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Are prostaglandins major mediators in perennial allergic rhinitis?*

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SUMMARY

Certain prostaglandins acting as inflammatory mediators have been implicated in the aetiology of perennial allergic rhinitis (PAR). Inhibition of prostaglandin synthesis in the nasal mucosa might therefore influence the symptoms associated with PAR. A randomised, double-blind, placebo-controlled cross-over trial using 0.1% Diclofenac eye-drops has been conducted to investigate this hypothesis. Diclofenac, a non-steroidal anti-inflammatory drug (NSAID), reduces prostaglandin synthesis through the inhibition of the cyclo-oxygenase pathway. Twenty-five patients with significant PAR and positive skin tests to relevant perennial allergens were recruited and two drops of the given preparation were administered bilaterally q.d.s.. Thirteen patients completed the study. Nasal symptom score (itch, rhinorrhoea, sneezing, and blockage), smell test score, saccharin transit time, total nasal airflow resistance, and nasal inspiratory peak flow measurements were obtained at each of three study visits. No significant treatment effects were found. The daily nasal symptom score over the entire study period showed no significant variation. Adverse effects such as local irritation, dry nose or throat were rare. No untoward changes in haematological, biochemical profiles and urinalysis occurred. In conclusion, topical 0.1% Diclofenac eye-drops applied nasally have no significant effect on PAR. Prostaglandins alone may not play a major role in mediation of symptoms in this condition.

Key words: allergic rhinitis, NSAID, prostaglandins

INTRODUCTION

In response to allergen challenge, a wide range of pre-formed or newly-generated inflammatory mediators are released from mast cells, eosinophils and other cells such as basophils and neutrophils, in patients with allergic rhinitis (Howarth, 1989; Albegger, 1990). Elevated levels of these mediators can be readily demonstrated in nasal lavage fluids under these conditions (Naclerio et al., 1986; Wachs et al., 1989) as well as in the natural disease state (Sugimoto et al., 1994). Prostaglandins are vasoactive mediators derived from mast cells during the initial allergic response and during the late response following antigenic rechallenge (Naclerio et al., 1985). Prostaglandins and thromboxanes are generated from arachidonic acid in the presence of cyclo-oxygenase, and leukotrienes are converted from the same parent compound by lipoxygenase. If these arachidonic acid metabolites are important mediators in allergic rhinitis, then inhibition of their formation should result in an alteration of the nasal allergic inflammatory response expressed as nasal blockage and rhinorrhoea (Bisgaard et al., 1984; Miadonna et al., 1987). Non-steroidal anti-inflammatory drugs (NSAID) are cyclo-oxygenase inhibitors which act primarily through inhibition of prostaglandin synthesis. Catalano et al. (1990) have reported that triaprofenic acid, a non-steroidal anti-inflammatory drug, improved the clinical symptoms, mucociliary transport time and rhinomanometric measurement of patients with rhinitis of multiple aetiology, which indicates that prostaglandins may be important in allergic and infectious inflammation. However, oral therapy with NSAID is associated with a significant side-effect profile, notably that of gastric irritation.

This study was designed to investigate whether prostaglandins play a major clinical role in perennial allergic rhinitis by attempting to block their formation in the nasal mucosa using topical 0.1% Diclofenac sodium originally formulated for ocular use.

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MATERIAL AND METHODS

Study design

A randomised, double-blind, placebo-controlled cross-over study was performed in a single centre between August 1993 and March 1994. The patients were recruited from the out-patient clinic and were randomised into one of the two treatment groups. In sequence A, two drops of 0.1% Diclofenac eye-drops (Voltaren ophthalmic solution) were instilled into each nostril four times a day for two weeks followed by placebo (same formulation without Diclofenac), two drops per nostril four times daily for two weeks at the same dose, frequency and duration. Sequence B followed the same regimen in reverse order. Each patient was given a pictorial leaflet showing the "Mecca" and supine position with neck in full extension as the correct posture for instillation of nasal drops.

Patients

Twenty-five subjects took part in the study, 13 patients entered sequence A and the remainder entered sequence B. The patients were all over 20 years of age and their skin prick tests were positive to house dust, *Dermatophagoides pteronysinus* extract, cat or dog dander. Nasal itch, sneezing, rhinorrhoea or nasal blockage were the four main symptoms used to score the severity of rhinitis (For each symptom: 0: no symptoms; 1: mild; 2: moderate; and 3: severe). Total symptom scoring of not less than 1 point was the minimum inclusion requirement.

The following patients were excluded from the study: (1) those with severe or total nasal obstruction; (2) those who had used inhaled, intranasal or systemic corticosteroids, sodium cromoglycate or nedocromil sodium or ipatropium bromide within one month of the study, astemizole within six weeks of the study or any other nasal medications during the study; (3) those receiving desensitisation therapy; (4) those with severe concomitant diseases, known intolerance to non-steroidal anti-inflammatory drugs; and (5) those who were pregnant, lactating, or at risk of pregnancy. The study was approved by the Local Ethics Committee and written informed consent was obtained from each patient before entering into the study.

Clinical procedure

At visit 1, demographic details, full medical history and skin prick test results of the patient were obtained. General and ENT examinations were performed. Any septal deviation, polyposis, oedema, crusting, bleeding, mucosal colour and rhinorrhoea were noted. At visits 2 and 3, nasal symptom scoring and physical examination were repeated. At visits 1 and 3, blood samples were taken for haematological and biochemical measurement and urinalysis was performed with dipsticks. Olfactory tests measured with the UPSIT (i.e., University of Pennsylvania Smell Identification Test) kit, anterior rhinomanometry, nasal inspiratory peak airflow measurement performed with a Youlten peak-flow meter, and saccharin transit time measurements were performed during all visits. No aspirin-challenge tests were carried out. Each patient was issued a diary for each of the two treatment periods, and careful instructions were given regarding the application of nasal drops. The daily nasal symptom score for itching, sneezing, rhinorrhoea or blockage was indicated on a 10-point visual analogue scale. Daily administration of study or other medicants, concurrent illness, unusual symptoms, any adverse effects and medical problems were also recorded. Patient's compliance was checked by weighing returned medication allowing calculation of the quantity of medication used.

Statistical analysis

The period, carry-over and treatment effects of nasal symptom scores were assessed using Wilcoxon ranked-sum tests (Altman, 1991). Shapiro-Wilks tests showed that smell score, saccharin time, total resistance and peak flow were normally distributed. A series of three two-sample t-tests were used to assess the period, carry-over and treatment effect of these variables. The effect of baseline measurements were assessed by comparing median or mean scores from visit 1 between the two patient groups using Wilcoxon or t-test. The daily symptom scores were analysed using a split-plot analysis of variance (Wallenstein and Fisher, 1977).

RESULTS

Thirteen patients completed the study. Five (42%) of the 12 patients who dropped out were from sequence A of the trial. Of these, failure to complete the trial was due to headache (two patients; one of them reported increased nasal obstruction), social reasons (two patients), and failure to continue with medications because of persistent nasal symptoms and increased sneezing (one patient).

In sequence B, the drop-out was due to failure to attend clinic (four patients), headache (one patient), worsening of asthma (one patient), and increased nasal obstruction (one patient).

Of the 13 patients who completed the study, eight entered sequence A and five sequence B. Eight (61.5%) were female and eight (61.5%) were non-Caucasian. The mean age was 30 years (range: 20-41 years). All patients had a positive skin test to housedust or house-dust mite. Five patients were allergic to grass pollen, while three patients had controlled asthma. No patients had a history of aspirin sensitivity. Each had complained of nasal symptoms for at least six months. Other reported symptoms included hyposmia, headache, and sore throat. Small intranasal polyps were detected during endoscopic examination in two patients.

The nasal symptom scores (Table 1) showed that nasal blockage and rhinorrhoea were the dominant symptoms. The mild rhinorrhoea and itching symptoms in sequence B were reduced during visits 2 and 3, but there were no significant treatment differences for any of the four symptoms. The baseline mean UPSIT scores for patients entering sequence A and B were 26 and 33.6, respectively (normal UPSIT score: 32-40 correct answers; partial anosmic score: 20-30; and total anosmic score: 7-14). These scores were clinically but not statistically different, and there were no significant differences between the treatment groups (Figure 1). The saccharin transit time measurements, which reflect nasal mucociliary clearance, were within the nor-

Table 1. Symptom scoring for each visit.

		vist 1 (before trial)		visit 2		visit 3	
sequence drug		A	B	A active	B placebo	A placebo	B active
nasal itch score (0-3)	median	0.5	1	0.5	0	0	0
	range	0-3	0-2	0-3	0-2	0-1	0-1
	n	8	5	8	5	7	5
rhinorrhoea score (0-3)	median	2	1	1.5	0	2	0
	range	0-3	0-3	0-3	0-3	0-3	0-3
	n	8	5	8	5	7	5
sneezing score (0-3)	median	1	1	1	1	0	1
	range	0-3	0-3	0-3	0-3	0-2	0-1
	n	8	5	8	5	7	5
nasal blockage score (0-3)	median	2	2	3	2	2	2
	range	0-3	1-3	0-3	1-3	0-3	1-3
	n	8	5	8	5	7	5

mal limits. There were no significant differences between the groups (Figure 2).

In normal subjects total nasal airflow resistance is about 0.35 kPa/s/l. At the end of each active treatment period from both sequences, the resistance was raised in comparison to the placebo group, although these differences were not significant (Figure 3). There was no significant symptomatic difference in nasal blockage between the groups over the treatment periods (Figure 5). Nasal inspiratory peak flow measurement should negatively correlate with nasal airflow resistance (Holmstrom et al., 1990). This was so in this study if the changes in measurements between visit 2 and 3 in the same patient group were compared. There were no significant differences between all the peak flow measurements (Figure 4). The nasal symptom scores were measured on an ordinal scale ranging from 0 to 3. No significant differences were found between the two groups.

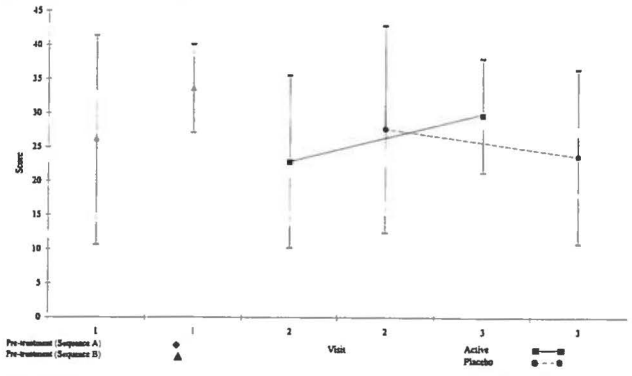

Figure 1. Smell test score.

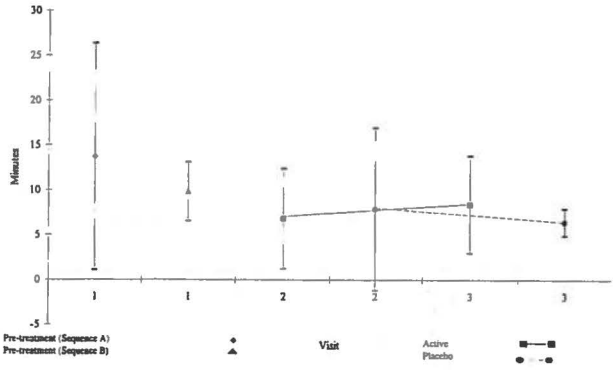

Figure 2. Mean saccharin transit time.

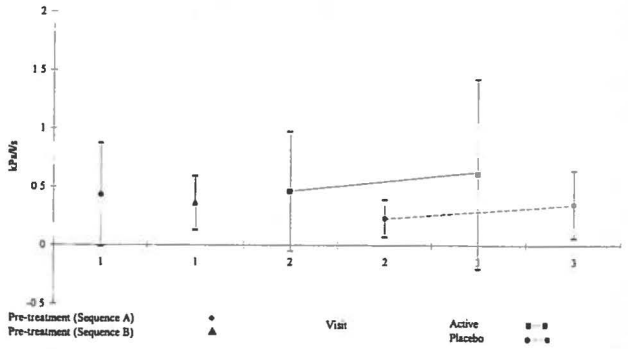

Figure 3. Total nasal airflow resistance (bars represent 95% confidence intervals).

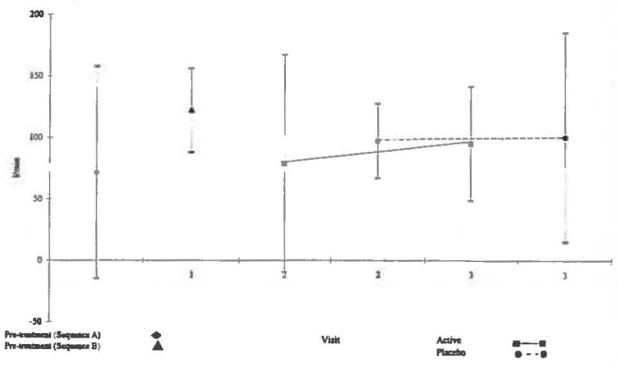

Figure 4. Nasal inspiratory peak flow (bars represent 95% confidence intervals).

Prior to testing whether Diclofenac had a significant effect on the measures, the period and carry-over effects were examined. No significant period or carry-over effects were found. The results of tests comparing treatments showed no significant difference between the active drug and the placebo for any measurement.

Table 2. Mean weight (in grammes) of drug or placebo used.

		period 1	period 2
Diclofenac:	mean	6.74	6.14
	s.d.	3.88	1.18
	n	7	3
placebo:	mean	8.7	5.62
	s.d.	1.82	1.77
	n	3	7

Table 3. Mean number of doses applied daily in 13 patients.

	active	placebo
mean	3.64	3.49
s.d.	0.75	0.85
median	4	4

The mean number of daily doses of study medicants applied and mean weight of drug or placebo used were calculated from the returned containers (Tables 2-3). A sample t-test comparing the differences between periods showed that time had no effect on the dose taken ($t=-1.7$, $p=0.13$). There are no significant differences between the drug or placebo used in the first and the second period. There is also no significant difference between the expected mean weight of 6.328 g, if the drops had been applied correctly and the mean weight of drops used in period 1 ($t=0.92$, $p=0.4$) or 2 ($t=-0.699$, $p=0.5$).

The total daily score of the four main nasal symptoms during the active and placebo periods are shown in Figures 5-8.

No significant differences have been found between placebo and the active drug for the mean scores of the four symptoms.

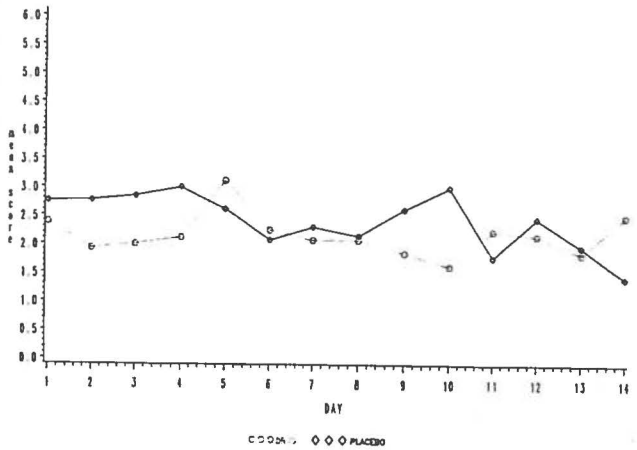

Figure 5. Mean itching nose/throat score over a 14-day period.

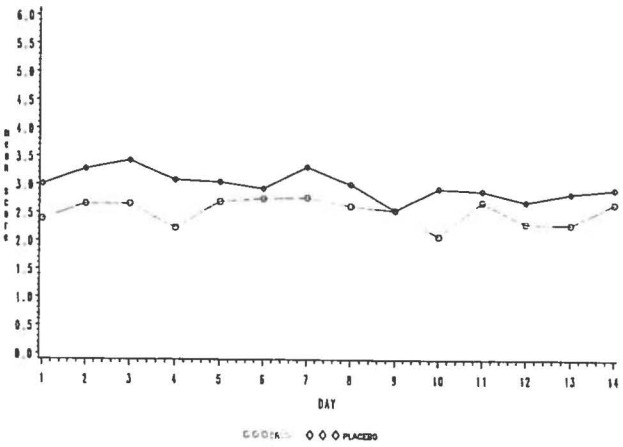

Figure 6. Mean sneezing score over a 14-day period.

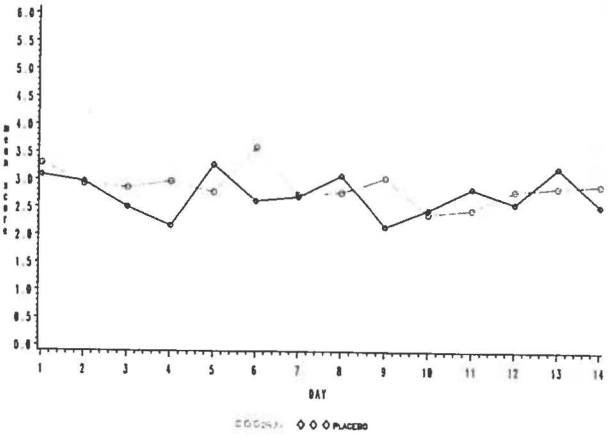

Figure 7. Mean running nose over a 14-day period.

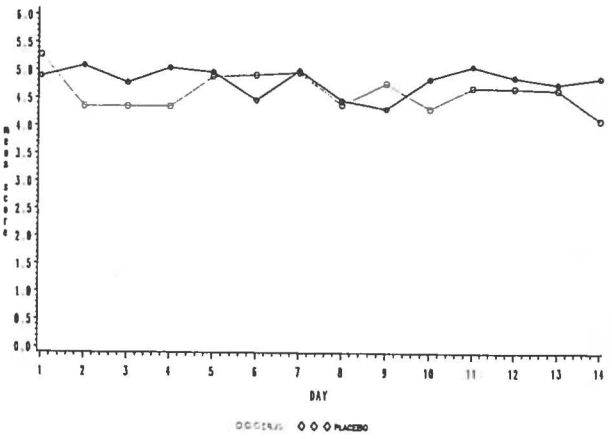

Figure 8. Mean blocked nose score over a 14-day period.

Local nasal irritation, dry throat and nose were reported in four patients while using Volteran ophthalmic solution, and two during placebo treatment. At the end of the study, one patient developed unilateral anterior septal crusting which subsided after treatment with naseptin cream. No abnormal changes in haematological and biochemical profiles and urinalysis were detected in this study. The small polyps noted in two patients showed no alteration in size.

DISCUSSION

The present study has shown that topical 0.1% Diclofenac eye-drops, applied nasally four times daily for two weeks, has no significant effect on perennial allergic rhinitis in terms of symptomatology and the measurement of various nasal physical and physiological parameters. This disagrees with the finding that an oral non-steroidal anti-inflammatory drug improved nasal symptoms, mucociliary transport time and rhinomanometric measurement of patients with rhinitis of various aetiology including allergy (Catalano et al., 1990). The high drop-out rate (48%) in this study is probably partly due to the perceived ineffectiveness of the trial medication and continuing nasal symptoms and headache. Social inconvenience and failure to attend the clinic despite further recalls are responsible for 50% of the drop-out. In this group, failed attendance may be due to lack of symptomatic relief, but this cannot be confirmed.

Using the small effect sizes found in this study, the power to detect a significant difference between the nasal itch scores of the two treatments is 7% (8% for rhinorrhoea; 15% for sneezing; and 2% for nasal blockage). However, using patients as their own control as in this study, should help to detect any nasal symptom changes fairly sensitively if Diclofenac significantly influences the state of the nasal mucosa, but no such effects were detected.

A number of nasal challenge experiments have shown that the nasal response is determined by individual types of prostaglandins. Nasal topical application of PGE_1 produces nasal irritation and throbbing, lacrimation, and headache whereas PGE_2 only induces occasional, transient nasal irritation. Nasal challenge with PGD_2 and $PGF_{2\alpha}$ causes rhinorrhoea, cough, Eustachian tube dysfunction and sore throat in normal subjects and patients with allergic rhinitis. PGE_1, PGE_2 and $PGF_{2\alpha}$ enhance nasal patency whereas PGD_2 produces nasal congestion (Änggård, 1969; Karim et al., 1978; Doyle et al., 1990). The concentrations of PGD_2 and PGE_2, but not of PGF_1 or $PGF_{2\alpha}$, in nasal lavage are raised in patients with allergic rhinitis as compared to normal subjects, implicating the significance of the first two prostaglandins in the allergic state (Sugimoto et al., 1994).

PGD_2, PGE_2 and $PGF_{2\alpha}$ levels in nasal lavage fluid of normal subjects are reduced by oral intake of aspirin, a cyclo-oxygenase inhibitor (Ferreri et al., 1988; Ramis et al., 1988; Ramis et al., 1990). Aspirin increases nasal airflow resistance significantly in these individuals at high dose (500 mg; Jones et al., 1985), but no nasal symptoms are elicited at low dose (100 mg; Marek et al., 1993). However, in allergic patients, although pretreatment with aspirin also reduces the levels of prostaglandins in nasal secretions, it does not alter nasal symptoms (Proud et al., 1987). The principal therapeutical effect of NSAID is attributed to the inhibition of cyclo-oxygenase, although they may also act as free radical scavengers modifying inflammatory reactions (Flower and Blackwell, 1979). It is possible that cyclo-oxygenase inhibition will proportionally reduce both PGD_2 and PGE_2, which explains the lack of influence on nasal obstruction by NSAID in allergic subjects. Indeed, oral administration of flurbiprofen, a cyclo-oxygenase inhibitor, has no effect on nasal obstruction, although it reduces rhinorrhoea, sneezing and the overall severity of induced allergic rhinitis (Brooks et al., 1984). Several cyclo-oxygenase inhibitors have been found to relieve symptoms of allergic rhinitis in one patient (Kumar et al., 1988). The lack of therapeutical response of topical Diclofenac as shown in this study may therefore be due to qualitative pharmacotherapeutical effects of cyclo-oxygenase inhibitors.

The 14-day course of treatment in the present study delivers approximately 6 mg of Diclofenac to the nose. Since the minimum recommended oral dose is 75 mg daily in rheumatic disease and other musculoskeletal disorders, the usual effective oral dose of Diclofenac is 175 times more than the daily treatment administered in the present study. Therefore, the dose of Diclofenac used in this study might have been sub-optimal, although a similar topical regimen used in the treatment of chronic bilateral conjunctivitis has been shown to be effective (Stodtmeister and Marquardt, 1986; Rodriguez-Ares et al., 1991). The high drug-compliance rate in this study indicates that the patients had instilled the nasal drops correctly as instructed, and this method of drug delivery has been shown to be highly effective.

Since the results of this study indicate that Diclofenac did not attenuate nasal symptoms in perennial allergic rhinitis, it is tempting to conclude that prostaglandins, in contrast to other mediators, do not play a dominant role in mediation of symptoms in this condition. However, since a number of other inflammatory mediators are released or synthesized in perennial allergic rhinitis, it is possible that selective blockade of the cyclo-oxygenase pathway is ineffective in the overall reduction in the symptoms of perennial allergic rhinitis.

Leukotrienes, other arachidonic acid metabolites, histamine, kinins, platelet-activating factor, complements and other mediators being unaffected by cyclo-oxygenase inhibitors could continue to sustain nasal symptoms in the absence of prostaglandins. However, with the knowledge of the actions of individual prostaglandins, it may be postulated that global inhibition of all by cyclo-oxygenase could be ineffective in allergic rhinitis due to the antagonistic biological actions amongst some of these mediators, with a few exceptions. If so, then any future agents that produce specific inhibition of individual prostaglandins (such as PGD_2), which produce an inflammatory response in the nasal lining, may potentially be more beneficial in allergic rhinitis.

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