Hay fever treatments — which should be tried first?

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SUMMARY. A series of comparative trials on nine popular and pharmacologically distinct regimens for the treatment of hay fever was undertaken in the course of normal general practice in the pollen seasons of 1981–83. One hundred and forty doctors recruited 640 patients to assess the overall usefulness of the treatments on daily diaries. 'Usefulness' was scored on a linear analogue scale weighing up the degree of hay fever symptoms during treatment, side effects and ease of use of the preparation.

The regimen with the highest overall usefulness score was beclomethasone diproprionate with sodium cromoglycate eye drops (Beconase and Opticrom). Although the score was not significantly higher than those for methylprednisolone acetate (Depo-Medrone), astemizole (Hismanal) or terfenadine (Triludan), Beconase/Opticrom scored significantly better than mequitazine (Primalan), chlorpheniramine maleate (Piriton), sodium cromoglycate nasal insufflation with xylometazoline/antazoline eye drops (Rynacrom and Otrivine-Antistin) and azatadine maleate (Optimine). Beconase/Opticrom was first in rank order with respect to all the other regimens for the treatment of both mild and severe hay fever. Dimethothiazine (Banistyl), also shown to be useful, has since been withdrawn from prescription.

Introduction

HAY FEVER is the second most common chronic condition seen in general practice[1] and it causes distress to as many as one in 10 of the population of the United Kingdom.[2] Because avoidance of pollen allergens is generally not practical, treatment rests chiefly on four different forms of medical management: steroids, antihistamines, sodium cromoglycate and immunotherapy.

In the UK there are at present over 40 different preparations approved for the treatment of hay fever.[3] There is, however, little scientific evidence available to doctors to guide their choices in either changing an unsuccessful medication or prescribing in new cases.

In an attempt to rationalize prescribing policies for hay fever a series of comparison trials were undertaken between nine different regimens. The emphasis was on comparing these treatments in the normal practice setting.

The choice of drugs was determined using the following criteria:

— all major types of hay fever treatments with the exception of immunotherapy were to be included, that is steroids, antihistamines and cromoglycates;

— combinations of drugs were to be employed which a pilot survey of 30 general practitioners had shown to be widely used;[4]

— only pharmacologically distinct types of antihistamines were to be compared;

— drugs available without a doctor's prescription were to be represented as well as those available only on prescription.

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Method

The method used in this investigation was developed in two previous studies carried out in 1979 and 1980.[4,5]

The trial was carried out during the successive grass pollen seasons of 1981, 1982 and 1983. In 1981 and 1982 seven regimens were compared:

1. Beclomethasone diproprionate nasal spray 100 mg (Beconase, A and H), twice daily with sodium cromoglycate 2% eye drops (Opticrom, Fisons) four times daily.
2. Methylprednisolone acetate 40 mg (Depo-Medrone, Upjohn) intramuscularly, one dose.
3. Dimethothiazine 20 mg (Banistyl, M and B) three times daily (subsequently withdrawn from prescription in the UK).
4. Azatadine maleate 1 mg (Optimine, Kirby-Warrick) twice daily (available without prescription).
5. Mequitazine 5 mg (Primalan, M and B) twice daily.
6. Chlorpheniramine maleate 4 mg (Piriton, A and H) three times daily (available without prescription).
7. Sodium cromoglycate nasal insufflation 10 mg (Rynacrom, Fisons) four times daily with xylometazoline hydrochloride 0.05%, antazoline sulphate 0.5% eye drops (Otrivine-Antistin, Zyma) three times daily (available without prescription).

In 1983 the regimen which had performed best in the initial trials was compared with two newly introduced antihistamines:

8. Astemizole 10 mg (Hismanal, Janssen) daily.
9. Terfenadine 60 mg (Triludan, Merrell) twice daily (available without prescription).

Six hundred research-minded doctors from the faculty lists of the Royal College of General Practitioners were approached, and 214 agreed to participate. In 1981 and 1982 each participating doctor was provided with two sets of seven diaries with the seven different treatment regimens written on their front pages. These were randomized by latin square design and enclosed in sequentially numbered sealed envelopes. In 1983 each doctor received two sets of three diaries for the three treatments.

All patients over the age of 11 years requesting treatment for hay fever were eligible for entry into the trial. The doctor was instructed to open the envelopes in sequence and prescribe the treatment written on the diary using a normal FP10 prescription. This prescription and the diary were handed to the patient with a stamped addressed envelope, so that on completion patients could return it directly to the trial centre. If a treatment was considered unsuitable by either the patient or the doctor, the uncompleted diary was returned to the trial centre after recording the reasons for the refusal on it. The patient was not then entered into the trial.

After allocation of treatment, patients were asked to complete the daily diary record of the 'usefulness' of the treatment for 28 days. In assessing usefulness patients were told to weigh up the severity of hay fever symptoms during treatment, side

effects and ease of using the preparation. Patients recorded their assessment by marking an 'X' on a 10 cm line; one end of the line represented 'very bad' and the other 'very good'. Doctors' evaluations of the treatments were not sought.

A measure of compliance for each regimen was obtained by requesting the patient to record on the diary the amount of drug used each day.

A short questionnaire for patients to complete was prefixed to the diary. This enabled variations in response to be related to patients' clinical characteristics. Space was also left for patients to record any additional comments.

Data on the pollen count was obtained wherever available so that the scores for usefulness of drugs could be related to variations in pollen count.

It was anticipated that many patients would agree to take part but fail to return the diaries. Because of the difficulties in following up such cases, the analysis was based only on returned diaries but a random sample of 12 doctors returned information on all patients to whom they issued diaries, so that comparisons could be made between those who returned data and those who did not.

Data analysis

The differences between the regimens were analysed by computer using generalized linear interactive modelling (GLIM).[6] Comparisons were made between all the regimens and repeated, taking into account potential confounding variables, including two-way interactions (F tests). The variables included in the model were: age, sex, previous severity of hay fever, type and frequency of symptoms. A separate analysis was also made using pollen count data in order to investigate whether it was necessary to allow for this in making fair inter-treatment comparisons. Pollen count data were only available in a subgroup of 185 patients but it was possible to compare pollen levels for each day that diaries were completed.

Residuals from this model were examined in each analysis to test that they were normally distributed. Also a special analysis was undertaken to check that drop-outs had not resulted in patients with different characteristics being on different regimens (chi-squared test).

Pilot trials

For the validation of the diaries 128 patients were recruited to a pilot study in 1980.[5] It was shown that symptom relief scores were highly significantly correlated with usefulness scores and accounted for 40% of their variance. Similarly, side effect scores significantly correlated with usefulness scores, accounting for 17% of their variance. Symptom scores on analogue lines showed a highly significant and logical association with variations in pollen count, a finding which corroborated the belief that such diary scores are clinically meaningful. Since precise clinical interpretations of analogue line scores are difficult, they were compared with those on the more easily understood four-point Likert scales. Likert category 'very good' for usefulness corresponded to a mean analogue line score of 86.3 mm (standard deviation 12.5), 'good' to 62.6 mm (SD 15.3), 'bad' to 31.4 mm (SD 12.8) and 'very bad' to 11.9 mm (SD 10.9).

In this same pilot study six doctors obtained clinical data from all hay fever sufferers presenting for treatment in their practice. No clinical or demographic differences were found between those who agreed to enter the clinical trial and those who refused to participate.

The discriminatory power of the diary method was calculated. It was found that 50 patients in each treatment group could reveal a real 13 mm difference between regimens (type I error = 5%, type II error = 10%).

Results

Of the 214 doctors who initially agreed to help, in 1981 and 1982, 140 recruited patients. In 1983, 66 doctors said they would help and 48 of them recruited patients. These doctors handed out a total of 1483 diaries of which 900 were returned to the trial centre. Of the returned diaries 185 were for treatments that had been refused by either the doctor or the patient. A further 75 diaries were excluded from analysis for one of the following reasons: extra concurrent medication had been used (18); the patient had perennial rhinitis with no summer seasonal peak (11); the patient was below the age limit (15); the diary was illegible (8); the treatment was not issued according to the trial design (23). Patients were not excluded, however, if they had symptoms all the year round but also had a summer seasonal peak. The total number of diaries available for analysis was 640 (Table 1).

Characteristics of the study population

Table 2 shows the demographic and clinical characteristics of the study population. As the findings were similar in each season of the study, the results have been pooled. Two-thirds of patients classified their symptoms as having been 'bad' in the previous hay fever season. The symptoms of hay fever were a combination of nasal blockage (89.3%), running nose (97.1%) and itching/sneezing (99.2%), with 97.4% of patients experiencing some eye trouble; 'muzzy head' was reported by 75.2% of patients (Table 3).

From the data provided by the sample of 12 doctors who recorded every patient entered into the trial no differences in characteristics were found between those patients who returned diaries and those who did not.

Diary score comparisons

The overall mean diary scores of usefulness for each treatment regimen are shown on Table 4 and a scattergram of individual scores is shown in Figure 1. These scores were normally

Table 1. Total number of diaries issued to patients, number analysed and number returned but not analysed.

Year and treatment	Diaries used in analysis	Diaries returned but not analysed: Regimen refused by doctor	Regimen refused by patient	Diary unsuitable for analysis	Total diaries issued
1981/1982					
Beconase/ Opticrom	88	3	2	7	185
Depo-Medrone	62	46	24	4	202
Banistyl	64	9	9	7	175
Optimine	84	6	7	12	175
Primalan	84	11	10	11	182
Piriton	56	4	32	14	166
Rynacrom/ Otrivine-Antistin	72	9	7	11	179
1983					
Beconase/ Opticrom	43	0	2	2	73
Hismanal	49	0	2	3	72
Triludan	38	0	2	4	74
Total	640	88	97	75	1483

Table 2. Demographic and clinical profile of study population.

	Number (%) of patients
Sex	
Males	281 (*43.9*)
Females	359 (*56.1*)
Age	
12–19 yrs	140 (*21.9*)
20–39 yrs	430 (*67.2*)
40–59 yrs	58 (*9.1*)
60+ yrs	10 (*1.6*)
Not recorded	2 (*0.2*)
Severity of hay fever in previous years	
'Mild'	197 (*30.8*)
'Bad'	413 (*64.5*)
Not recorded	30 (*4.7*)
Symptom frequency	
'On odd day'	146 (*22.8*)
'Continuously'	463 (*72.3*)
Not recorded	31 (*4.8*)
Seasonality	
'Only in summer'	513 (*80.2*)
'Perennial but worse in summer'	117 (*18.3*)
Not recorded	10 (*1.5*)
Use of treatments	
'Only when symptomatic'	230 (*35.9*)
'Every day of season'	336 (*52.5*)
Not recorded	74 (*11.6*)

distributed after adjustment was made for age, sex and severity in previous year. The regimen that showed the highest scores for usefulness was beclomethasone diproprionate nasal spray (Beconase)/sodium cromoglycate eye drops (Opticrom). Of the patients taking this regimen, 75.6% used both, 1.7% used Opticrom alone, and 22.6% Beconase alone. All patients were included in the group as it was considered important to compare treatments as they are actually used. The analysis showed that Beconase/Opticrom was significantly better than the regimens of Optimine ($P<0.05$), Primalan ($P<0.01$), Rynacrom/Otrivine ($P<0.01$) or Piriton ($P<0.01$). Four of the other regimens were not significantly worse than Beconase/Opticrom: Banistyl (now withdrawn from prescription), Depo-Medrone, Hismanal and Triludan. The only clinical or demographic factors related to outcome were age, sex and the patient's own classification of the severity of his previous season's hay fever. Males and older people tended to attribute significantly higher usefulness scores to all regimens. In contrast, patients who had more severe symptoms in the previous year recorded worse outcomes. Depo-Medrone was prescribed less often for mild hay fever but the patients on all treatment regimens were otherwise similar with respect to demographic and clinical characteristics.

Table 4 also shows that even when allowances were made in the analysis for the previous severity of hay fever, Beconase/Opticrom was still the regimen with the highest overall score for usefulness and there were only minor variations in the rank order of the other regimens. The same was found with respect to rank ordering even when variation in pollen count was taken into account.

Intention to treat analysis

Because of the high proportion of diaries issued which were not returned, an intention to treat analysis would have involved inventing dummy data for large numbers of cases. This was considered scientifically unacceptable and unnecessary in view of the finding that those who did not return their diaries did not differ clinically or demographically from those who did.

Side effects

Patients were asked to take account of side effects when assessing the usefulness of the treatments. However, there was space on the questionnaire for patients to record comments, including side effects. The principal recorded side effect was sedation on antihistamines, while the lowest prevalence for any record of side effects was for Depo-Medrone.

Self-recorded drug usage and compliance

The average daily dosage of drug reported by patients was calculated and compared with the actual recommended dose. Depo-Medrone could not be compared with other regimens since it was a single injection administered by the doctor. All regimens were recorded as having been used on a high proportion of the trial days. However, for those regimens used three or four times daily compliance was lower. On the other hand, for drugs requiring simpler twice or once daily use, in some instances more doses were taken per day than was recommended.

Discussion

In seeking guidance for their clinical decisions doctors often only have the results of placebo-controlled intervention studies which are far removed from the context of their routine work. The central aim of this study was to compare drugs in general practice using a method which interfered as little as possible with the usual clinical process. Outcome was measured by patients' own daily diary scores for each treatment's overall usefulness. These scores of usefulness were shown to be logically and significantly related to both symptom relief and side effects. The Beconase/Opticrom regimen were used on two successive trials and its scores were found to be reproducible.

Patients consistently gave the highest scores for usefulness to a regimen consisting of beclomethasone diproprionate nasal spray (Beconase) and sodium cromoglycate eye drops (Opticrom). Patients' comments and recording of side effects were also favourable to the Beconase/Opticrom regimen, and this held true even when allowance was made for variations in pollen count and severity of hay fever. In the initial pilot studies nasally

Table 3. Distribution of hay fever symptoms in the study population.

Symptom	Percentage of patients			
	'Never'	'A little'	'A lot'	'Very bad'
'Nose blocks' ($n=583$)	*10.7*	*30.6*	*37.5*	*21.2*
'Nose runs' ($n=625$)	*2.9*	*24.5*	*47.6*	*25.0*
'Nose itching or sneezing' ($n=635$)	*0.9*	*10.1*	*51.8*	*37.3*
'Eyes give trouble' ($n=636$)	*2.6*	*20.4*	*45.2*	*31.8*
'Gets muzzy heads' ($n=521$)	*24.8*	*52.6*	*22.0*	*0.6*

Table 4. Mean scores for usefulness of nine treatments: overall data and distribution according to self-assessed severity of hay fever in previous years.

Year and treatment	Previously mild symptoms			Previously severe symptoms			Overall		
	Mean score	(SD)	n^a	Mean score	(SD)	n^a	Mean score	(SD)	n
1981/1982									
Beconase/Opticrom	74.4	(20.0)	22	65.6	(19.1)	64	68.0	(19.5)	88
Depo-Medrone	60.1	(19.3)	11	64.0	(23.3)	48	62.6	(22.3)	62
Banistyl	59.0	(16.9)	22	63.7	(18.5)	40	62.6	(18.0)	64
Optimine	60.1	(18.4)	32	60.3	(21.0)	50	60.0	(19.7)	84
Primalan	58.1	(22.6)	26	54.8	(17.0)	53	56.6	(18.9)	84
Piriton	57.7	(17.4)	21	54.8	(20.8)	29	55.6	(19.5)	56
Rynacrom/Otrivine-Antistin	59.5	(17.7)	20	54.3	(22.2)	49	55.3	(21.8)	72
1983									
Beconase/Opticrom	62.9	(20.8)	13	66.9	(16.0)	28	66.6	(17.8)	43
Hismanal	61.2	(13.3)	16	58.7	(22.3)	31	60.5	(19.7)	49
Triludan	59.6	(13.9)	14	57.9	(15.9)	21	57.2	(15.2)	38

n = total number of patients. [a]30 missing observations because severity not recorded.

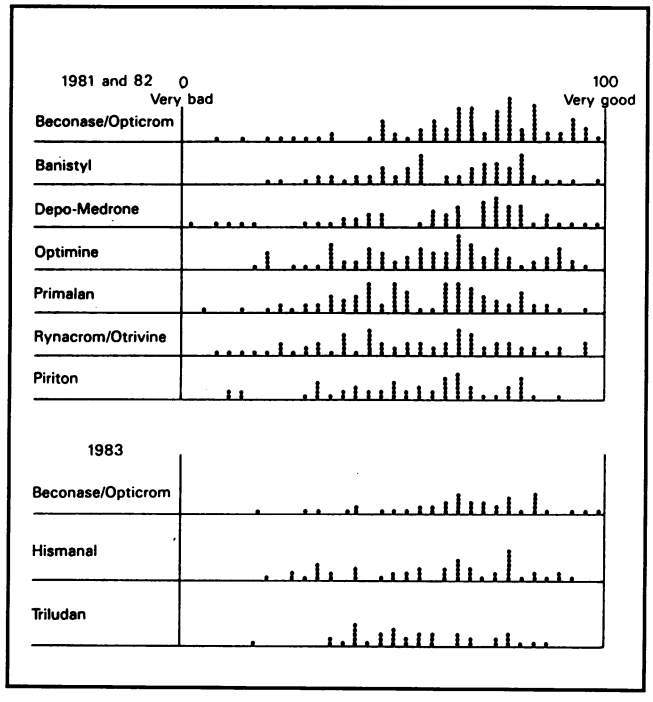

Figure 1. *Distribution of individual mean daily scores of usefulness for each patient and regimen.*

sprayed local steroids were also found to be the most effective treatment when compared with sodium cromoglycate, oxatomide and placebo.[4] For all grades of severity, medically prescribed treatments were superior, on average, to those available from pharmacists without prescription.

None of the regimens in these trials helped everybody and for each treatment a large number of patients remained symptomatic despite daily use of the drugs (Figure 1).

It is not clear why men tended to find current hay fever treatments more useful than did women. However, the fact that the older patients were helped more than the younger patients probably reflects the diminishing severity of this condition with age. Contrary to popular belief, there were no clinical sub-groups who did better on different treatments, for example, those with severe nose blocking did not respond better to steroids.

Clearly it was not feasible to evaluate all possible therapies for hay fever but these trials were fairly comprehensive in their choice of both treatments and regimens. In particular we compared treatments and regimens which are commonly prescribed. The decision not to include hyposensitization treatment was motivated by concerns for safety as much as for any technical difficulties,[7,8] and by the fact that a previous study has shown that hyposensitization is in no way superior to methylprednisolone acetate (Depo-Medrone) which was included in these trials.[9] The fact that hyposensitization has now been virtually withdrawn from use in general practice in the UK vindicates its exclusion from a study of first line therapy.

The inclusion of the single-dose intramuscular steroid preparation Depo-Medrone might be criticized on the grounds of hazard to the patient, however, unlike hyposensitization, there is no reported mortality from its use in hay fever. Anxieties have also been raised about prescribing even topical steroids such as beclomethasone to mild hay fever sufferers but this is unsupported by any evidence of hazard.

In conclusion the regimen of beclomethasone diproprionate nasal spray (Beconase) and sodium cromoglycate eye drops (Opticrom) emerged from these trials as being perceived by patients as most useful. It should therefore be one of the first treatments to be considered in prescribing to new hay fever patients and one of the first to bear in mind when others have failed. Furthermore, the value of any new treatment or new regimen for hay fever would be most stringently assessed when compared with Beconase and Opticrom. Four of the other regimens were not significantly worse than Beconase and Opticrom namely Banistyl, Depo-Medrone, Hismanal and Triludan. Banistyl has since been withdrawn from prescription but all the other drugs should be used in preference to Optimine, Primalan, Piriton and Rynacrom with Otrivine-Antistin.

At a time when, in the interests of economy, formularies and limited lists of drugs are being created, comparative trials such as this may prove helpful in the selection of treatments. Where medical interventions which have side effects are aimed at improving the symptomatic quality of life, it is both logical and feasible to use the patients own self-weighted assessments of the usefulness of treatments in making comparisons.

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