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(Accepted 20 March 2003)

Stepping down inhaled corticosteroids in asthma: randomised controlled trial

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Abstract

Objectives To determine whether the dose of inhaled corticosteroids can be stepped down in patients with chronic stable asthma while maintaining control.

Design One year, randomised controlled, double blind, parallel group trial.

Setting General practices throughout western and central Scotland.

Participants 259 adult patients with asthma receiving regular treatment with inhaled corticosteroids at high dose (mean dose 1430 µg beclomethasone dipropionate).

Interventions Participants were allocated to receive either no alteration to their dose of inhaled corticosteroid (control) or a 50% reduction in their dose if they met criteria for stable asthma (stepdown).

Main outcome measures Comparison of asthma exacerbation rates, asthma related visits to general practice and hospital, health status measures, and corticosteroid dosage between the two groups.

Results The proportions of subjects with asthma exacerbations were not significantly different (stepdown 31%, control 26%, $P=0.354$). Similarly, the numbers of visits to general practice or hospital and the disease specific and generic measures of health status over the one year period were not significantly different. On average the stepdown group received 348 µg (95% confidence interval 202 µg to 494 µg) of beclomethasone dipropionate less per day than the controls (a difference of 25%), with no difference in the annual dose of oral corticosteroids between the two treatment regimens.

Conclusions By adopting a stepdown approach to the use of inhaled steroids at high doses in asthma a reduction in the dose can be achieved without compromising asthma control.

Introduction

Inhaled corticosteroids are highly effective in the treatment of asthma.¹⁻³ Their potential for causing dose related side effects has, however, led to asthma management guidelines recommending a reduction in their dose once asthma control is established.²⁻⁴ Research evidence shows that a reduction can be

achieved in the short term, in mild disease, or with the addition of other antiasthma treatments.⁵⁻⁸ The clinical implications of this approach to treatment have not, however, been tested by means of a randomised controlled trial over the longer term or for patients with moderate to severe disease. We therefore tested the hypothesis that a stepdown approach to the use of inhaled corticosteroids at high dosage can be adopted safely in adults with chronic stable asthma.

Methods

Participants

We recruited 259 participants from general practices throughout western and central Scotland. Participants were aged 18 years and older, had a diagnosis of asthma⁹ for at least one year, and were being treated with at least 800 µg inhaled beclomethasone dipropionate daily (or budesonide or fluticasone propionate at equivalent dosage). We excluded patients if they had required oral corticosteroids or visited general practice or hospital for asthma in the preceding two months.

Study design

We conducted a multicentre, randomised, double blind, parallel group trial over a period of one year.

Protocol, assignment, and masking

Run-in—We collected baseline data and use of inhaled corticosteroids before the study during a one month run-in period.

Randomisation visit—After run-in, we randomised participants to either a reduction in their dose of inhaled corticosteroid (stepdown) or a sham reduction (control). Treatment allocation was withheld from the investigators until completion of the study.

Study inhalers—A central pharmacy produced two packs of inhaled corticosteroid for each participant according to the randomisation code. The packs were identical in appearance and labelled either “usual dose” or “reduced dose” (see bmj.com).

Study visits—At randomisation, participants received a pack containing inhaled corticosteroids at usual dosage. Subsequent study visits took place at three, six, nine, and 12 months, when asthma control

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BMJ 2003;326:1115-8

was assessed and an inhaler pack issued accordingly (good control=reduced dose, poor control=usual dose). Thus the dosage of inhaled corticosteroid remained unaltered in the control group, and in the stepdown group it went down or up according to asthma control.

Assessment of asthma control

Patients kept diaries of their peak expiratory flow during run-in and for two weeks before each study visit. Measurements were made morning and evening and the best of three attempts recorded. A "target" peak flow was calculated for each participant, defined as 80% of the mean peak flow during run-in.

We calculated a short asthma morbidity score at each visit.¹⁰ This was derived from a four item questionnaire relating to asthma symptoms and use of a reliever inhaler over the preceding month. Scores ranged from 0 (perfect control) to 8 (very poor control).

Study criteria for good control were an asthma morbidity score of 2 or less, no visits for asthma to general practice or hospital since the previous visit, and a peak flow greater than or equal to the "target" peak flow on eight of the past 14 days. If peak flow data were not available we used the first two criteria.

Management of worsening asthma

Participants were advised to use their reliever inhaler on a regular basis and to seek medical attention if symptoms failed to settle or their peak flow dropped to below 70% of the mean run-in peak flow. The attending doctor treated exacerbations with a course of oral corticosteroids as considered necessary.

Objectives and outcome measures

The primary objective was to compare between the two groups the proportion of participants who had an exacerbation of their asthma. Secondary objectives were to determine in the stepdown group the proportion of participants achieving a 50% reduction in their daily dose of inhaled corticosteroids while maintaining asthma control, and to compare between the two groups the number of asthma related events, the total dose of inhaled and oral corticosteroid administered, and any changes in health status over the one year period.

An asthma exacerbation was defined as any worsening of asthma requiring a course of oral corticosteroids. Asthma related events were defined as any admission to hospital, attendance at accident and emergency departments, visit to general practice, or home visit by the general practitioner, with worsening asthma. Participants graded compliance with study inhalers on a scale of 1 (poor) to 10 (excellent).¹¹

Participants completed two measures of health status, the St George's respiratory questionnaire and

EuroQol, at each visit.^{12 13} A score measuring the impact of chest disease on daily life and wellbeing was derived from the St George's respiratory questionnaire. This ranged from 0 (minimum impact) to 100 (maximum impact). The EuroQol is a generic measure of health related quality of life, including a visual analogue scale, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured before and after administration of inhaled salbutamol (200 µg from a volumatic spacer) by using a dry spirometer (Vitalograph, Buckinghamshire, United Kingdom), and the best of three attempts was recorded.

Analysis

We aimed to recruit 120 patients per group, to give the trial 80% power at a significance level of 5% to detect a clinically relevant difference in exacerbation rate of 15% between the two groups.

We performed intention to treat analyses for the full one year period. We calculated an annual dose of inhaled corticosteroids for each participant and expressed this in units of beclomethasone dipropionate (by using a conversion rate of 2 mg beclomethasone dipropionate=1 mg fluticasone propionate). Where participants were withdrawn before completing one year follow up we calculated an annual equivalent dose from the average daily dose.

For the St George's respiratory questionnaire, the short asthma morbidity score, and the EuroQol visual analogue scale we expressed the worst score recorded during follow up as a change from baseline and compared scores between the two groups.

Results

Between May 1999 and October 2001 we randomised 259 participants to the trial, and 212 (82%) completed one year follow up. The groups were similar with regard to baseline demographics and clinical characteristics. Altogether 109/130 (84%) of the stepdown group and 105/129 (81%) of the control group met criteria for good control, and these were issued with a "reduced dose" pack of inhaled corticosteroids at some point during the study. Sixty four (49%) participants in the stepdown group completed the study taking a reduced dose of inhaled corticosteroid (50% of starting dose) and with good control. Both groups reported good compliance with study inhalers (mean score 10/10).

Asthma exacerbations and asthma related events

We found no significant difference in the rate of asthma exacerbation or asthma events between the two groups (table).

Asthma exacerbations and asthma related events in the two groups. Values are numbers (%) of patients

	Stepdown group (n=130)	Control group (n=129)	Odds ratio (95% CI)	P value (χ^2 test)
Asthma exacerbation	40 (31)	33 (26)	1.29 (0.75 to 2.23)	P=0.354
Asthma related events:				
Visit to general practice	45 (35)	41 (32)	1.14 (0.68 to 1.91)	P=0.629
Home visit by general practitioner	3 (2)	6 (5)	0.48 (0.12 to 1.98)	P=0.304
Visit to accident and emergency department	2 (2)	1 (1)	2 (0.18 to 22.3)	P=0.567
Admission to hospital	4 (3)	1 (1)	4.06 (0.45 to 36.86)	P=0.179

Health status measures and short asthma morbidity score

The differences between the two groups in the mean change in score from baseline were not significantly different for the St George's respiratory questionnaire (difference 0.13, 95% confidence interval -2.76 to 3.03, $P=0.93$), the short asthma morbidity score (0.16, -0.34 to 0.66, $P=0.54$), or the EuroQol visual analogue scale (2.32, -1.67 to 6.32, $P=0.25$).

Annual corticosteroid dose

We found a significant difference in the mean annual dose of inhaled corticosteroid between the two groups (stepdown 390 mg beclomethasone dipropionate, control 517 mg beclomethasone dipropionate, $P<0.001$; mean difference -127 mg, -180 to -74). This represents a mean daily saving of 348 µg of beclomethasone dipropionate for participants in the stepdown group (95% confidence interval 202 to 494). We found no significant difference in the mean annual dose of oral corticosteroid (prednisolone) between the two groups (stepdown 117 mg, control 109 mg; $P=0.252$).

Adverse events—Fourteen participants (seven in each group) experienced a serious adverse event during the study, and three events were asthma related. These three events occurred in the stepdown group and were all non-fatal asthma exacerbations requiring admission to and treatment in hospital. Of the three participants experiencing an asthma related adverse event, only one was taking a reduced dose of inhaled corticosteroid at the time of the event whereas the dose of the other two had not been reduced at any time before the event.

Discussion

Inhaled corticosteroids are widely accepted as the treatment of choice for patients with chronic asthma.¹⁻³ However, they have been associated with a number of dose related side effects including bruising, cataract formation, glaucoma, reduced bone density, and adrenal suppression.^{1 4 14} The therapeutic response may plateau at doses below 1000 µg of inhaled beclomethasone dipropionate (500 µg of fluticasone propionate),¹⁵⁻¹⁷ and it should therefore be possible for a substantial proportion of patients receiving inhaled corticosteroids at high dosage to reduce their dose, thereby reducing the risk of side effects while maintaining control.

Strengths of the study

This was a pragmatic trial with a complex intervention.¹⁸ We enrolled patients typical of those managed in primary care and used outcome measures achievable in the primary care setting.^{19 20} Our findings are therefore pertinent to the population for which stepdown is recommended, and our management approach can be adopted easily by primary care teams, which are responsible for the care of most asthma patients. We recruited from six health board areas, across a wide range of deprivation categories and rural and urban settings. We believe therefore that our findings can be generalised to the population at large. As our study was limited to patients receiving high doses of inhaled corticosteroids our findings may not be reproducible in patients with milder disease who receive lower doses.

Not all patients allocated to the stepdown regimen received a reduction in their dose of inhaled

What is already known on this subject

Asthma management guidelines recommend a stepwise reduction in the dosage of inhaled corticosteroids for patients with well controlled asthma

Research evidence shows that such a reduction can be achieved in patients with mild disease, in the short term, or with the addition of other anti-asthma treatments

The clinical implications of stepping down inhaled corticosteroids have not previously been tested by means of a randomised controlled trial over the longer term or in patients with moderate to severe disease

What this study adds

Adopting a stepdown approach to the use of high dose corticosteroids in patients with chronic stable asthma can lead to a significant reduction in the daily dose of inhaled corticosteroids without compromising asthma control

corticosteroids. However, sufficient numbers (83%) received the intervention for the study to be valid, and the inclusion of patients who did not makes this a true intention to treat analysis, reflecting the reality of managing this group of patients in practice. We included smokers in our study, a group often excluded from trials but estimated to represent up to 30% of adult asthma patients.²¹ A proportion of the smokers may have had mixed disease with an element of irreversible airflow obstruction, but any influence this may have had on the results is likely to be minimal because of the small numbers involved.

Previous research has shown that the dose of inhaled corticosteroids can be reduced in patients with mild disease.⁵ Results from other trials show that it should also be possible to reduce the dose of inhaled corticosteroids in moderate or severe asthma without jeopardising control.^{6 7} However, these studies have been limited by short term follow up and have used an "open label" design for reducing the dose of inhaled corticosteroids. As the stepdown approach to using inhaled corticosteroids in asthma has been adopted into international asthma guidelines largely as a result of expert opinion our study provides valuable evidence in support of this management strategy.

Over the one year period, participants in the stepdown group received, on average, 348 µg (25%) less inhaled beclomethasone dipropionate per day than controls, and the use of oral corticosteroids did not differ significantly between the two groups. This finding shows that a stepdown approach to inhaled corticosteroids can reduce the risk of steroid related side effects in this group of patients.

We thank GlaxoSmithKline UK for donating the study inhalers; Annemarie Crowe, Adele Johnstone, and colleagues in the pharmacy department, Gartnavel General Hospital, Glasgow for blinding and packaging the study inhalers; Karon Carson and Joyce Thompson for data collection; West of Scotland (WestNet) and Forth Valley Research Networks for their help with practice recruitment; all general practitioners who participated in the study and their practice staff.

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Funding: NHS R&D Programme on Asthma Management.

Competing interests: NCT has been reimbursed by AstraZeneca (AZ), GlaxoSmithKline (GSK), and Schering Plough (SP), the manufacturers of budesonide, beclomethasone and fluticasone,

and mometasone, respectively, for attending several conferences and has acted as a consultant to GSK and Altana. His department has received research funds for clinical trials from AZ, GSK, Novartis, and Merck; SFW has received fees for speaking, chairing, or advising from GSK, AZ, SP, and Aventis; IF has received research funding and committee honorariums from GSK and a committee honorarium and speaking fee from AZ.

Ethical approval was granted by the multicentre research ethics committee for Scotland and appropriate local research ethics committees.

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Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment

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BMJ 2003;326:1118-21

Abstract

Objective To compare the efficacy of a “*Helicobacter pylori* test and treat” strategy with that of an empirical trial of omeprazole in the non-endoscopic management by empirical prescribing of young patients with dyspepsia.

Design Randomised controlled trial.

Setting Hospital gastroenterology unit.

Participants 219 patients under 45 years old presenting with dyspepsia without alarm symptoms.

Intervention Patients received treatment with omeprazole 20 mg (group A) or with a urea breath test followed by an eradication treatment in case of *H pylori* infection or omeprazole alone in non-infected patients (group B). Lack of improvement or recurrence of symptoms prompted endoscopy.

Main outcome measures Improvement in symptoms assessed by a dyspepsia severity score every two months; use of medical resources (endoscopic workload and medical consultation); clinical outcome.

Results 96/109 (88%) patients in group A and 61/110 (55%) in group B ($P < 0.0001$) had endoscopy: in 19 patients in group A and 32 in group B (20/67 infected and 12/43 non-infected) because of no improvement; in 77 further patients in group A and 29 in group B (7 infected and 22 non-infected) because of recurrence of symptoms during follow up. Endoscopy showed peptic ulcers only in group A; oesophagitis occurred significantly more often in group B than in group A. About 80% of examinations

were normal in both groups, but nine duodenal scars occurred in group A.

Conclusions Eradication treatment allows resolution of symptoms in a large number of patients with dyspepsia and reduces the endoscopic workload. After a trial of omeprazole, symptoms recur in nearly every patient. Such treatment is also likely to mask an appreciable number of peptic ulcers and cases of oesophagitis.

Introduction

Dyspepsia is a common condition in the general population of industrialised countries. The increasing cost of treatments for dyspepsia has led to a search for safe and cost-effective management strategies. Agreement exists that patients older than 45 with dyspeptic symptoms and patients with alarm symptoms should undergo endoscopy. To reduce endoscopic workload empirical treatment with proton pump inhibitors has been proposed for young patients.¹⁻⁴ In industrialised countries people under the age of 45 who are not taking non-steroidal anti-inflammatory drugs are unlikely to be affected by serious gastroduodenal disease if they have a negative *H pylori* test. On the basis of these observations, the European *H pylori* Study Group advised that young dyspeptic patients without alarm symptoms and found to be infected by means of non-invasive tests should receive empirical eradication treatment without endoscopy.³