

Intranasal Verapamil in Allergen-Induced Rhinitis

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Twenty-six pollen-allergic subjects participated in a double-blind, placebo-controlled trial of the protective effect of the calcium antagonist, verapamil, on allergen-provoked nasal symptoms. Intranasal verapamil, 1 mg, had a weak protective effect in that "tickling score" was 22% lower ($P < 0.01$) and the number of sneezes 29% lower (nonsignificant) after verapamil as compared with placebo pretreatment. There were no differences with regard to nasal blockage or discharge. It is concluded that the verapamil spray used, cannot be recommended for clinical trials, but that further investigations of other formulations of calcium antagonists are justified in order to analyse the potential role of this type of drugs in the treatment of allergic rhinitis.

Key words: allergic rhinitis; calcium antagonist; nasal provocation; verapamil.

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Calcium channel blockers (calcium antagonists), such as verapamil and nifedipine, inhibit calcium ion flux across cell membranes and also have effects on calmodulin. As a result of this action, they inhibit the contraction of myocardial and smooth muscle cells, and are used for cardiac arrhythmias, angina, and hypertension (14).

Recent studies have also paid attention to the potential role of calcium antagonists in the treatment of bronchial asthma, and both inhaled verapamil (10), and sublingual nifedipine (5, 11) are found to have some effect in preventing exercise-induced bronchoconstriction; it is debated whether this is due to an effect on mast cells, bronchial smooth muscle, or both (4). Recent studies have shown only a slight or no protective effect of calcium antagonists on histamine- (6, 12, 18), metacholine- (12), and allergen-induced bronchoconstriction (16).

As far as we are informed there are no studies on the effect of calcium antagonists in the nose. In the present trial we have investigated the protective effect of intranasal

verapamil on allergen-induced nasal symptoms in hay fever patients, provoked out of the pollen season.

PATIENTS AND METHODS

Subjects

Twenty-six medical students (6 females and 20 males) volunteered to take part in the study. Mean age 23.3 years (range, 16-31). All had hay fever symptoms in June and July and a positive skin prick test to timothy grass pollen (according to the Scandinavian allergy reference system (1)). The study was undertaken from December 1981 to January 1982. None suffered from asthma or perennial rhinitis, and rhinoscopy did not reveal any gross anatomic abnormalities.

Allergen extract

Dialysed timothy grass pollen extract without preservatives was used. It was supplied freeze-dried from ALK (Allergological Laboratory,

Copenhagen, Ved Amagerbanen 23, DK-2300 Copenhagen). Every Monday during the study a series of four-fold dilutions (1:52,200, 1:12,800, 1:3,200, 1:800 and 1:200 w/v) was made, using distilled water. The solutions were stored at 5°C and kept at room temperature for 1 h before provocation.

Nasal allergen provocation

The nasal provocation tests were performed, insofar as possible, with 1 week's interval at the same time of the day, which for practical reasons varied between 1 p.m. and 4 p.m. Metered-dose pump sprays (Ciba-Geigy AG, Basel, Switzerland) were filled with the solution and delivered 0.1 ml per actuation. Two puffs were given into each nostril. It was first determined by allergen titration which was the lowest dosage causing at least two of the following symptoms: five or more sneezes, 0.2 g secretion in a 5-min period, and a significant increase of nasal airway resistance (that is a 20 degree increase of v_2 ; see later). The lowest allergen dose, which caused the above reaction, was then used for the nasal provocation tests, as the second of three dilutions with four-fold increased concentrations. These three challenges were given at 5-min intervals.

Calcium antagonist

Verapamil was chosen because it is a potent calcium influx inhibitor, commercially available as a solution for intravenous injection. It was supplied as such from Meda, Copenhagen

(manufacturer: Knoll, Ludwigshafen, West Germany). The pH and osmolarity of the 2.5 mg/ml solution were measured to 6.8 and 10 mosm. The volunteers were pretreated 10 min before the allergen provocation. Two puffs into each nostril were given from the metered-dose pump sprays used for allergen solution. This gives a total dose of 1 mg verapamil. The most commonly used intravenous dose for the reversion of atrial arrhythmias is 10 mg. Saline with 0.02% benzalkonium chloride and kinine chloride was used as placebo in order to match the taste and irritation of the active spray. We assume that benzalkonium chloride and kinine have no effect on the allergen-induced symptoms, but this has not been studied. All pump sprays were coded by a technician, not participating in the study, which was undertaken with a double-blind design.

Study design

The trial consisted of three visits and provocation series. First, the individual challenge dose was determined, and then the volunteer was provoked on two occasions with the same allergen dose after pretreatment with verapamil and with placebo in a randomized order.

Recording of adverse effects

Ten minutes after spraying with verapamil and placebo the patient filled in a questionnaire about side effects (see Table 1).

Table 1

Volunteers were asked, 10 min after use of the spray, whether they had experienced any irritation in the nose or bitter taste, and if so, whether it had been slight, moderate or pronounced. Slight symptoms: Insignificant with continuous use of the spray. Moderate symptoms: Between slight and pronounced. Pronounced symptoms: Incompatible with continuous use of the spray. Figures in the table refer to number of observations

	Slight	Placebo Moderate	Pronounced	Slight	Verapamil Moderate	Pronounced
Irritation in the nose	2		1	8	4	6
Bitter taste	5	3		4	2	1

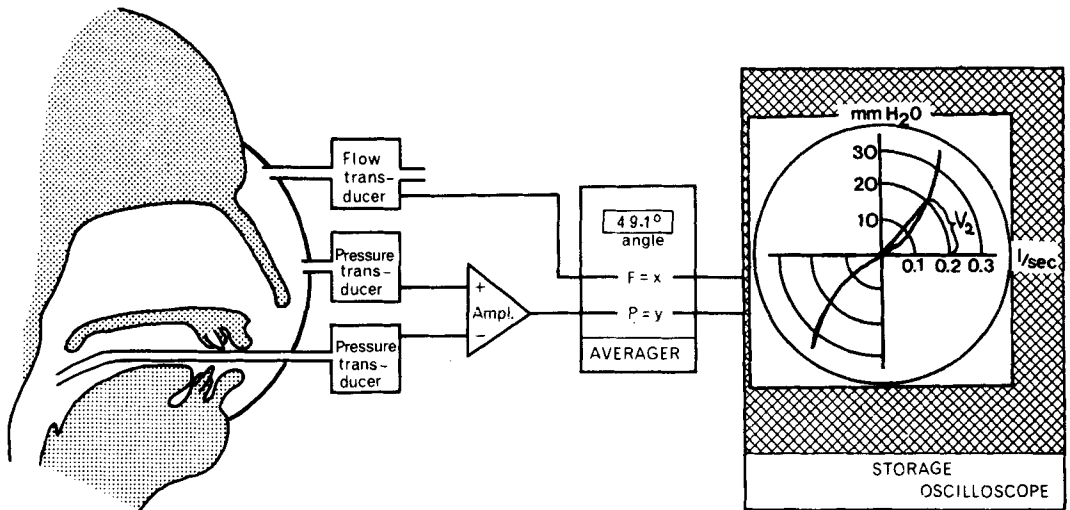


Fig. 1. Measurement of nasal airway resistance. The test subject breathes into a mask that fits closely around nose and mouth. A thin rubber tube, attached to the inner part of the mask, passes through the mouth into the oropharynx. The apparatus records continuously the pressure in the mask (i.e. in front of the nostrils) and in the oropharynx, as well as the airflow through the nose, inasmuch as the subject breathes through the nose with the mouth closed around the rubber tube. The corresponding values of flow and fall in pressure through the nose are fed into a computer and a storage oscilloscope. The computer averages five full in- and expirations, and on this mean curve calculates the angle v_2 (defined in text), which is expressed in a digital display. From Secher et al. (13). By courtesy of The Journal of Allergy and Clinical Immunology.

Symptom recording

Nasal airway resistance was measured by active posterior rhinomanometry, and the result was expressed as v_2 (3). The v_2 value is defined as the angle between the horizontal axis and a straight line between zero and the intersection between the respiration curve and a circle cutting the Y-axis (pressure difference) at 2 cm H_2O and the X-axis (flow) at 0.2 litre/sec (Fig. 1). A computerized reading was made of five consecutive respiration curves. Nasal airway resistance was measured immediately before medication (-10 min), before the first allergen challenge (0 min), 5 min after (i.e. before the second challenge), 10 min after (i.e. before the third challenge), 25 min after and finally 40 min after the first allergen challenge. In the intervening periods the following symptoms were measured: a) The volunteer gave a score for tickling in the nose (0–3). b) The number of sneezes was counted. c) The amount of secretion was measured by the increase in weight of a paper handkerchief, in which the volunteer blew his nose at the end of the recording period.

Statistical analyses

For each volunteer the tickling score, number of sneezes, and amount of discharge in a 40 min period after the first allergen provocation (i.e. time 0–40 min) were used for paired significance tests, using a Wilcoxon sign rank test. The same analysis was employed for the change in v_2 (Δv_2) from time 0 to 40 min. A P -value over the 5% level in a two-tailed probability test was considered non-significant.

RESULTS

Side effects from verapamil/placebo

A few volunteers felt a slight bitter taste after use of the spray, both with verapamil and placebo. Immediate irritation in the nose, on the other hand, was most marked on active medication. After use of the verapamil spray, the nasal airway resistance increased slightly, but significantly ($P < 0.01$). There was also an increase after placebo spraying ($P < 0.02$), but no signif-

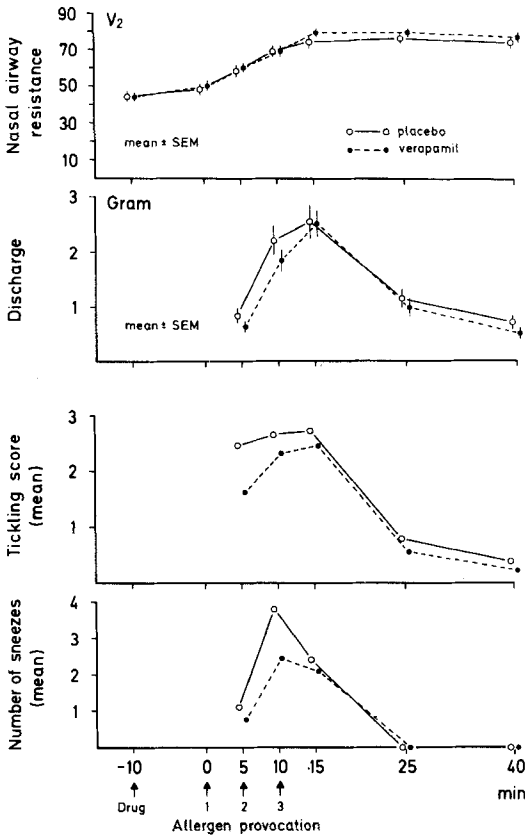


Fig. 2. Nasal symptoms after three consecutive challenges with four-fold increasing allergen dosages and verapamil or placebo pretreatment.

icant difference between verapamil and placebo (Fig. 2).

Response to repeated allergen provocations

Nasal airway resistance increased stepwise and remained raised during the observation period. The amount of discharge increased in a similar pattern, but fell during the two last observation periods. A similar pattern was seen for nasal tickling, although the initial increase was less obvious. There were no sneezes 5 min after the third allergen provocation, and the number was lower after the third than after the second provocation (Fig. 2).

Comparison between verapamil/placebo protection

There was no difference between allergen-induced nasal blockage and discharge after verapamil and placebo pretreatment. The number of sneezes was 29% lower after verapamil and the tickling score 22% lower, but only the latter was statistically significant ($P < 0.01$) (Fig. 3).

DISCUSSION

Allergen provocation of the nose for investigating drug effect implies some methodo-

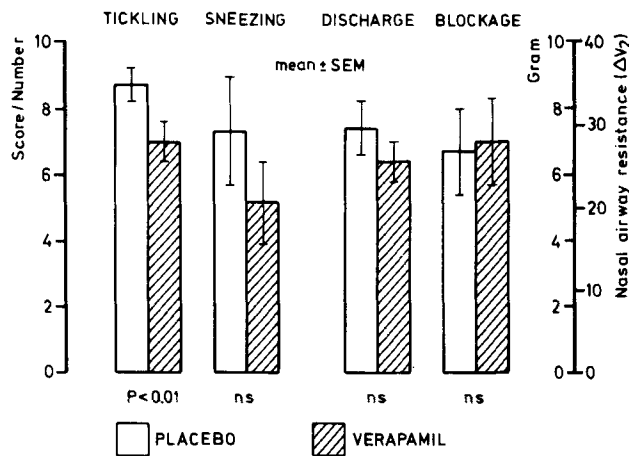


Fig. 3. Effect of the calcium antagonist, verapamil (1 mg) on allergen-induced nasal symptoms in 26 pollen-allergic subjects. All symptoms in a 40-min period after the first allergen provocation are compiled.

logical problems. As the reproducibility of the test is relatively low (2), a weak reaction cannot be reproduced with sufficient certainty; on the other hand, a strong reaction may overcome a moderate drug effect. In the present study we have therefore made serial provocations with increasing allergen doses, and the dose-time-response curve for tickling score seems to justify the choice of this procedure. It is interesting that allergen provocations at 5-min intervals, in contrast to histamine provocations (13) did not result in a reduced responsiveness or development of tachyphylaxis. There was a tendency for a lower response for the number of sneezes, but this might be due to poor allergen distribution in the nose. It is a serious problem in undertaking sequential allergen provocations in the nose that the increase of nasal airway resistance from the first provocation changes the baseline and can prevent adequate allergen application in the nose.

In spite of these methodological problems we feel confident in concluding that intranasal spraying with the calcium antagonist, verapamil, can inhibit allergen-induced tickling and possibly also sneezing, but the effect was slight. It seems most likely that this activity is explained by an effect on mast cells, as calcium influx is an initial step in histamine release (7, 9, 17), but an effect on sensory nerves must also be considered. These results indicate that 1 mg verapamil has no or only a minor effect on vascular smooth muscle and on submucosal glands.

In the formulation used, verapamil was a moderate irritant, and the effect on the allergen-induced symptoms was poor. Clinical trials with this spray cannot therefore be encouraged. However, it is too early to conclude that drugs which modulate calcium metabolism will not play any role in the treatment of allergic rhinitis. Perhaps other substances or combined preparations will prove to be useful. The calcium-binding molecule, EDTA, has long been used as an "inactive" additive to nasal sprays, as for example the sodium cromoglycate spray.

In conclusion, the weak but significant effect of verapamil in the present study justifies further investigations into the potential role of

calcium antagonists in the treatment of allergic rhinitis. In clinical studies, the importance of calcium for ciliary motility (15), and for epithelial permeability (8) should also be considered.

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