

Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial

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Summary

Background Asthma self-management plans that include doubling the dose of inhaled corticosteroid when the condition deteriorates improve asthma control. Whether doubling the dose of corticosteroid in isolation is effective is unknown. We undertook a randomised controlled trial to investigate the effects of doubling the dose of inhaled corticosteroids when asthma deteriorates.

Methods 390 individuals with asthma who were at risk of an exacerbation monitored their morning peak flow and asthma symptoms for up to 12 months. When peak flow or symptoms started to deteriorate, participants added an active or placebo corticosteroid inhaler to their usual corticosteroid for 14 days to produce a doubling or no change in dose. The primary outcome was the number of individuals starting oral prednisolone in each group.

Findings During 12 months, 207 (53%) started their study inhaler and 46 (12%) started prednisolone—22 (11%) of 192 and 24 (12%) of 198 in the active and placebo groups, respectively. The risk ratio for starting prednisolone was therefore 0.95 (95% CI 0.55–1.64, $p=0.8$).

Interpretation We recorded little evidence to support the widely recommended intervention of doubling the dose of inhaled corticosteroid when asthma control starts to deteriorate.

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Introduction

Asthma guidelines recommend regular inhaled corticosteroid treatment for patients with persistent asthma and daily symptoms needing β -agonist treatment.^{1,2} In patients with symptomatic but fairly stable asthma, doubling^{3,4} or quadrupling⁵ the dose of inhaled corticosteroid leads to modest changes in spirometry and peak flow. Doubling the dose of inhaled corticosteroid when asthma control deteriorates is widely advocated but is of unproven value. We aimed to investigate whether doubling the dose of inhaled corticosteroid when asthma control starts to deteriorate reduces the number of patients needing prednisolone, and to establish the effect on the severity and duration of the subsequent exacerbation.

Patients and methods

Patients

We recruited individuals aged 16 years and older with a clinical diagnosis of asthma and taking an inhaled corticosteroid (100 to 2000 μg per day) on a regular basis from local general practices and our asthma research register. To be included, individuals had to have taken a course of oral corticosteroids or doubled their dose of inhaled corticosteroid temporarily in the previous 12 months to treat or prevent an asthma exacerbation. Exclusion criteria were history of smoking of more than 10 pack-years and unstable asthma during a 2-week run-in period (ie, if the lowest morning peak flow were more than 20% lower than mean peak flow or if the highest symptom score were more than 1 point higher than the median symptom score). All participants provided written informed consent to be included in the trial, which was approved by Nottingham City Hospital ethics committee.

Procedures

Forced expiratory volume in 1 s (FEV_1) (the highest of two readings within 100 mL) and forced vital capacity (FVC) were measured in the clinic, and morning peak flow (highest of three measurements) and daytime symptom scores (4-point scale; 0=no symptoms, 3=incapacitating symptoms) were recorded daily at home.

Patients underwent a 2-week run-in period during which they recorded morning peak flow and daytime symptom scores. A further 2-week run-in period was allowed if asthma were unstable during the first period. An independent pharmacist randomly allocated individuals to active or placebo inhalers using computer-generated random number tables. Patients were stratified into low-to-moderate and high dose groups dependent on the dose of inhaled corticosteroid at entry (low-to-moderate dose was beclometasone dipropionate up to 1000 $\mu\text{g}/\text{day}$ by metered-dose inhaler or equivalent⁶). A range of active and placebo study inhalers was available to enable the type of inhaler and daily dose to be matched to patients' regular inhaled corticosteroid, type of inhaler, and dose.

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	Randomised individuals		Participants who started study inhaler	
	Active	Placebo	Active	Placebo
Number	192	198	110	97
Age (years)	50 (13)	48 (14)	50 (13)	48 (13)
Female (%)	122 (64%)	141 (71%)	71 (65%)	74 (76%)
FEV ₁ (L)	2.4 (0.8)	2.4 (0.8)	2.3 (0.8)	2.3 (0.7)
FEV ₁ (% predicted)	79 (19.6%)	81 (21.1%)	78 (20%)	82 (22%)
PEF (L/min)	382 (97)	386 (96)	379 (98)	384 (95)
Symptom score	0.5 (0.7)	0.4 (0.7)	0.5 (0.7)	0.4 (0.7)
Inhaled corticosteroid dose on entry				
Mean (μ g/day)	708 (378)	711 (389)	719 (411)	772 (425)
Low-to-moderate	158 (82%)	162 (82%)	88 (80%)	74 (76%)
High	34 (18%)	36 (18%)	22 (20%)	23 (24%)
Long-acting β agonist (%)	72 (38%)	68 (34%)	43 (39%)	43 (44%)
Smoking				
Never	118 (61%)	119 (60%)	72 (66%)	62 (64%)
Ex-smoker	67 (35%)	73 (37%)	32 (29%)	32 (33%)
Current	7 (4%)	6 (3%)	6 (5%)	3 (3%)
Inclusion criteria satisfied				
Oral corticosteroids	106 (55%)	111 (56%)	61 (56%)	62 (64%)
Double inhaled corticosteroid	81 (42%)	82 (41%)	43 (39%)	32 (33%)
Both	5 (3%)	5 (3%)	5 (5%)	3 (3%)

PEF=mean peak flow. Data are number (%) or mean (SD).

Table 1: Baseline characteristics of participants

Participants were instructed to continue their usual treatment throughout the study. They were asked to take their study inhaler for 14 days in addition to their usual treatment if their morning peak flow fell by 15% or if their daytime symptom score increased by 1 point from the mean peak flow and median symptom score recorded in the run-in period. Once the study inhaler was started, patients continued to record their peak flow and symptom scores for 28 days and were then withdrawn from the study. Participants were given a 10-day course of prednisolone (30 mg per day) to be taken if their asthma control deteriorated to the point that they would usually start oral corticosteroids, or if their peak flow fell by 40% from the mean run-in value.

The primary endpoint was the proportion of individuals who needed prednisolone in each group. With 200 patients in each group, the study had 90% power to detect a 40% reduction in the proportion of those starting prednisolone, on the assumption that 40% of controls started prednisolone. Secondary outcomes were maximum fall in peak flow and increase in symptom scores whilst taking the study inhaler compared with values immediately before starting the study inhaler, and time to recovery of peak flow and symptom scores (defined as the number of days that peak flow or symptom scores remained below or above the values immediately before starting the study inhaler).

Statistical analysis

We compared the proportion of patients who started prednisolone in the active and placebo groups using χ^2 test with Yates correction. Our analysis was by intention-to-treat and per protocol (ie, patients who used their study inhaler as instructed before starting prednisolone). Student's *t* test, Mann Whitney *U* test and log rank test were used to compare peak flow, symptom score, and days to recovery, respectively. Data from patients stratified to the low-to-moderate dose group were also analysed separately.

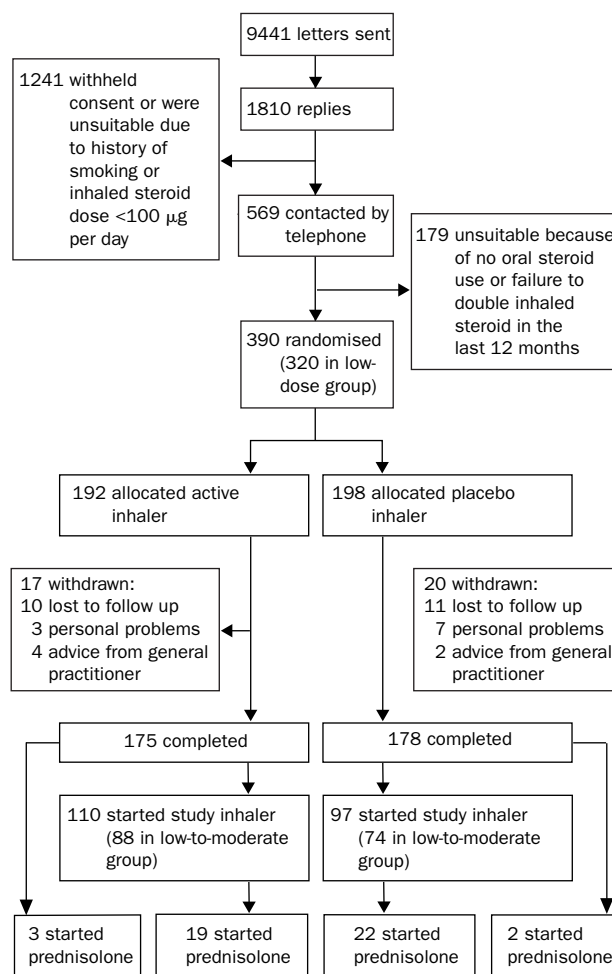


Figure 1: Trial profile

Role of the funding source

The study sponsor, through the National Asthma Campaign, provided critical review of the protocol but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 shows details of 390 participants who fulfilled the entry criteria and were randomly allocated to provide two well matched treatment groups. 17 and 20 individuals withdrew from the active and placebo groups, respectively (ten and 11 were lost to follow-up, three and seven for personal reasons, and four and two on the advice of their general practitioner [figure 1]). About half (207) started the study inhaler; almost 60% in the active group and about 50% in the placebo group. Of the 207 patients who started the study inhaler, 162 (78%) were in the low-to-moderate dose group, 88 (54%) and 74 (46%) in the active and placebo groups, respectively (table 1).

22 (11%) of 192 and 24 (12%) of 198 participants in the active and placebo groups, respectively, started prednisolone, giving a risk ratio for starting prednisolone of 0.95 (95% CI 0.55–1.64, *p*=0.8). The reasons for starting prednisolone were 40% fall in peak flow (six in the active group and four controls), advice from general practitioner (ten active and 14 placebo), and a subjective deterioration in asthma control (six active and six placebo). Of those who started the study inhaler (per-protocol analysis), 19 (17%) of 110 in the active group

	Placebo	Active	Difference (95% CI)	p
Mean peak flow				
Immediately before starting study inhaler	341	332	10 (–17 to 36)	0·8
Lowest value while taking study inhaler*	326	326	–0·6 (–28 to 27)	0·9
Maximum fall while taking study inhaler†	16	6	10 (–0·8 to 21)	0·07
Symptom scores				
Immediately before starting study inhaler	1·4	1·2	0·1 (–0·08 to 0·3)	0·2
Highest value while taking study inhaler*	1·9	1·8	0·1 (0·09 to 0·4)	0·2
Maximum rise while taking study inhaler†	0·5	0·5	0·03 (–0·2 to 0·3)	0·8

*Mean value recorded at any time while using study inhaler. †From value before starting the study inhaler.

Table 2: Mean peak flow and symptom scores immediately before and during treatment with the study inhalers

and 22 (23%) of 97 in the placebo group started prednisolone (risk ratio 0·8, 95% CI 0·45–1·4, $p=0·53$).

In the low-to-moderate dose group, 13 (8%) of 158 in the active group and 17 (10%) of 162 in the placebo group started prednisolone, giving a risk ratio 0·8 (0·4–1·6, $p=0·66$). In the per-protocol analysis, 11 (12%) of 88 in the active group and 16 (22%) of 74 in the placebo group started prednisolone (risk ratio 0·63, 95% CI 0·31–1·27, $p=0·27$). There was no difference in the proportion of

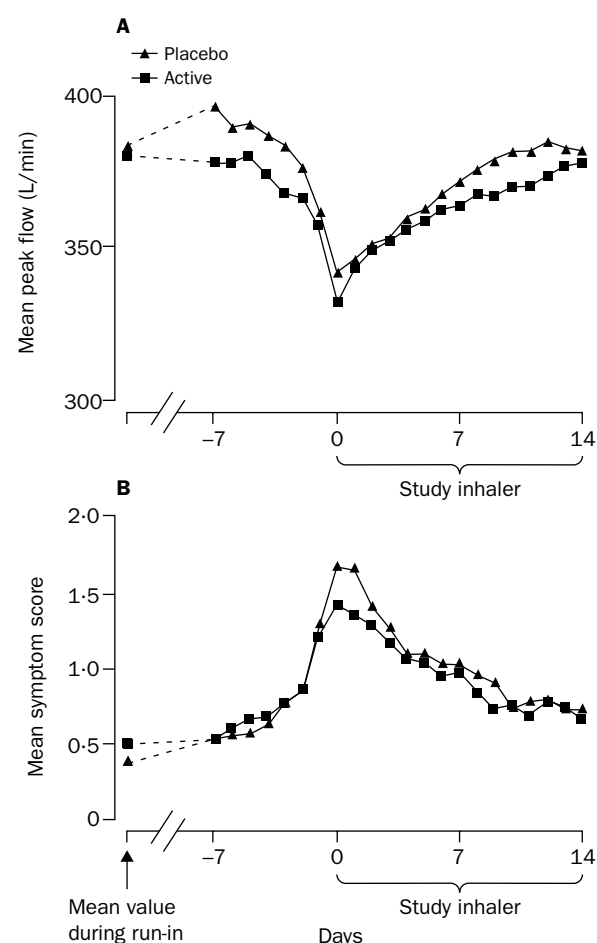


Figure 2: Mean peak flow (A) and symptom scores (B) 7 days before and while taking the study inhaler compared with mean value during the run-in period

patients who visited their general practitioner (31 [16%] active, 28 [14%] placebo, $p=0·8$) or in the proportion who were prescribed antibiotics (19 [10%] and 15 [8%] respectively). Before starting the study inhaler, mean peak flow had fallen by 47 (12%) L/min and 43 (11%) L/min from baseline, to 332 L/min and 341 L/min in the active and placebo groups, respectively (table 2 and figure 2). During the same period, symptom scores increased by

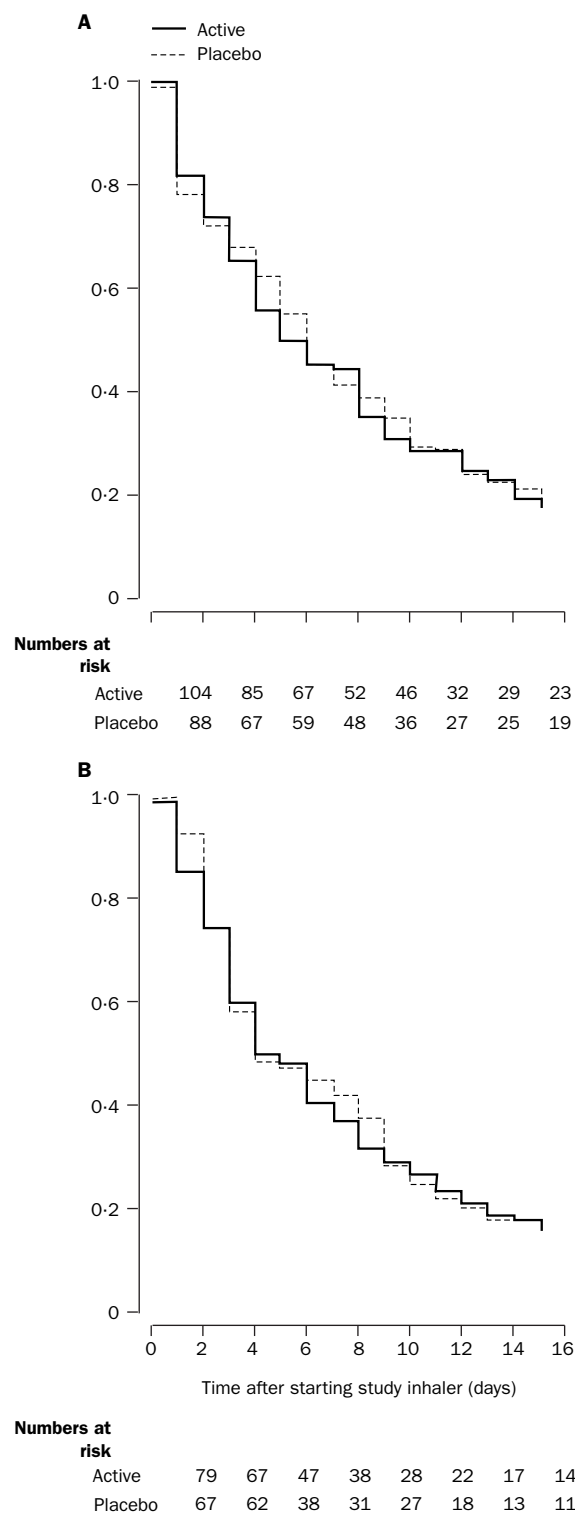


Figure 3: Proportion of participants with peak flow lower than prestudy inhaler value (A) and those with symptom score higher than prestudy inhaler value (B)

	Placebo	Active	Difference (95% CI)	p
Mean peak flow				
Immediately before starting study inhaler	353	343	10 (–18 to 39)	0.6
Lowest value while taking study inhaler*	340	340	0.5 (–29 to 30)	0.9
Maximum fall while taking study inhaler†	15	4	11 (–0.7 to 23)	0.06
Symptom scores				
Immediately before starting study inhaler	1.4	1.3	0.1 (–0.2 to 0.3)	0.5
Highest value while taking study inhaler*	1.8	1.7	0.1 (–0.1 to 0.4)	0.3
Maximum rise while taking study inhaler†	0.4	0.4	0.0 (–0.3 to 0.3)	1.0

*Mean value recorded at any time whilst using study inhaler. †From value before starting the study inhaler.

Table 3: Mean peak flow and symptom scores immediately before and during treatment with the study inhalers in individuals taking 1000 µg/day or less of inhaled corticosteroid (n=162)

0.7 and 1 to 1.2 and 1.4 in the active and placebo groups, respectively (figure 2).

Doubling the dose of inhaled corticosteroid led to a small reduction in the mean maximum fall in peak flow (mean difference between active and placebo –10 L/min [95% CI –21 to 0.8, $p=0.07$]). There was no difference, however, in the lowest peak flow recorded, rise in symptom scores, or highest symptom score recorded when compared with remaining on the same dose (table 2). Doubling the dose of inhaled corticosteroid had no effect on the time taken for peak flow or symptom scores to return to the baseline values (active *vs* placebo 6.8 days (95% CI 5.7–7.9) *vs* 7 days (5.7–8.2) for peak flow, and 6.8 days (5.7–7.8) *vs* 6.1 days (7–7.5) for symptom scores, figure 3). Results were much the same when participants in the lower dose group were analysed separately (table 3).

Controls who had a fall in peak flow of 15% or more before starting the study inhaler, were more likely to need oral prednisolone than were those with a smaller reduction. The sensitivity and specificity of a 15% fall in peak flow in prediction of an exacerbation that needed oral prednisolone was 43% and 66%, respectively.

Discussion

We have recorded little evidence to lend support to the widely recommended intervention of doubling the dose of inhaled corticosteroid when asthma control starts to deteriorate. When compared with placebo, doubling the dose of inhaled corticosteroid had no effect on the number of patients needing prednisolone, lowest peak flow recorded, rise in symptom scores, highest symptom score recorded, or time to recovery for peak flow and symptom scores. The fall in peak flow while taking the study inhaler was slightly smaller in the active group than in controls, and of borderline significance. The results for patients taking lower doses of inhaled corticosteroids were much the same as those for the group as a whole.

Although doubling the dose of inhaled corticosteroids when asthma control deteriorates is recommended in the 1995 edition of the British asthma guidelines,⁷ the latest version recognises the absence of evidence for this advice.¹ To make the study as generalisable as possible to patients in primary care, inclusion and exclusion criteria were few. We increased the likelihood of exacerbations during the study by including only those who had needed oral corticosteroids or a temporary doubling of their inhaled

corticosteroid dose in the previous 12 months. We excluded those with a smoking history in excess of 10 pack-years to avoid including individuals with chronic obstructive pulmonary disease.

Our results emphasise the difficulties of investigation of an infrequent outcome such as asthma exacerbations. Despite being a large trial with nearly 400 participants at risk of an exacerbation, only 24 (12%) controls started prednisolone. We have not, therefore, excluded the possibility that doubling the dose of inhaled corticosteroid leads to a worthwhile reduction in prednisolone use, but the absence of clinically important differences between groups for the secondary outcomes, for which the study was adequately powered, is evidence against this conclusion. The smaller fall in peak flow in the active group than in the placebo group came close to significance but this was an isolated finding and is difficult to interpret in view of the difference in peak flow immediately before starting the study inhaler (active 332 L/min *vs* placebo 341 L/min). The primary and secondary outcomes were much the same in the lower dose group and the group as a whole. Few individuals started prednisolone in the lower dose group in the per-protocol analysis, but with small numbers the CIs around the estimate were wide.

Asthma self-management plans that improve asthma control have recommended doubling the dose of inhaled corticosteroid when peak flow falls by 15–30%.^{8–13} We chose a 15% fall as indication to double the dose because peak flow falls rapidly during an exacerbation,¹⁴ and waiting for a larger fall would mean that the opportunity for prevention might have been missed. Our criteria for starting the study inhaler also included a rise in daytime symptoms since this is a sensitive predictor of an exacerbation,¹⁴ and because many patients do not usually record peak flow.

We have considered why doubling the dose of corticosteroid was ineffective. First, some patients might have used their trial medication incorrectly or stopped their usual inhaled corticosteroid when starting the study inhaler. The importance of following study instructions was emphasised at every visit, however, and since compliance with medication is better in clinical trials than in practice, any bias is likely to favour the intervention. Second, the slow onset of action of inhaled corticosteroids compared with the rapid deterioration in asthma control might leave insufficient time for inhaled corticosteroids to prevent an exacerbation. The fall in peak flow before starting the study inhaler was on average less than 15%, so an earlier increase in dose is unlikely to have been feasible. Finally, doubling the dose of inhaled corticosteroids might be an inadequate increase in dose to prevent an exacerbation. A four-fold increase in maintenance treatment with budesonide reduced exacerbations needing prednisolone in one investigation,⁵ but whether a similar increase would be effective when asthma is deteriorating is unknown. Researchers in a small study of 36 exacerbations concluded that pre-emptive treatment with a five-fold increase in inhaled corticosteroid treatment reduced exacerbations, but this was presumably a chance finding because the criteria for defining an exacerbation and for increasing the dose of inhaled corticosteroid were identical.¹⁵

Our findings provide little support for the recommendation that patients taking an inhaled corticosteroid should double the dose when asthma control is deteriorating. Whether a larger increase in inhaled corticosteroid dose would be effective needs to be established.

Contributors

T W Harrison had the original idea for the study, and, together with A E Tattersfield, designed and supervised the trial. J Osborne and S Newton recruited the participants. All authors contributed to data analysis and writing of the report.

Conflict of interest statement

The Department of Respiratory Medicine, Nottingham City Hospital, has received funding from AstraZeneca and Glaxo-Wellcome.

A E Tattersfield has a consultancy with Schering-Plough and has received lecture fees and travel support from Schering-Plough and AstraZeneca. T W Harrison has received lecture fees and travel support from AstraZeneca, Glaxo-Wellcome, and 3M Pharmaceuticals. J Osborne and S Newton have no conflicts of interest.

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