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Short communications

Azelastine reduces allergen-induced nasal response: a clinical and rhinomanometric assessment

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Summary. The effect of azelastine 2 mg b.d. p.o. for 10 days on grass pollen-induced nasal responses in 16 patients with grass pollen allergic rhinitis has been assessed. The study was a double blind, randomized, placebo controlled, crossover trial, with a 10–14 day wash-out period. Patients were challenged with grass pollen before and after placebo and azelastine. The response was assessed by measurement of nasal resistance using active posterior rhinomanometry, by weighing nasal secretions, and by counting sneezes. The sensation of nasal obstruction was assessed with a visual analogue scale. After measurement of baseline total nasal resistance, doubling doses of allergen were sprayed into both nostrils at 15 min intervals until the nasal resistance was doubled.

Cumulative doses of allergen that doubled prechallenge nasal resistance, numbers of sneezes and the amounts of nasal secretions were similar before azelastine as well as before and after placebo (cumulative dose, mean, (μg): 2.3, 4.2 and 2.1 respectively, N.S.). After azelastine, the cumulative dose of allergen was increased (7.3 μg), and nasal secretions and the number of sneezes were decreased. The visual analogue scores were similar before and after azelastine as well as before and after the placebo.

It is concluded that azelastine reduced the allergen-induced nasal responses.

Key words: Azelastine, Allergic rhinitis; rhinomanometry, clinical pharmacology

Azelastine is an antiallergic drug with potent antihistamine properties, which inhibits the release and/or the action of inflammatory mediators [Mc Tavish & Sorkin, 1989]. It relieves nasal symptoms in seasonal and perennial, allergic rhinitis [Perhach et al., 1984; Connell et al., 1985; Weiler et al., 1986; Meltzer et al., 1988]. Nasal symptoms in patients with allergic rhinitis can be induced by exposure to allergens. The importance of the nasal response depends on the severity of the disease, so the study of nasal responsiveness is an important and objective method of assessing the efficacy of new drugs for the treatment of allergic rhinitis [Borum et al., 1983]. There appear to be only a few controlled studies of the effects of drugs, including antihistamine agents, on the early nasal response to allergen challenge [Pipkorn et al., 1987; McLean et al., 1983; Brooks et al., 1984; Borum and Mygind, 1980]. Such drug trials may also further understanding of the pathophysiology of allergic rhinitis.

The effect of azelastine 2 mg b.d. p.o. for 10 days on grass pollen-induced nasal responses in patients with allergic rhinitis has now been assessed.

Subjects and methods

Design of the study

The study was a randomized, double blind, cross-over, two-period study. Each period of treatment lasted 10 days, during which patients received either 2 mg azelastine b.d. or a placebo. The two periods were separated by a 10–14 days wash-out period. Nasal provocation tests were performed on Days 1 (D1) and 10 (D10) of both periods, at the same time of day.

Patients

Ten male and 6 female patients (age, mean with SEM) : 26.4 (1.1) y), with a clear-cut history of allergic rhinitis were investigated. All the patients had seasonal or perennial allergic rhinitis with clearly identifiable provoking allergens and an appropriate positive skin prick test (wheal >5 mm). Patients were tested out of the grass pollen season. None had evidence of nasal polyposis on rhinoscopy. Their nasal resistance at inclusion was low (mean with (SEM): 0.20 (0.01) $kPa \cdot l^{-1} \cdot s^{-1}$). On the first study day baseline nasal resistance in each patient doubled after allergen challenge. They had not taken any medication and had not suffered from a respiratory tract infection during the 2 months preceding nor during the study.

The protocol was approved by the Ethical Committee of Cochin-Port-Royal University Hospital. Each patient signed an informed consent form.

Technical details

After baseline measurement of nasal resistance, 4 nasal washes with saline (37 °C) were performed and immediately afterwards the measurements were repeated to verify that nasal resistance remained $\leq 0.35\ kPa \cdot l^{-1} \cdot s^{-1}$.

Table 1. Nasal response to allergen provocation

		Day 1						Day 10					
		Before challenge	Doses of allergen (μg)					Before challenge	Doses of allergen (μg)				
			0.5	1	2	4	8		0.5	1	2	4	8
Number of patients	A	16	16	13	5	1	0	16	16	12	11	8	5
	P	16	16	11	8	1	0	16	16	12	6	3	3
Nasal airway resistance ($kPa \cdot l^{-1} \cdot s^{-1}$)	A	0.18 (0.01)	0.48 (0.15)	0.89 (0.39)	1.05 (0.48)	0.79 –	– –	0.22 (0.01)	0.45 (0.14)	0.27 (0.04)	0.37 (0.07)	0.38 (0.08)	0.26 (0.05)
	P	0.21 (0.01)	0.65 (0.23)	0.6 (0.2)	0.7 (0.1)	1.7	–	0.20 (0.01)	0.40 (0.08)	0.72 (0.33)	0.38 (0.07)	0.26 (0.05)	0.26 (0.04)
Number of sneezes	A	0	1.3 (0.6)	1.1 (0.4)	5.4 (2.3)	0 –	– –	0	0	0.23 (0.1)	0.09 (0.09)	0.22 (0.22)	0
	P	0	2 (0.9)	4 (1.1)	3.1 (1.3)	16	–	0	1.6 (0.8)	2.0 (1.1)	1.3 (0.8)	1.0 (1.0)	1.6 (1.6)
Weight of secretions (g)	A	0	1.2 (0.4)	1.4 (0.4)	2.4 (1.2)	0.3 –	– –	0	0.2 (0.03)	0.3 (0.09)	0.09 (0.4)	0.61 (0.3)	0.16 (0.04)
	P	0	1.4 (0.5)	2.1 (0.8)	2.1 (0.7)	7.5 –	–	0	0.95 (0.32)	1.32 (0.50)	1.13 (0.56)	1.24 (0.78)	2.68 (1.75)
Visual analog scale (mm)	A	13.8 (3.1)	42.7 (6.7)	66.8 (5.4)	71.4 (7.3)	94 –	– –	23.5 (4.2)	50.6 (6.8)	52.2 (9.1)	54.7 (10.3)	58.7 (11.7)	42.4 (19.1)
	P	13.4 (3.4)	51.2 (7.2)	48.0 (7.1)	65.8 (9.4)	59	–	13.3 (2.9)	48.5 (6.8)	55.3 (7.2)	48.0 10.9	34.6 (14.6)	41.3 (19.4)

A: azelastine; P: placebo. Mean (SEM)

Doubling doses of allergen (0.5, 1, 2, 4, and 8 μg per nostril; phenol-free, dry extract of grass pollen, Stallergènes Laboratories, Paris, France) were then sprayed into each nostril at 15 min intervals, until doubling of nasal resistance was observed. After each spray, the patient was fitted for 13 min with a "nose-clip". After removal of the nose-clip, the subjects gently blew the nose before the measurement of nasal resistance 2 min later by active posterior rhinomanometry (Mediprom, Paris, France), as previously described [Devillier et al., 1988]. In addition, the level of discomfort associated with nasal obstruction was self-assessed on a horizontal 10 cm long visual analogue scale, anchored by the words "my nose is not at all obstructed" and "my nose is completely obstructed". Nasal secretions were collected by asking subjects slightly to incline the head forwards and gently to blow the nose over a test tube.

Statistical analysis

The treatment groups at inclusion were compared (patients receiving azelastine first versus those receiving placebo first) by Student's t, Wilcoxon t or the CHI^2 tests. The baseline values in the two treatment periods were compared by cross-over analysis of variance, which allowed simultaneous testing of the effect of the period of administration, the treatment itself and the "treatment × period of administration" interaction. Treatment-effects were compared by cross-over analysis of variance. $P < 0.05$ was considered significant. The SAS statistical package (SAS Institute) was used.

Results

Comparability of D1 data before the two treatment periods

In both groups on D1 baseline total nasal resistance did not differ, pre-challenge nasal washes with saline caused no significant change in nasal resistance or in the sensation of nasal obstruction (visual analogue scale), and the dose-dependent increase in nasal resistance, visual analogue score, numbers of sneezes and volumes of secretion induced by nasal allergen challenge were not significantly different (Table 1). Thus, patients were similar at the beginning of each period of treatment.

Effect on allergen-induced nasal responses of azelastine or placebo (Tables 1 and 2)

The cumulative dose of allergen that doubled prechallenge nasal resistance, the numbers of sneezes and the quantity of nasal secretions were similar before and after 10 days on placebo. Conversely, on azelastine, the cumulative dose of allergen required to cause a twofold increase in nasal resistance was increased ($P < 0.05$), and the number of sneezes ($P < 0.05$) and the weight of nasal secretion was decreased ($P < 0.02$). The visual analogue scores for nasal obstruction were similar before and after azelastine, as well as before and after placebo. There was a significant multiple correlation between the analogue score and nasal resistance, weight of nasal secretion and number of sneezes ($n = 225$, $r = 0.49$, $P < 0.001$).

Table 2. Cumulative dose of allergen that doubled prechallenge, post-saline nasal resistance [mean (SEM)]

	Cumulative dose of allergen (μg)	
	Placebo	Azelastine
Before treatment (D1)	2.3 (0.5)	2.1 (0.5)
After treatment (D10)	4.2 (1.4)	*7.3 (1.5)

The cumulative dose of allergen was similar on D1 and D10 after placebo and was increased at D10 on azelastine ($P < 0.05$)

Discussion

Azelastine has been shown to diminish immediate allergen-induced nasal responses both by rhinomanometric and clinical criteria. The results are similar to those or previous studies: cetirizine, terfenadine, azatadine, astemizole loratadine and intra-nasally administered levocabastine all reduced allergen-induced nasal responses [Klementsson et al., 1990; Small et al., 1990; Bousquet et al., 1988; Rokenes et al., 1988; Kolly et al., 1986; Holmberg et al., 1989]. These antihistamines reduce the number of sneezes, nasal secretions and nasal blockade when nasal symptoms were assessed by symptom scoring [Klementsson et al., 1990; Small et al., 1990; Bousquet et al., 1988]. They had no significant effect on nasal blockade assessed by rhinomanometry [Rokenes et al., 1988; Kolly et al., 1986; Holmberg et al., 1989].

The lack of a protective effect of azelastine on the allergen-induced increase in nasal resistance is only apparent. On azelastine, the increase in nasal resistance occurred after challenge with a higher dose of allergen than on placebo. In addition, the dose of allergen which caused at least a twofold increase in nasal resistance on placebo did not significantly increase nasal resistance in patients on azelastine. The absence of full protection against an increase in nasal resistance may be due to an excess of allergen with respect to the dose of azelastine used. It is possible that a higher dose of azelastine would have more completely inhibited the increase in nasal resistance. Furthermore, allergen challenge leads to release of mediators other than histamine, which can increase nasal reistance, and whose actions are not fully inhibited by azelastine treatment. The inhibitory effect of azelastine on the release and/or the action of mediators such as leukotrienes and bradykinin, which are also able to increase nasal resistance in patients with allergic rhinitis, may be too weak in vivo fully to inhibit an allergen-induced increase in nasal resistance [McTavish and Sorkin, 1989].

Therapeutic trials of antiallergic drugs in patients with allergic rhinitis must be done during a period of natural exposure to allergens when patients are symptomatic, and are often of long duration. In such clinical trials, assessment criteria are frequently subjective, although some authors have also employed objective measurements [Gleeson et al., 1986; Meltzer et al., 1988; Wihl and Malm, 1988]. Nasal allergen provocation in the laboratory may be used as a first step in the assessment of anti-allergic drugs before starting a therapeutic trial but they must be done when the patient is asymptomatic and has not been affected by any spontaneous exposure. Although laboratory studies of specific nasal responses cannot replace clinical trials, they have the advantages of short duration in a homogeneous group of subjects.

Different techniques are available for objective and subjective assessment of nasal obstruction. Rhinomanometry is probably the method of choice for studying nasal patency, as it is more sensitive than peak-flow methods [Wihl and Malm, 1988]. Active posterior rhinomanometry is preferable to sequential anterior rhinomanometry when the objective is to measure the patency of the nose at a precise time [Dvoracek et al., 1985]. A visual analogue scale was used to assess the allergen-induced sensation of nasal obstruction. There was a significant though rather loose multiple correlation between visual analogue scale scores, and three objective criteria, nasal resistance, number of sneezes and weight of nasal secretions ($r = 0.49$, $n = 225$, $P < 0.001$). However, the sensation of nasal obstruction was not significantly different after azelastine compared to placebo, whereas there were significant differences in the three objective criteria used. This probably reflects the large inter-individual variation in visual analogue scores.

In conclusion, azelastine has been shown to reduce allergen-induced nasal responses. As an objective method posterior active rhinomanometry appears to be useful for assessing drug effects in allergic rhinitis.

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