was derived from the sum of the two composite scores. A lower uncorrected AUC value indicated a better outcome. Symptom relief scores were calculated as differences between the baseline symptom score (defined as the symptom assessment just before administration of treatment) and each of the post-dose scores. The AUCs of the symptom-relief scores over time allowed a baseline-corrected comparison of efficacy, in which a larger AUC value indicated better symptom relief.

Safety was assessed at every visit by evaluation of slit-lamp biomicroscopy examinations and vital sign readings, as well as by tabulation of ocular and non-ocular adverse event reports.

Statistical Analysis

A sample size of 30 subjects was calculated to produce a 95% confidence interval with a lower limit exceeding 50%, assuming that the observed percentage of subjects exhibiting relief within 60 minutes was at least 70%.

The Kaplan-Meier technique was used to describe the time-to-onset distribution of the two treatments, with the planned observation times as the time intervals. The time-to-onset distributions were compared between the two treatment groups, using a log-rank test and a general linear means model. The log-rank test was to be used to test the primary efficacy variable. This test is most sensitive to late differences in two curves. To examine early differences in the curves, a confirmatory post-hoc analysis was performed with a generalised linear model, assuming a gamma distribution with a log-link function. The Wilcoxon-signed rank test was used to analyse the differences between the AUCs of the individual symptoms, composite symptoms, and the total symptom complex for the two treatments as well as the digital imaging data. No correction was made for multiple statistical comparisons.

SAS® version 8 was used for statistical analyses. For non-parametric tests not available in SAS®, SPSS® was used.

Results

Forty-one subjects were screened for the study and 37 were randomised to treatment. All 37 subjects completed the study; 49% received ketotifen then emedastine, and 51% received emedastine then ketotifen. Subject demographics are shown in table II.

Primary Efficacy Variable

The median time to onset of action was 15 minutes for ketotifen versus 30 minutes for emedastine.

Table II. Subject baseline demographics

Characteristic	Subjects
Total subjects (n)	37
Gender [n (%)]	
Female	18 (48.6)
Male	19 (51.4)
Race [n (%)]	
Caucasian	36 (97.3)
Black	1 (2.7)
Age (y)	
Mean ($\pm$ SD)	27.30 ($\pm$ 4.8)
Range	20-43
Iris colour [n (%)]	
Blue	6 (16.2)
Brown	23 (62.2)
Green	4 (10.8)
Grey	2 (5.4)
Blue-grey	1 (2.7)
Brown-green	1 (2.7)

Onset of action was defined as the first time interval in which at least a 20% decrease in the composite ocular symptom score occurred during the first 2 hours of the dosing session. At each post-dose time-point, more subjects receiving ketotifen had 20% or more symptom reduction than those receiving emedastine (figure 1).

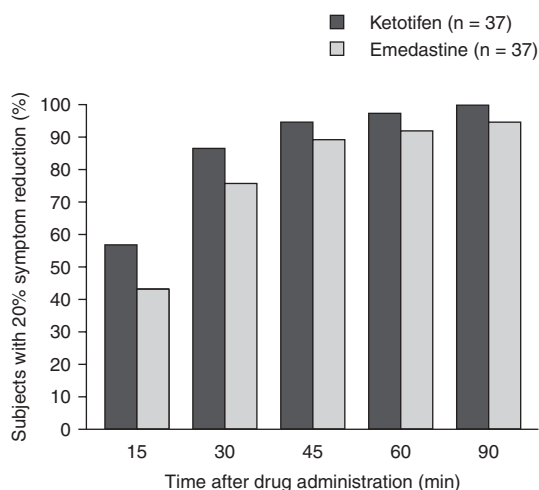


Fig. 1. Onset of action (time to first observation of 20% reduction from baseline in composite ocular symptom score) by treatment group and number of subjects.

Table III. Ocular and nasal symptom scores: 0–2 hours post dose

Symptom	Area under the curve (AUC) ^a [uncorrected (mean ± SD)]		p-Value
	ketotifen (n = 37)	emedastine (n = 37)	
Itchy eyes	2.46 ± 1.04	2.63 ± 1.12	0.262
Tearing	1.31 ± 0.94	1.40 ± 1.18	0.727
Redness	1.97 ± 1.10	2.25 ± 0.87	0.046
Foreign-body sensation	1.59 ± 1.17	1.62 ± 1.28	0.961
Ocular symptoms	7.34 ± 3.11	7.90 ± 3.32	0.232
Runny nose	3.87 ± 1.10	3.98 ± 1.19	0.583
Blocked nose	3.29 ± 1.45	3.56 ± 1.45	0.221
Sneezing	3.35 ± 1.32	3.47 ± 1.42	0.484
Itchy nose	3.76 ± 1.43	3.75 ± 1.41	0.844
Nasal symptoms	14.27 ± 3.99	14.76 ± 4.12	0.248
Total symptom complex	21.61 ± 5.63	22.66 ± 6.55	0.103

a A lower AUC value for symptom scores indicates a better outcome.

Analyses of the time to onset distribution (figure 1) using the generalised linear model, which is sensitive to early differences in the curves, showed ketotifen to be statistically superior to emedastine ($p = 0.048$). Analyses using a log-rank test analysis, sensitive to late differences between the curves, found the difference in time to onset was not statistically significant ($p = 0.117$).

Secondary Efficacy Variables

Analyses of the AUCs for the (uncorrected) symptom scores and for the (baseline-corrected) symptom relief scores for the 0- to 2-hour post-dose interval showed ketotifen to be statistically superior to emedastine for the uncorrected redness score ($p = 0.046$) and the symptom relief scores for ocular symptoms ($p = 0.026$) and total (ocular + nasal) symptom complex ($p = 0.014$) [table III and table IV]. Ketotifen was found to be numerically better than emedastine for all other individual and composite mean scores, with the exception of the itchy nose symptom score (table III and table IV). Analyses of the AUCs for the symptom scores and the symptom relief scores for the 5- to 8-hour post-dose interval (table V and table VI) showed a similar trend, with ketotifen being numerically superior to emedastine for most parameters, although the results did not reach statistical significance.

Analysis of the mean composite ocular symptom scores versus time showed ketotifen to have a faster

onset of action in the relief of ocular symptoms (0–2 hours post dose; figure 2). Both medications were effective in reducing symptoms 5–8 hours after dose administration (figure 2). Digital imaging techniques did not reveal any significant differences in conjunctival redness between treatments.

Safety

No adverse events were reported during or after the study, and there were no clinically relevant abnormalities in slit-lamp examinations or vital signs for either treatment group.

Discussion

The VCC model is a controlled method for studying environmental exposure to allergens, which accurately represents the natural environment.^[16,17] It has been used extensively to compare the efficacy of medications in seasonal and perennial allergic rhinitis. Recent studies have also shown the model to be a valuable method for investigating the efficacy of ocular medications in the prevention and treatment of SAC.^[18,19]

In the current study using the VCC model, ketotifen was found to have a faster onset of action than emedastine and to provide better symptom relief during the initial 2 hours post dose. In terms of efficacy, ketotifen was numerically superior to emedastine for the majority of the individual symptom scores, the composite scores and the total symp-

Table IV. Ocular and nasal symptom relief scores: 0–2 hours post dose

Symptom	Area under the curve (AUC) ^a [baseline-corrected (mean ± SD)]		p-Value
	ketotifen (n = 37)	emedastine (n = 37)	
Itchy eyes	2.62 ± 0.96	2.19 ± 1.31	0.086
Tearing	1.71 ± 0.86	1.41 ± 0.93	0.091
Redness	1.54 ± 0.92	1.37 ± 1.08	0.401
Foreign-body sensation	2.19 ± 1.19	2.00 ± 1.23	0.371
Ocular symptoms	8.06 ± 2.46	6.97 ± 3.19	0.026
Runny nose	0.67 ± 0.83	0.51 ± 1.05	0.542
Blocked nose	0.44 ± 0.90	0.33 ± 0.92	0.918
Sneezing	0.81 ± 0.95	0.74 ± 1.00	0.638
Itchy nose	0.94 ± 1.11	0.63 ± 0.97	0.232
Nasal symptoms	2.86 ± 2.37	2.21 ± 2.72	0.074
Total symptom complex	10.93 ± 3.53	9.18 ± 4.77	0.014

a A higher AUC value for symptom relief scores indicates a better outcome.

tom complex scores during the first 2 hours post dose. For several secondary efficacy variables including ocular redness, composite ocular and total (ocular + nasal) symptoms 0–2 hours after dosing, ketotifen was statistically superior to emedastine. Both medications demonstrated a sustained effect of at least 8 hours. Ketotifen and emedastine were safe and well tolerated, with no adverse events reported.

Allergic signs and symptoms impair the quality of life of the patient with allergy. Topical medications offer multiple therapeutic advantages over systemic products, including a rapid onset of action and minimal systemic adverse effects. New multiple-action agents like ketotifen have pharmacological mechanisms that include an antihistaminergic effect

to provide immediate relief and additional effects to act on the mediators of the late phase reaction. Differences in efficacy between ketotifen and emedastine may be a result of their pharmacological mechanisms. Ketotifen has been shown to be a potent histamine H₁-receptor antagonist as well as a mast cell stabiliser, thereby preventing degranulation and release of mediators that trigger the inflammatory response.^[6] In addition, *in vitro*^[7] and animal studies^[20,21] have shown that ketotifen inhibits the activation and chemotaxis of eosinophils into the conjunctiva, which is an important step in the late phase of the immune response. Studies with emedastine have shown it to only be a potent high-affinity histamine H₁-receptor antagonist.^[10]

Table V. Ocular and nasal symptom scores: 5–8 hours post dose

Symptom	Area under the curve (AUC) ^a [uncorrected (mean ± SD)]		p-Value
	ketotifen (n = 37)	emedastine (n = 37)	
Itchy eyes	3.56 ± 1.88	3.62 ± 1.82	0.823
Tearing	1.52 ± 1.61	1.44 ± 1.44	0.385
Redness	2.25 ± 1.45	2.62 ± 1.59	0.171
Foreign-body sensation	2.01 ± 2.07	2.03 ± 2.18	0.746
Ocular symptoms	9.34 ± 5.65	9.70 ± 5.36	0.774
Runny nose	5.20 ± 2.00	5.51 ± 1.86	0.447
Blocked nose	4.85 ± 2.25	5.08 ± 2.30	0.572
Sneezing	4.86 ± 1.95	4.61 ± 2.14	0.334
Itchy nose	5.31 ± 1.89	5.23 ± 1.97	0.392
Nasal symptoms	20.22 ± 6.33	20.44 ± 6.30	0.883
Total symptom complex	29.56 ± 10.13	30.14 ± 9.12	0.937

a A lower AUC value for symptom scores indicates a better outcome.

Table VI. Ocular and nasal symptom relief scores: 5–8 hours post dose

Symptom	Area under the curve (AUC) ^a [baseline-corrected (mean $\pm$ SD)]		p-Value
	ketotifen (n = 37)	emedastine (n = 37)	
Itchy eyes	4.06 $\pm$ 2.12	3.60 $\pm$ 2.12	0.228
Tearing	3.02 $\pm$ 2.00	2.78 $\pm$ 1.89	0.447
Redness	3.02 $\pm$ 1.96	2.81 $\pm$ 2.29	0.778
Foreign-body sensation	3.67 $\pm$ 2.15	3.41 $\pm$ 2.06	0.874
Ocular symptoms	13.77 $\pm$ 6.03	12.59 $\pm$ 6.32	0.284
Runny nose	1.61 $\pm$ 1.89	1.22 $\pm$ 2.14	0.617
Blocked nose	0.75 $\pm$ 1.74	0.75 $\pm$ 1.83	0.994
Sneezing	1.38 $\pm$ 1.45	1.72 $\pm$ 2.04	0.322
Itchy nose	1.74 $\pm$ 1.74	1.33 $\pm$ 1.88	0.232
Nasal symptoms	5.84 $\pm$ 4.65	5.02 $\pm$ 5.65	0.700
Total symptom complex	19.25 $\pm$ 8.48	17.61 $\pm$ 9.37	0.382

a A higher AUC value for symptom relief scores indicates a better outcome.

The rapid onset of action observed in this study was confirmed by a recent study comparing the onset of action of ketotifen with emedastine.^[22] In that study using the conjunctival provocation test, the onset of action was within 5 minutes for both

ketotifen and emedastine. No significant differences were found between the two medications, although both were significantly better than the placebo control.

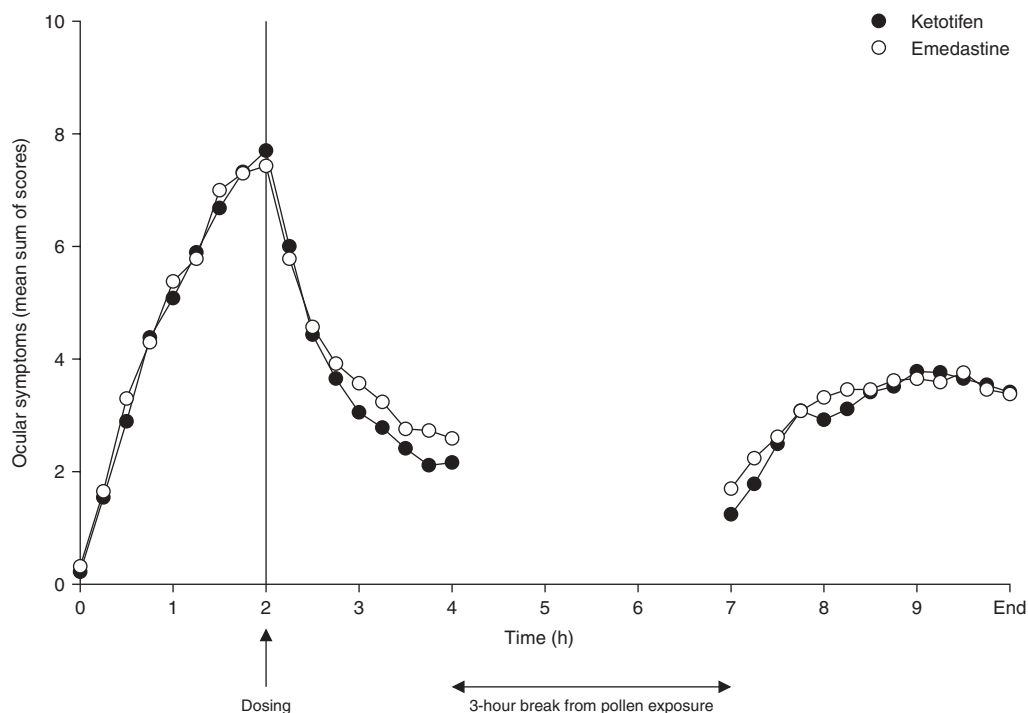


Fig. 2. Change in mean composite ocular symptom scores over time. Dose administration occurred after 2 hours of allergen exposure, and there was a 3-hour break from allergen exposure between 2 and 5 hours after dosing.

Conclusion

In the VCC model, ketotifen fumarate 0.025% and emedastine difumarate 0.05% both effectively alleviated ocular symptoms of SAC for a period of at least 8 hours after single-dose administration. The faster onset of action and better symptom relief observed with ketotifen during the initial 2 hours post dose, along with the favourable safety and tolerability profile, make ketotifen a valuable treatment option for patients with allergic conjunctivitis.

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