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A double-blind, placebo-controlled trial of beclomethasone dipropionate 600 μg/day in the treatment of non-atopic rhinitis

B. J. O'Reilly F.R.C.S.Ed, G. S. Kenyon M.D., F.R.C.S. (London)

Introduction

The role of inhaled steroids in the management of atopic rhinitis is well established (Cockroft *et al.*, 1976; Incaudo *et al.*, 1980; Mygind, 1973) with a positive response rate of 80–90 per cent (Cockroft *et al.*, 1976; Morrison Smith *et al.*, 1975; Tarlo *et al.*, 1977). In contrast, their role in non-atopic rhinitis is under-researched: only a handful of trials have identified patients with this condition as a sub-group in a larger rhinitis trial (Gibson *et al.*, 1974; Knight and Kolin, 1983; Kohan *et al.*, 1989; Tarlo *et al.*, 1977) and only three trials have been aimed exclusively at patients with non-atopic rhinitis (Bende and Rundcrantz, 1985; Jones and Kenyon, 1988; Pipkorn and Berge, 1983). In a double-blind, cross-over study of 25 patients with perennial rhinitis, Gibson *et al.* (1974) isolated a subgroup of nine patients with non-atopic rhinitis and found that six of them (66 per cent) preferred beclomethasone dipropionate (BDP) 200 μg daily to placebo. In a similar trial, Tarlo *et al.* (1977) found that the response rate of nine patients with non-atopic rhinitis to BDP 400 μg daily rose from 54 per cent at three weeks to 73 per cent at six months. They suggested that some patients may require a longer period of treatment and others may need a higher dose of BDP to elicit a positive response. Jones and Kenyon (1988), in the only controlled trial designed to look solely at non-atopic rhinitis, matched 22 patients with non-atopic rhinitis after six weeks of BDP 400 μg against 22 untreated controls with non-atopic rhinitis and 22 'normal' patients. Measured by rhinomanometry and symptom scoring they found a response rate of only 23 per cent in the treated group and suggested that a longer course of BDP might have improved upon this result. This argument is given weight by the results of Knight and Kolin (1983) who found a greater response in patients with non-atopic rhinitis when treatment was prolonged to 48 weeks.

In an uncontrolled trial of 12 patients Pipkorn and Berge (1983) found budesonide to be effective in non-atopic rhinitis. Bende and Rundcrantz (1985) compared a ten day course of budesonide with a ten day course of ipatropium bromide in 14 patients with non-atopic rhinitis and found the former to be more beneficial.

From the limited evidence available, it would appear that non-atopic rhinitis does not respond as well as allergic rhinitis to BDP and there is no agreement on the optimum daily dose for the condition. Likewise, there is no agreement on the length of the course needed to produce the maximum response but the consensus is that this may need to be prolonged (Knight and Kolin, 1983; Jones and Kenyon, 1988; Tarlo *et al.*, 1977). To test the hypothesis that non-atopic rhinitis will respond to a high dose of BDP given over a long period a double-blind, placebo-controlled, crossover trial of 600 μg of BDP/day (four puffs t.d.s.) for 12 weeks was commenced at the London Hospital, Whitechapel and Princess Mary's Hospital, Halton.

Materials and methods

Patients were selected from those attending the general ENT clinics at Whitechapel and Halton with perennial, rhinitis, defined as the presence of nasal obstruction, paroxysmal sneezing and seromucinous rhinorrhoea. Patients with a personal or family history of atopy were excluded as were patients with a positive skin prick test to any of the common inhaled allergens (mixed tree pollen (B3), weed pollen (B5), grass pollen (B2), house dust, house dust mite, feathers, cat and dog fur). Patients with nasal polyps, nasal sepsis, a deviated septum or abnormal sinus X-rays were excluded. All treatment was stopped for a period of four weeks before admission to the trial after which the patients underwent baseline symptom scoring on a scale of 0–5 for nasal obstruction, anterior rhinorrhoea, posterior rhinorrhoea, sneezing and facial pain. All patients were given detailed instructions and a demonstration of the use of the spray; they were asked not to take any other medication for their nasal symptoms. Symptom scoring was repeated at the crossover point (12 weeks) and at the end of the trial (24 weeks). Rhinomanometry using Brom's method was performed with the symptom scoring but showed too wide a variation between baseline and placebo values for the results to be considered significant. Each p atient was asked at the end of the trial and before disclosure if they wished to continue using either treatment and, if so, from which phase of the trial.

Results

Twenty-three patients were recruited into the trial. Five patients withdrew in the placebo phase and two patients withdrew in the treatment phase, in all cases because their symptoms became intolerable. There were no adverse reactions.

Symptom scoring

Each of the five symptoms scored was analysed using

the Wilcoxon paired-sample test procedure comparing BDP with placebo and BDP with baseline phases. The total score for each symptom tested was lower for BDP than for either placebo or baseline. However the difference was only significant for nasal obstruction (baseline vs BDP, $p = 0.02$), anterior rhinorrhoea (baseline vs BDP, $p = 0.03$) and posterior rhinorrhoea (placebo vs BDP, $P = 0.03$).

When the composite scores for all five symptoms were compared there was a significant difference between BDP and baseline ($p = 0.01$) and BDP and placebo ($p = 0.02$).

Patient preference

Eleven patients expressed a preference for BDP, one patient preferred placebo and four patients did not wish to continue with either treatment. This difference is highly significant (Chi-square = 14.81, 2 d.f., $p<0.01$).

Discussion

In this study all the patients had long-standing and severe symptoms of perennial rhinitis for which most had already received courses of topical steroids without benefit. We found that 69 per cent of the patients experienced an overall improvement in their symptoms after BDP 600 μg/day for 12 weeks. Of the five symptoms considered nasal obstruction showed the most marked improvement, a finding in common with other studies (Gibson *et al.*, 1974; Jones and Kenyon, 1988; Tarlo *et al.*, 1977). However it may be that this is the symptom which the patient finds most easy to evaluate. Perhaps more significantly, 69 per cent of patients completing the trial opted to continue on this regimen. This figure is somewhat lower than the 80 to 90 per cent response usually achieved by steroid inhalers in allergic rhinitis but very much better than the 23 per cent response rate found by Jones and Kenyon (1988) in non-atopic rhinitis after six weeks of BDP 400 μg/day. We believe that this provides some support for the hypothesis that patients with non-atopic rhinitis require a longer course and/or a higher dose of inhaled steroids to control their symptoms than those with allergic rhinitis.

The high rate of withdrawal from the study was disappointing but unsurprising: our patients were selected for the severity of their symptoms, the trial was protracted (nearly 6 months) and patients were not permitted to use any additional medication. However amongst the trial patients there was a minority who clearly did not respond to inhaled steroids even in a high dose for a long period. It is recognized that some cases of non-atopic rhinitis are refractory even to intraturbinate steroid injections (Mabry, 1983) and it seems likely that patients with non-atopic rhinitis are a heterogeneous group containing a minority who are unresponsive to steroids in any form or concentration. A better understanding of the aetiology of the condition might allow this group of steroid-resistant patients to be recognized at an early stage and submitted for alternative treatment.

The complete absence of side-effects was encouraging given that we were prescribing a dose 50 per cent above the recommended daily doses. Previous studies of inhaled steroids (Bende and Rundcrantz, 1985; Kohan *et al.*, 1989; Pipkorn and Berge, 1983; Tarlo *et al.*, 1977) have shown strikingly few side-effects and mucosal biopsies have revealed no significant change after as long as 48 weeks treatment (Knight and Kolin, 1983; Pipkorn and Berge, 1983). Gibson *et al.* (1974) found no evidence of adrenal suppression from their use of BDP and a dose of 1500 μg/day can be given by a pulmonary inhaler without causing adrenal suppression in adults (Smith and Hodson, 1983). Further studies are required to establish the relative efficacy of a higher dose of BDP in non-atopic rhinitis but there appear to be no significant risks associated with it.

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Squadron Leader B. J. O'Reilly, F.R.C.S.Ed.,
Consultant ENT Surgeon,
Princess Mary's Air Force Hospital,
Halton, Aylesbury,
Bucks HP22 5PS.