

Effect of terfenadine and placebo on symptoms after nasal allergen provocation

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Summary

Terfenadine (60 mg b.i.d.) was compared with placebo in a randomized, double-blind, cross-over study in twenty-three patients with birch pollen allergy. The patients were treated during two 7-day periods separated by a 2-week wash-out period during a season free from birch pollen. Nasal provocations with birch pollen extracts were made at study entry and after each treatment period. Blockage (rhinomanometry), secretion (weight) and sneezings (number) were compared between treatments. The results showed a significant inhibitory effect of terfenadine on secretion and sneezing, but no significant difference between treatments with regard to blockage. Terfenadine showed no signs of sedative properties or inhibition of salivation.

Introduction

Antihistamines, or histamine H₁-receptor antagonists, have for many years been regarded as first-line therapy in treating allergic disorders [1], although their clinical value may be limited by anti-cholinergic and sedative actions [2,3]. Good symptomatic relief without these side-effects is achieved with topically applied drugs, e.g. cromoglycate and corticosteroids [4,5]. However, the more general symptoms of the nasal allergic response such as itching in the mouth and pharynx, fever chills and malaise, may not always be adequately managed by the topical drugs, but usually respond favourably to systemic antihistamines.

The aim of this investigation was to evaluate the effect of one of the new non-sedative H₁-blockers, terfenadine [6], on allergen induced nasal symptoms. The

allergen chosen was birch pollen, a common cause of allergic rhinitis during early summer in the Scandinavian countries.

Subjects and methods

Study design

The trial was carried out as a randomized, double-blind, cross-over study during a period without birch pollination (January–March). The effect of placebo and terfenadine on symptoms caused by nasal birch pollen provocation was compared in patients with verified allergy.

At study entry an optimal response to provocation was established. After a recovery period of 2 weeks, the patients were treated with terfenadine (60 mg b.i.d.) or matching placebo (b.i.d.) during two 7-day periods, separated by a 2-week wash-out and recovery period. Nasal provocations were made after each treatment period, approximately 2 hr after the last dose was taken.

Patients

Twenty-six patients with a positive response to nasal provocation with birch pollen were accepted. Patients were not entered if significant nasal pathology was present. No other treatment likely to affect nasal symptoms was permitted.

Three patients were excluded from the study. Two of them had a common cold and the third had an outbreak of urticaria after the first provocation.

Thus, twenty-three patients were available for analysis. Their mean age was 26 years (range 20–39 years), sixteen were men and seven were women.

Nasal provocation

Nasal provocations according to the method described by Ingelstedt & Rundcrantz [7] and modified by Pipkorn [8] were made at the entry visit and after each treatment period. All provocations were made with the same batch of freeze-dried birch pollen extracts (Pharmalgen[®], Pharmacia AB, Uppsala, Sweden) in a series of dilutions from 10 to 1000 BU/ml. Reconstitution and dilution were made with human serum albumin diluent (Pharmacia AB, Uppsala, Sweden) immediately before the trial. Pollen extracts were stored in a refrigerator and adjusted to room temperature before being used.

The pollen extracts were delivered with a mechanical pump spray device commercially available for delivering nasal DSCG solution (Lomudal[®] nasal) into one nasal cavity of each patient. Each spray delivers 0.13 ml fluid.

At the entry visit all provocations started with a concentration of 6.5 BU, which was then increased stepwise until sufficient nasal blockage was reached. This was defined as an increase in nasal airway resistance (NAR) of about 50%, 15 min after provocation. The final individual dose was used for all the following provocations.

Registration of nasal symptoms

A quantitative estimation of the amount of secretion produced was made by weighing the paper handkerchiefs available *ad libitum*, before and after usage. Recordings were made at 10-min intervals during 90 min after each provocation.

Sneezings were counted and the number during 10-min periods was recorded during 90 min after provocation.

Nasal blockage was evaluated by the use of a rhinomanometer (No 1, Mercury

Electronics Ltd, U.K.) and a personal computer (ABC 80, Luxor, Sweden). Anterior rhinomanometry of the provoked nasal cavity was performed, and the results recorded according to the method of Broms *et al.* [9]. The recordings commenced with the patient resting for 15 min in the test room to allow acclimatization to room temperature and humidity. Thereafter, three recordings of NAR were made at 5-min intervals to obtain stable baseline values. After provocation, NAR was followed for 90 min and recordings made every 10 min. All measurements were made after the patients had blown their noses to ensure registration of mucosal swelling only.

An attempt to register both the early- and late-phase response to nasal allergen provocation was made. The patients were asked to record the severity of nasal secretion, sneezings, and nasal blockage in a diary according to a 4-graded scale from 0: no symptoms to 3: severe symptoms. Recordings were made at 30 and 60 min after provocation and then hourly for the next 10–12 hr.

Adverse experiences

Signs of CNS-depression and anti-cholinergic effects were specifically sought by asking if the patient had been (i) very tired, (ii) less alert than usual, (iii) as alert as usual, (iv) more alert than usual or (v) very alert; or had experienced (i) dry mouth, (ii) normal salivation or (iii) excessive salivation.

Other adverse experiences were recorded by the patients in diary booklets.

Statistics

The number of patients to be included in the study was calculated to twenty-five. This was based on an improvement rate (i.e. positive response to treatment) of 65–80% of the patients on terfenadine and of 15–30% of the patients on placebo [6]. This would give an 80% chance of detecting a difference in efficacy between the active drug and placebo, significant at the 5% level (2-tailed test).

The number of sneezes, the amount of secretion and the nasal airway resistance were plotted against time, and the area under the curve (AUC) was compared between the treatments. Significance testing was made by Student's paired *t*-tests. The symptom scores from the diary cards were plotted and analysed in a similar manner.

The subjective assessments of tiredness and salivation were analysed with Wilcoxon's signed rank test.

Ethics

The patients were informed of the study both verbally and in writing, and verbal consent was obtained before inclusion into the trial. Approval was given by the committee for ethics in medical research at the Gothenburg University.

Results

Nasal provocation

The doses of birch pollen extract used for the nasal provocations are presented in Table 1. These final provocation doses caused a mean increase in NAR of $38.0^{\circ} (\pm 2.9^{\circ})$ at the entry visit, slightly less than our aim of a 50° increase.

Pre-challenge values in NAR did not differ between the groups after treatment (Fig. 1). There was a similar increase in NAR after provocation regardless of the treatment, and during the following 90 min a slight decrease was seen in both groups. The only

Table 1. Doses of allergen (birch) used for nasal provocation throughout the study

Amount (BU)	No. patients
65	7
130	9
260	2
520	1
1300	4

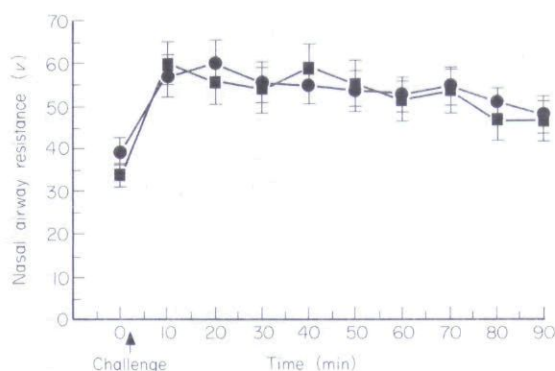


Fig. 1. The effect of terfenadine (●) and placebo (■) on nasal airway resistance (mean $\pm$ s.e.m.) after birch pollen provocation.

difference found between the treatments was a lower maximal increase in NAR after terfenadine ($28.2 \pm 3.8^\circ$) than after placebo ($37.1 \pm 3.9^\circ$) therapy. This difference was, however, not statistically significant.

The majority of sneezings took place during the first 10 min after provocation (Table 2). Only two patients sneezed later, one from each group. Although the number of sneezes was low, there was a significant difference ($P < 0.05$) between the treatments in favour of terfenadine.

Table 2 illustrates the amount of nasal secretion recorded. We were only able to record secretion in five patients later than 20 min after provocation, three after terfenadine and two after placebo treatment. There was less secretion in patients treated with terfenadine. The difference was statistically significant ($P < 0.05$) 10 min after provocation, but not significant when the entire 90-min period was considered.

Late-phase response

A spontaneous recurrence of symptoms after several hours without symptoms was found in only two patients. In one treated with terfenadine the symptoms returned between 5 hr and 8 hr after provocation, and in one patient on placebo the symptoms increased after 8 hr and lasted for 4 hr.

Table 2. The effect of terfenadine and placebo on sneezings (number) and secretion (mg) after birch pollen provocation

Minutes after provocation	Terfenadine (n = 23)				Placebo (n = 23)			
	Sneezings	No. patients	Secretion	No. patients	Sneezings	No. patients	Secretion	No. patients
10	0.30 ± 0.23*	2	0.13 ± 0.07	5	1.74 ± 0.76	11	0.67 ± 0.14	17
20	0		0.07 ± 0.04	4	0.04 ± 0.04	1	0.09 ± 0.05	4
30	0		0.04 ± 0.02	3	0		0.10 ± 0.01	1
40	0		0.03 ± 0.02	2	0		0	
50	0		0.04 ± 0.04	1	0		0.10 ± 0.01	1
60	0.09 ± 0.09	1	0.06 ± 0.04	3	0		0	
70	0		0.03 ± 0.02	2	0		0.10 ± 0.01	1
80	0		0		0		0	
90	0		0.04 ± 0.04	2	0		0	

* Values are given as means ± s.e.m.

Table 3. Mean scores (± s.e.m.) for tiredness and salivation during treatment (for explanation of rating scale, see text)

	Terfenadine (n = 23)		Placebo (n = 23)	
	Morning	Evening	Morning	Evening
Tiredness	2.92 ± 0.04	2.89 ± 0.06	2.98 ± 0.04	2.98 ± 0.04
Salivation	1.93 ± 0.06	1.98 ± 0.08	1.97 ± 0.02	1.96 ± 0.02

Adverse experiences

The mean scores for tiredness and salivation during the treatments are shown in Table 3. There were no significant differences between the terfenadine and placebo groups.

The total number of adverse experiences registered by the investigator and/or reported by the patients was small and similar during both treatments (terfenadine five patients, placebo four patients). No serious adverse experiences were reported.

Discussion

The difference in the degree of antihistamine inhibition of individual nasal symptoms found in our study is in agreement with several other provocation studies [10–12]. Clinical trials of antihistamines generally also show a better effect on sneezing and secretion than on obstruction [2,13,14]. There are several possible explanations for these differences.

Histamine seems to be the most important mediator of sneezing and secretion. This view is supported by the similarity in the response to histamine and allergen challenge [15], and by the fact that H₁-antihistamines are clinically effective on these symptoms [2,13,14]. Sneezing and a major part of the hypersecretion are mediated via a

parasympathetic reflex [16], and the inhibitory effect of antihistamines on these symptoms appears to be due to a blockage of nervous H_1 -receptors [12]. However, mediators released later than histamine in the allergic reaction, e.g. leukotrienes and prostaglandins [17] may be of some importance to the production of nasal secretion [15]. This finds some support in this study in that a few patients on terfenadine continued to produce small amounts of secretion for at least 90 min after provocation.

The degree of nasal blockage during an allergic reaction is determined by the filling of the erectile cavernous tissue [17]. This change in the vasculature is brought about by the direct action of mediators on their respective receptors and not by reflex activation [15]. The presence in the nose of a number of inflammatory mediators has been established after allergen provocation [18], but their vascular actions largely remain to be determined. Histamine reduces nasal patency and it has been shown that H_1 , as well as H_2 , receptors are of importance, but that blockage of both classes of receptors can not completely abolish symptoms [19]. Bisgaard *et al.* applied LTD₄ intranasally and found that it induced nasal blockage but not sneezing or secretion [20]. Challenge with bradykinin has also been shown to cause nasal obstruction [21]. Some putative mediators appear to act as vasoconstrictors when applied to the nasal mucosa. PAF-acether induces vasoconstriction of capacitance as well as resistance vessels [22], while prostaglandins cause a constriction of resistance vessels [23] accompanied by a decrease in nasal airway resistance [24]. When interpreting these results it is, however, important to remember that the relevant concentration of mediators at their site of action is unknown and that challenge with mediators must be regarded as pharmacological studies.

Taking all available data into account, nasal patency thus seems to be affected by several mediators, while sneezing and secretion are likely to be caused by the action of fewer mediators, one of the more important being histamine. An H_1 -antagonist may, therefore, be expected to have less effect on blockage while showing good inhibitory effect on sneezing and secretion.

Valuable information about the effects and mechanisms of pharmacological treatment of allergic rhinitis can be gained from studying induced immediate reactions. Several different methods of delivering an allergen into the nasal cavity exist. We used a mechanical pump spray to deliver a pollen extract because the device is easy to use and the reproducibility with commercially available standardized extracts is very good [8]. The allergen provocation test is more controlled and, in many respects, safer than the investigation of patients during the pollen season. When provocation is used, the exact amount of allergen can be determined. Conversely, the pollen season is characterized by great variations in the pollen density, making it difficult to discriminate between pollen-related fluctuations of symptoms and drug effects.

When using provocation studies to evaluate different treatments we believe that it is more relevant to use allergens rather than single mediators. The use of allergens will ensure the release of a 'soup' of mediators, a reaction closer to the clinical disease than that caused by one selected mediator. Provocation with a single mediator is relevant only when the objective is to evaluate the properties of that mediator.

Allergic rhinitis may be a complex mixture of immediate and late reactions [25]. Since only two patients developed any signs of late-phase reactions in this study it is not possible to conclude anything about the effect of terfenadine on the delayed allergic response. The low incidence of late-phase reactions may be due to the relatively mild provocation [25].

This study supports the findings of many other investigations that terfenadine is without sedative and anti-cholinergic effects [6].

In conclusion, after nasal allergen provocation, terfenadine offered significant protection with regard to sneezing and secretion, but was ineffective against blockage. Terfenadine showed no signs of sedative properties.

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