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Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis

Andreas Schapowal on behalf of Petasites Study Group

Allergy Clinic, Hochwangstrasse 3, CH-7302 Landquart, Switzerland

Andreas Schapowal *consultant in ear, nose, and throat medicine*

andreas.schapowal@freesurf.ch

BMJ 2002;324:144–6

Abstract

Objectives To compare the efficacy and tolerability of butterbur (*Petasites hybridus*) with cetirizine in patients with seasonal allergic rhinitis (hay fever).

Design Randomised, double blind, parallel group comparison.

Setting Four outpatient general medicine and allergy clinics in Switzerland and Germany.

Participants 131 patients were screened for seasonal allergic rhinitis and 125 patients were randomised (butterbur 61; cetirizine 64).

Interventions Butterbur (carbon dioxide extract tablets, ZE 339) one tablet, four times daily, or cetirizine, one tablet in the evening, both given for two consecutive weeks.

Main outcome measures Scores on SF-36 questionnaire and clinical global impression scale.

Results Improvement in SF-36 score was similar in the two treatment groups for all items tested hierarchically. Butterbur and cetirizine were also similarly effective with regard to global improvement scores on the clinical global impression scale (median score 3 in both groups). Both treatments were well tolerated. In the cetirizine group, two thirds (8/12) of reported adverse events were associated with sedative effects (drowsiness and fatigue) despite the drug being considered a non-sedating antihistamine.

Conclusions The effects of butterbur are similar to those of cetirizine in patients with seasonal allergic rhinitis when evaluated blindly by patients and doctors. Butterbur should be considered for treating seasonal allergic rhinitis when the sedative effects of antihistamines need to be avoided.

Introduction

Allergic rhinitis, whether seasonal or perennial, is characterised by sneezing, rhinorrhoea, obstruction of the nasal passages, conjunctival and pharyngeal itching, and lacrimation. Allergic rhinitis, often inappropriately called hay fever, is caused by the deposition of allergens (often pollen) on the nasal mucous membranes, resulting in a type I hypersensitivity reaction.[1 2]

Butterbur (*Petasites hybridus*; butter dock, bog rhubarb, exwort) is an Asteraceae herbaceous plant native to Europe, northern Africa, and south western Asia.[3] The leaves and roots of butterbur contain a mixture of eremophilan type sesquiterpenes (petasines). Extracts of butterbur have been used in bronchial asthma, smooth muscle spasms, and headache.[4] Petasines inhibit the biosynthesis of leukotrienes, which may be associated with antispasmodic activity and anti-inflammatory action in type I hypersensitivity.[5–7]

The usual treatment for seasonal allergic rhinitis is antihistamines. These reduce rhinorrhoea and sneezing but are less effective for nasal congestion and may cause sedation and drowsiness. Antihistamines can be obtained over the counter for treatment of hay fever, and all may interact with alcohol and decrease driving ability.[8] We conducted a randomised controlled trial of butterbur extract tablets (ZE 339) and a commonly used non-sedating antihistamine (cetirizine) to compare the effectiveness of these two treatments.

Participants and methods

All participants were outpatients attending four general medicine and allergy clinics between June 1999 and June 2000. Study medication consisted of butterbur (petasites carbon dioxide extract ZE 339 standardised to 8.0mg of total petasine per tablet; one tablet, four times daily) or cetirizine (one 10 mg tablet daily), as recommended by the manufacturers. Each day, participants took five tablets, four of which contained either placebo or butterbur, and one contained either cetirizine or placebo, depending on the treatment group. The study was approved by the relevant ethics committees in Germany and Switzerland.

Participants

All participants were aged ⩾18 years, had a history of seasonal allergic rhinitis for at least two consecutive years, and fulfilled the seasonal allergic rhinitis diagnostic criteria. Baseline assessment was made at the referral consultation, when the inclusion and exclusion criteria were checked. All participants had skin allergy tests, and all but one were allergic to pollen. They also had a full medical examination, after which they were given treatment for two weeks. Participants could return after one week if they experienced adverse events or deterioration. At the visit at the end of week 2, participants had a full medical examination and we checked compliance and adverse events. Exposure to pollen was confirmed for each participant through crosschecking the treatment period with the online regional pollen count service (www.pollenallergie.de).

Statistics, assignment, and analysis

Randomisation was provided centrally in blocks of four. Analysis was on an intention to treat basis, defined as all randomised patients who had at least one baseline and one follow up value and took any medication. The planned sample size was a minimum of 120 patients, based on previous studies of allergic rhinitis,[9 10] with a 10% expected withdrawal rate and an assumed effect size of 0.5.

The main outcome variable was change from baseline to end point in the score of each item on the medical outcome health survey questionnaire (SF-36).[10] The secondary outcome variables were the physicians' clinical global impression score and the SF-36 score for overall status.[11]

Between treatment comparisons were tested by the Mann-Whitney test (two sided). The exploratory secondary variables were evaluated by inference statistics with a shifted null hypothesis adjustment to

baseline according to the method of Abt,[12] with means, standard deviation, medians, 95% confidence intervals, and absolute and relative frequencies. For participants who withdrew we carried forward the last observation. The mean of both treatment groups was used to substitute missing values.

Results

Patients' characteristics and flow through study

A total of 131 patients were initially screened; six did not give consent, and 125 were randomised. Participants' characteristics at entry were similar in the two groups (table 1). The population was representative of patients with seasonal allergic rhinitis who seek treatment in the primary care sector

Table 1 Patients' characteristics at entry to study

Characteristic	Butterbur (n=61)	Cetirizine (n=64)
Demographics:		
Mean (SD) age (years)	39 (12)	35 (14)
Mean (SD) height (m)	1.72 (0.08)	1.71 (0.09)
Mean (SD) weight (kg)	71 (14)	69 (15)
No (%) of women	38 (62)	46 (72)
No (%) of smokers	20 (32)	24 (37)
Diagnostic characteristics:		
Sneezing (No (%) moderate or worse)	47 (77)	51 (79)
Rhinorrhoea (No (%) moderate or worse)	56 (92)	55 (86)
Itchy nose or eyes (No (%) moderate or worse)	43 (71)	49 (76)
Nasal congestion (No (%) moderate or worse)	45 (74)	50 (78)
Mean (SD) SF-36 item score (main outcome measures):		
Physical function	78 (19)	82 (21)
Emotional function	77 (38)	75 (39)
Vitality	54 (23)	52 (26)
Mental health	72 (20)	70 (20)
General health	60 (24)	60 (22)
Physical activity	46 (39)	46 (40)
Social functioning	71 (24)	70 (26)
Pain	69 (22)	71 (25)
Secondary outcome measures:		
Mean (SD) clinical global impression score (severity of condition)	5.6 (0.8)	5.6 (0.8)
SF-36 score for overall status (No (%) worse or much worse than 1 year ago)	27 (44)	32 (50)

Efficacy results

At the end of the treatment period none of the scores in the butterbur group was more than 10% worse than in the cetirizine group (table 2). The secondary outcome measures were also comparable in the two treatment groups.

Safety results

The overall incidence of adverse events was similar for the two treatments: 16% in the butterbur group (10/61) and 17% in the cetirizine group (11/64). No event could be considered to be typically associated with butterbur, all having been reported once or twice only. Conversely, two thirds of events in the cetirizine group were typical of antihistamines—that is, drowsiness and fatigue. One patient was withdrawn (butterbur group) because she required corticosteroids for previously existing asthma.

Discussion

Although seasonal allergic rhinitis is common, methodologically robust studies are difficult to conduct, not least because of the easy access to anti-allergic treatments by patients. These treatments include a large number of antihistamines and corticosteroid nasal sprays available without prescription. To overcome the possible contamination of results by the use of other treatments, we monitored patients closely and allowed them to visit the clinics whenever they felt their condition needed further intervention. To enhance patient compliance, and bearing in mind the acutely debilitating symptoms of hay fever, we also kept the treatment period as short as possible (two weeks). In our experience, patients with this condition do not tolerate ineffective treatments for longer periods.

The number of randomised controlled trials with herbal medicines has increased substantially recently.[13–15] Herbal treatments are being used more often by doctors and, in our experience, are often requested by patients.

Table 2 Results of primary and secondary outcome measures after two weeks' treatment

	Median score (minimum-maximum)		Median of differences	P value for comparison between medians*
	Butterbur (n=61)	Cetirizine (n=64)		
Primary outcome measures (SF-36 score)				
Physical function	95 (50-100)	95 (15-100)	0	0.75
Emotional function	100 (0-100)	100 (0-100)	0	0.89
Vitality	65 (15-95)	60 (5-95)	5	0.17
Mental health	80 (28-100)	84 (24-100)	0	0.50
General health	72 (30-100)	67 (25-97)	7	0.29
Physical activity	100 (0-100)	75 (0-100)	0	0.16
Social functioning	87.5 (50-100)	87.5 (0-100)	0	0.15
Pain	84 (41-90)	84 (22-90)	0	0.44
Secondary outcome measures				
Clinical global impression score:				
Severity of condition‡	–3 (–2-–6)	–3 (–2-–7)	0	0.82
Global improvement§	3 (2-7)	3 (2-6)	0	0.82
Risk to benefit§	4 (0.25-4)	4 (0.33-4)	0	0.79
SF-36 score for overall status (No (%) worse or much worse than 1 year ago)§	7 (11)	8 (13)	—	0.20

*Mann-Whitney test (two sided). Significant values mean the treatment effects are different.
†Mann-Whitney rank sum test (one sided). Significant values mean butterbur is not inferior.
‡Negative values represent improvement in scores.
§Results for these items are medians at endpoint not adjusted for baseline.
Note: Data are non-normally distributed for all items (Shapiro-Wilk: $P \leqslant 0.01$).

What is already known on this topic

Seasonal allergic rhinitis (hay fever) is common in countries with temperate climates.

Most patients have their symptoms treated for short periods, particularly during peaks in atmospheric pollen count

What this study adds

After two weeks, the effects of butterbur and cetirizine were comparable in patients with hay fever

Butterbur produced fewer sedating effects than cetirizine

Butterbur should be considered when the sedating effects of antihistamines must be avoided

Value of butterbur

Although the effects of butterbur have been linked to its constituents,[5–7] we set out to test whether its clinical effects in seasonal allergic rhinitis were comparable to those of antihistamines as judged separately and blindly by patients and their doctors. The results showed that the effects of the two treatments are similar. The trends in favour of butterbur in some measures need to be confirmed in future prospective trials. With regard to safety, butterbur was well tolerated and did not have the sedative effects associated with antihistamines. We believe butterbur should be considered for treating seasonal allergic rhinitis, particularly in cases where the sedative effects of antihistamines need to be avoided.

Contributors: see bmj.com

Funding: Zeller AG (Switzerland) supplied study medication and sponsored the study through the Clinical Research Organisation Praxis Klinische Arzneimittelforschung, Pohlheim, Germany. The interpretation of the results was the prerogative of the principal investigator and the study group.

Competing interests: None declared.

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(Accepted 13 September 2001)

Analysis of adherence to peak flow monitoring when recording of data is electronic

Helen K Reddel, Brett G Toelle, Guy B Marks, Sandra I Ware, Christine R Jenkins, Ann J Woolcock

Correspondence to:
H K Reddel
hkr@mail.med.usyd.edu.au

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BMJ 2002;324:146–7

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Peak flow monitoring is widely recommended in international asthma guidelines. However, suspicions about the accuracy of conventional pen and paper records were confirmed when studies with electronic spirometers showed poor adherence and falsification of data.[1] There seems to be a prevailing nihilistic attitude to peak flow monitoring, largely based on the perception that satisfactory adherence cannot be achieved. We aimed to measure long term adherence to electronic peak flow monitoring when participants were aware that data were being stored and used to guide treatment.

Participants, methods, and results

We obtained data from a 72 week randomised study comparing two starting doses of budesonide in patients aged 18-75 with poorly controlled asthma. The design and outcomes of the study are reported elsewhere.[2] The study incorporated two novel features: twice daily monitoring with electronic diary spirometers (MicroMedical DiaryCard; MicroMedical, Rochester, UK) and titration of dose of budesonide (weeks 17-72) by using a clinical algorithm based on peak flow and diary data. A cumulative chart of peak flow and forced expiratory volume in one second was discussed with each participant at each eight weekly visit. We assessed adherence to monitoring as the percentage of scheduled sessions recorded.

Median overall adherence to monitoring over weeks 1-72 or until withdrawal was 89% (interquartile range 69-97). Adherence declined gradually from 96% in weeks 1-8 to 89% in weeks 64-72 (Spearman's $R = -0.20$, $P < 0.0001$ for correlation between eight week period and adherence) (figure). Eight participants were withdrawn because of problems with adherence.

Comment

With appropriate use of electronic devices it is possible to achieve high levels of adherence to monitoring,