PRACTICE OBSERVED

Practice Research

Randomised double blind controlled clinical trial of intranasal budesonide in treatment of hay fever

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Abstract

The effectiveness of budesonide, a new non-halogenated glucocorticoid administered by nasal inhaler, was evaluated in a double blind comparison with placebo in patients presenting with hay fever. Patients were supplied with antihistamine tablets and eye drops for use when they considered that their symptoms were inadequately controlled by their inhaler. Patients recorded the severity of their symptoms in a daily diary card and visited their general practitioner for assessment weekly for four weeks.

All nasal symptoms of hay fever were appreciably reduced in the group taking budesonide and, although their eye symptoms were more severe than in the group taking placebo, they did not use appreciably more eye drops than the latter. The placebo group used appreciably more antihistamine tablets than those in the budesonide group. No patients were withdrawn from the budesonide group because of treatment failure or unacceptable side effects. The results suggest that budesonide is an acceptable and effective treatment for the nasal symptoms of hay fever.

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Introduction

The clinical picture of hay fever is familiar to general practitioners, with its combination of eye and nasal symptoms that result in degrees of upset from mild inconvenience to severe, almost disabling distress. The results of the 1971 general practice morbidity survey showed an annual consultation rate of 11.0 per 1000 patients.¹ Over longer periods Fry observed a consultation rate of 20 per 1000 patients and Hodgkin 3.1 per 1000.^{2,3} The latter differences in frequency may reflect local factors.

Several preparations for hay fever are prescribed in general practice, including antihistamines, nasal vasoconstrictors, sodium cromoglycate, and corticosteroid and desensitising injections.⁴ The nasal inhalation of a topical steroid, such as bedomethasone dipropionate, has recently proved an acceptable treatment in many patients. Topical corticosteroids seem to be efficient and safe in both adults and children.^{5,6}

Budesonide is a new non-halogenated glucocorticoid that has been introduced for the treatment of asthma.⁷ In vasoconstrictor tests on the human skin to determine the topical anti-inflammatory potency of corticosteroids budesonide was roughly twice as potent as bedomethasone dipropionate.⁸ In a single blind comparison in patients with hay fever induced by grass pollen, sections of an ear, nose, and throat department in Sweden budesonide given intranasally twice daily gave better relief from symptoms than bedomethasone given four times daily, the total daily dosages being identical.⁹

The results of a double blind Danish study in which staff members of a Copenhagen hospital volunteered to participate showed the superiority of budesonide over placebo in relieving the nasal symptoms of hay fever induced by grass pollen.¹⁰ Appreciably better results for budesonide over placebo were found in another double blind Swedish study of patients attending an ear, nose, and throat department as outpatients.¹¹

When these patients are included in a further end point analysis, symptoms free day accounted for 1720 of the 2041 daily reports of nasal symptoms made by the patients taking budesonide. Thus 66% of all reports from patients regarding nasal symptoms in the budesonide group show that they were free of these symptoms. The figure for the patients taking placebo was 34%. The daily reports of moderate or severe nasal symptoms account for only 10% of the reports by patients taking budesonide, compared with 26% for patients taking placebo.

SIDE EFFECTS

No patients were withdrawn from either group because of unacceptable side effects. Although one patient in the placebo group was withdrawn because of a combination of lack of efficacy and headaches. Nine patients in the budesonide group and six in the placebo group reported headaches at some point in their diary cards. Nine patients in the budesonide group and 10 in the placebo group reported a sore throat or hoarseness, or both. Six patients in the budesonide group and five patients in the placebo group reported nosebleeds. Drowsiness was reported by 10 patients who had taken antihistamine tablets, but also by 18 taking placebo and 20 taking budesonide who had not taken antihistamine tablets at any time during the week when this symptom was reported.

Discussion

Although no data were available for the pollen counts experienced by individual patients, analysis of the pooled data using daily pollen counts from the one centre in Leeds suggests that variation in the pollen counts between the budesonide and placebo groups was unlikely so as to bias the results in favour of the budesonide group. The pollen count recorded at the centre in Leeds was in the range 0 to 40 counts/m³ of air for about 30% of the days in the study of each group. At this level a comparable percentage of symptom free days would be expected in the data used for analysis of the effectiveness of the treatments, and this would reduce the level of any differences in symptoms experienced by patients in the placebo and budesonide groups. None the less, there was an appreciable excess in the level of the four nasal symptoms—stinging, itching, nasal blockage, runny nose, and nasal itching—experienced by patients taking placebo despite the greater number of antihistamine tablets taken by this group.

Table II suggests that patients in the budesonide group used slightly more eye drops than those in the placebo group: 75% of patients in the budesonide group used 21 eye drops or fewer between days four and 28 inclusive and 75% of patients in the placebo group 18 drops or fewer. Patients in the budesonide group, however, used appreciably fewer tablets: 75% of patients using five tablets or fewer, and in the placebo group 24 tablets or fewer. Clearly, any difference in use of eye drops is slight compared with the difference in use of tablets.

The increased use of tablets attenuated the severity of eye symptoms in patients in the placebo group, but, interestingly, patients in the budesonide group do not seem to have compensated for this lack of attenuation of eye symptoms by an appreciably comparable increase in the use of eye drops. This finding may imply some lack of concern for the remaining eye symptoms given that the severity of their nasal symptoms was being reduced by the use of budesonide.

In considering the results, however, the analysis of those 60 patients who completed the full four weeks' study underestimates the actual effect of budesonide in controlling nasal

symptoms since it does not allow for the withdrawal of the eight patients who used the placebo inhaler and considered this ineffective. A final analysis including these patients showed that the mean percentage of symptom free reports for nasal symptoms were 66 and 34 for the budesonide and placebo groups respectively. Perhaps more strikingly, 61% of patients in the budesonide group were free of nasal symptoms for 75% of their reports compared with 9% in the placebo group. None of the patients in the budesonide group was withdrawn from the study because of possible side effects, and analysis of all reported events in the diary cards showed no evidence that patients taking budesonide experienced more problems associated with treatment than patients in the placebo group.

The results show that intranasal budesonide in a dose of 200 µg twice daily is appreciably superior to placebo in controlling the nasal symptoms of hay fever. There is also evidence that some hay fever patients who have their nasal symptoms well controlled may not feel the need to resort to further medication for their eye symptoms.

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There have been no studies in the community of budesonide. Our study was designed to investigate the efficacy and possible side effects of treatment with intranasal budesonide compared with placebo in patients who present to their general practitioners and have free access to antihistamine tablets and eye drops for their hay fever.

Methods

Patients between the ages of 16 and 40 who had hay fever symptoms between 1 April and 31 August in each of the two preceding years were admitted to the study. In April and 31 July 1983 if they presented to their general practitioners with at least three of the following six symptoms: bouts of sneezing, nasal blockage, runny nose, nasal itching, eye itching, and running eyes.

Patients who had received desensitising injections in either of the two previous years were excluded from the study as were patients using inhaled or oral steroids, bronchodilators, or sodium cromoglycate treatment, or any combination of these. Also excluded were patients who were pregnant or who had an intermittent respiratory tract infection.

The study was performed as a double blind controlled trial, patients being randomly allocated into one of two treatment groups after they had given written informed consent to their participation. One group was supplied with a nasal inhaler that administered 50 µg of budesonide per inhalation, while the control group received a placebo nasal inhaler. Both groups were asked to administer two puffs of the inhaler into each nostril twice a day. The budesonide group therefore received 200 µg twice daily.

Patients in both the budesonide group and the placebo group were supplied with chlorpheniramine tablets and atropine-phenylephrine eye drops to be used in appropriate dosage if their hay fever symptoms were not controlled sufficiently by the trial medication within three days. An information sheet was supplied to patients that reinforced the instructions that they were given by their general practitioner.

On admission to the study patients were asked to rate the six symptoms of hay fever as none, mild, moderate, or severe and were given a diary card on which to record, at the end of each day of the subsequent seven days, the level of their symptoms and the number of chlorpheniramine tablets and eye drops used. Patients were asked to record any side effects or other medication used and instructed to post the diary card directly to the division of general practice at the end of the seven day period. Patients were seen weekly for a further four weeks for review; a further diary card for seven days was issued at each of the first three follow-up visits. Patients in both the budesonide group and the placebo group were, therefore, expected to use their inhaler for four weeks.

Patients were withdrawn from the study if they considered that the medication was not helping their symptoms or if they had any unacceptable side effects. Daily pollen counts were recorded at a site in Leeds during the study. Subsequently, data from the patient diary card were related to the pollen count for the corresponding day.

Results

Eighty four patients were entered into the study. Of these, 16 patients did not complete the study for reasons other than to the lack of efficacy or possible side effects of medication. A further eight patients, all in the placebo group, were withdrawn at their request during the trial because of unacceptable levels of hay fever symptoms. No patients were withdrawn from the budesonide group because of treatment failure or side effects. Of the remaining 60 patients, 30 each had been randomly allocated to the placebo group or to the budesonide group. The following analysis relates to the 60 patients.

COMPARABILITY OF PLACEBO AND BUDESONIDE GROUPS

Pollen exposure during the study.—Comparison of the treatment groups in respect of severity of initial symptoms and exposure to pollen using a χ^2 test of independence showed no significant differences between the placebo and budesonide groups.

Symptom severity on entry into the study.—Data for all nasal symptoms were grouped together as were data for both eye symptoms since the frequencies were too small to make statistical comparisons of the

two treatment groups symptom by symptom. Subsequent analysis by the χ^2 test of independence showed no significant difference in severity of initial symptoms between the budesonide and placebo groups.

EFFECTIVENESS OF BUDESONIDE AND PLACEBO IN CONTROLLING SYMPTOMS

Use of antihistamine tablets and eye drops.—The median number of tablets used by the placebo and budesonide groups as recorded in the diary cards was 7.5 and 0 respectively. Table I shows the frequency distribution for tablet use. The result of the Wilcoxon

TABLE I—Frequency distribution of consumption of antihistamine

No. of patients receiving placebo (n = 30)	No. of antihistamine tablets taken					
	0	1-10	11-20	21-30	31-40	41-50
	6	12	3	2	3	4
No. of patients receiving budesonide (n = 30)	18	7	2		2	1

rank sum test showed that the placebo group took significantly more antihistamine tablets than the budesonide group ($p < 0.005$). Similar analysis was carried out for the use of eye drops, the median number of eye drops used by the placebo and budesonide groups being 8 and 0 respectively. There was no significant difference between the median number of eye drops used by the two groups (Wilcoxon rank sum test $p = 0.31$). Table II shows the frequency distribution for use of eye drops.

TABLE II—Frequency distribution of use of antihistamine eye drops

No. of patients receiving placebo (n = 30)	No. of eye drops used					
	0	1-20	21-40	41-60	61-80	81-100
	11	13	1	3	2	
No. of patients receiving budesonide (n = 30)	8	14	1	2	2	2

Levels of symptoms recorded by patients.—The data on the diary cards for the six symptoms were analysed separately. Patients who had not had a particular symptom in the previous two years and who were not complaining of that symptom on entry into the trial were excluded from the analysis of that symptom. To ensure that the patient's response to treatment had achieved a steady state, data for days 1, 2, and 3 of each patient's diary card were excluded from the analysis. Statistical comparisons were made using the χ^2 test of independence, the null hypothesis being that the severity of symptoms was independent of the treatment group. Analysis showed that patients in the budesonide group experienced all four nasal symptoms less severely than those in the placebo group. In contrast patients in the placebo group suffered the two eye symptoms less severely than those in the budesonide group, possibly reflecting the greater use of antihistamine tablets in the placebo group. The difference for each of the six symptoms was statistically significant. Table III shows the frequency distribution of the level of severity of all four nasal symptoms combined, as reported by patients in the placebo and budesonide groups. The comparison excludes the eight patients who used the placebo inhaler and did not complete the 28 days of their study period because of ineffective control of symptoms.

TABLE III—Frequency distribution for severity of nasal symptoms

No. (%) of reports from 30 patients receiving placebo (n = 30)	Severity of symptoms			
	None	Mild	Moderate	Severe
	8 (26.7)	10 (33.3)	4 (13.3)	8 (26.7)
No. (%) of reports from 30 patients receiving budesonide (n = 30)	17 (56.7)	6 (20.0)	2 (6.7)	5 (16.7)

Life Changes

Leaving school

ALEXANDER L BROWN

The following accounts were written by two young men who had left school some time before.

Personal account

The decision what to do on leaving school seemed to come suddenly, though for years I knew that I had to face it. Sixteen years of school is enough for most people, and if you have got nowhere academically staying on is a waste of time. I decided to try college. The rules were different, the teachers had stopped running about after you. I stepped into a faster life and enjoyed it to the full, forgetting the future and living for the moment. But I got fed up with having no money and wasn't interested in the course so I left to get a job.

You take it for granted that getting a job will be quite easy but you find that there is hardly any work around. When you are first unemployed you are not really too concerned. But then being out of work affects you. You become lethargic and the less you do, the less you want to do. This creates tension in the family and everybody ends up rowing. Even though you are paid benefit, money is less important than actually working. From having something to do each day and feeling as though you are getting somewhere, a lot of days become the same and you get bored.

I personally regret not working harder at school, but it is no good dreaming about the past because that will not change it. When I left I didn't at first realise that I had responsibilities. I don't hold anyone but myself responsible now and know that I will sort things out.

Personal account

"Enjoy your school days—they are the best days of your life" was what I was told. Mine were happy and successful. I did well academically and at sport. Long hours of study to get the necessary grades for university entrance had, however, made me irritable at home. I felt that it was right for me to enter a new, more independent life. My only regret was that I would not see my girlfriend as much: she was going to a college 200 miles away from mine.

At first I lived in an all male hall of residence that housed 400 students, and felt lucky to be in a corridor of affable, friendly blobs. Superficially I mixed well, but did not seem to feel the excitement the other freshers exuded, nor become involved in their frenetic proceedings. I was disappointed at being treated like a schoolboy and felt that my fellows were rather immature. I drifted from one group of freshers to another but felt that mem-

bership of any group compromised any sense of independence. It was a Catch 22: if you didn't swing along you swung alone. My loneliness was especially acute when I found myself at "cattle market" parties and discos. The "grab a woman while you can still stand up or before they have all gone" philosophy made me feel out of place. I wondered if my girlfriend was similarly placed.

I felt that I was losing my identity because I did not know the people around me sufficiently well to be able to compare myself with them. When I met my girlfriend neither of us was happy. I tried to transfer to a university nearer to her college but this was not possible. I was shocked to find out, on returning home once, that my father had been seriously ill and I had not been told.

I began my second year well enough academically, but had begun to doubt myself and whether I could complete the course. I became depressed and was put on tablets for this by my general practitioner. My tutor agreed with me that I could not take further examinations while in this state. I decided to take a year out and worked as a nurse in a hospital for mentally handicapped children. I am now back at university and this time enjoying it: the place hasn't changed but I have.

Doctor's comment

The school days of everyone are similar in at least one respect. Order is imposed on daily life by external authority. Thus not only are lessons timetabled but private study is arranged to a schedule and exercise is taken in the form of prescribed games. Attitudes and beliefs are moulded by the ethos of the school. The security engendered by such regimentation is mentioned by both writers above. A decision about future career is usually taken with parents, but a young person is faced with some freedom of choice in an important matter, probably for the first time. A great deal of the future may be at stake so the decision is an important one. Even those, like the first writer, who find school tedious and experienced a sense of release on leaving, soon found that freedom carries with it accountability and the feeling of being responsible for oneself can be alarming.

Some of the problems encountered on leaving school by three groups of youngsters will now be considered.

Those who go straight to work seem to have fewest problems. Though many may continue living at home, a new status, that of a wage earner, has been achieved. Until marriage, when a young man may spend in pursuit of pleasure. Problems include tiredness at the end of a working day and boredom with repetitive work. Some may resent being exploited as "cheap labour." For the more ambitious continuing education is now possible—for example, evening classes and the Open University. The recently introduced Youth Training Scheme guarantees employment and training for a year, but many probably feel uncertain about the prospect of longer term employment.

Those who become unemployed—Society faces a dilemma in regard to unemployment in school leavers. The traditional "work ethic" continues and is likely to lead to frustration and a sense of

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