

A single high dose of inhaled corticosteroids: a possible treatment of asthma exacerbations

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Summary

Recovery from an asthma exacerbation may take days or weeks even after the introduction of appropriate exacerbation therapy. However airway responsiveness and sputum eosinophils can be reduced within 6 hours by a single dose of inhaled corticosteroids.

Aim: To determine if a single dose of 3200 µg of budesonide increases the rate of recovery from an asthma exacerbation.

Methods: Nineteen asthmatic subjects with an asthma exacerbation following withdrawal of inhaled corticosteroids were randomised to receive either usual care (doubling their dose of inhaled corticosteroids) plus placebo or usual care plus a single dose of 3200 µg of budesonide in a double-blind manner. Subjects monitored peak flow (PEF), symptoms, and beta agonist use daily for four weeks. The lowest PEF reading for each week was calculated as a percentage of the best peak flow

value achieved in the recent past (PEF lowest % best).

Results: In the first week following exacerbation, PEF (lowest % best) was significantly greater in the budesonide group than in the placebo group (87.4 ± 4.7 vs. 76.7 ± 5.3 ; $p = 0.029$). However in the fourth week following exacerbation PEF was not significantly different ($p = 0.728$). The proportion of subjects who had a symptom free day during the first week was significantly higher in the budesonide group ($p = 0.0012$).

Conclusion: A single high dose of inhaled corticosteroids added to usual exacerbation treatment might increase the rate of recovery from a mild exacerbation of asthma.

Key words: single high-dose inhaled corticosteroids; asthma

Introduction

Asthma exacerbations are a common emergency department presentation [1]. International asthma guidelines recommend a course of oral prednisone following an acute asthma attack [2]. A recent Cochrane review has also clearly shown that a short course of oral corticosteroids following assessment for an acute asthma exacerbation significantly reduces the number of relapses and decreases beta 2 agonist use [3]. However oral prednisone treatment carries the risk of prednisone-induced side effects [4].

Adult asthmatic patients treated with a short course of high dose corticosteroids recover from their asthma exacerbations in a median time of three days [5] and children with mild asthma exac-

erbations within five days [6]. Treatment with inhaled corticosteroids (ICS) reduces inflammatory cells in the airways, improves lung function and reduces airway hyperresponsiveness [7-9]. These effects of ICS are apparent as early as six hours after administration [10].

It has been shown that the use of a course of high dose budesonide is as effective as a course of oral steroid in the treatment of an asthma exacerbation [11]. However it is not clear if a single high dose of ICS would have a comparable effect on recovery. Therefore we wanted to assess whether the addition of a single high dose of budesonide to usual care (at least a doubling of the ICS dose) accelerates recovery from an asthma exacerbation.

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Methods

Subjects

Subjects were recruited from the Asthma Clinic of the Royal Prince Alfred Hospital, Australia. Fifty asthmatic subjects using ICS to control their asthma with a past history of wheezing and chest tightness and in whom asthma had previously diagnosed by a physician participated in a recent ICS-dose reduction study [12, 13]. Nineteen of these subjects subsequently developed an exacerbation of their asthma and were included in this study. The subjects' characteristics are summarized in table 1. All subjects were atopic and all used short acting beta agonists when needed. Exclusion criteria were current smoking and the use of oral steroids within the previous six months.

The study was approved by the Central Sydney Area Health Service Ethics Committee (protocol No X97-0230). The trial was carried out under the Clinical Trial Notification Scheme of the Therapeutics Goods Administration of Australia (CTN No 1997/373). All subjects gave written informed consent prior to commencement of the study.

Study design

This was a double blind, placebo controlled, parallel group study undertaken as the final phase of an inhaled corticosteroids (ICS) dose reduction study. The results of the ICS dose reduction study have been reported elsewhere [12, 13]. Before the start of the dose reduction study, subjects were screened and a staff physician confirmed the clinical diagnosis of asthma on examination and history. Subjects recorded their asthma symptoms, beta agonist use and peak expiratory flow (PEF) twice daily in a diary card before inhaling their asthma medication for four weeks prior to commencing the ICS dose reduction and then throughout the study. In the dose reduction phase the subjects' current ICS dose was halved every 8 weeks. Nineteen subjects developed an asthma exacerbation defined as a fall in PEF of greater than 3 SDs from the mean of the run-in PEF plus an increase of asthma symptoms [14]. These subjects were asked to attend the laboratory within 1–2 days of exacerbation having refrained from taking short acting beta agonists for 6 hours, long acting beta agonists for 24 hours and antihistamines for 2 days prior to each study day. No ICS were taken on the day of the study. On the exacerbation study day, following initial spirometry, all subjects were prescribed treatment for their exacerbation by the physician according to the current guideline [2] – in most cases by doubling the dose of ICS. In addition subjects were randomised to receive either 8 puffs of budesonide (3200 µg) or 8 puffs of placebo administered by a member of the research staff unconnected with this study. The physician treating the exacerbation was unaware of which treatment the patient received.

Lung function measurements

Spirometry was performed using a MicroLoop II Spirometer (Micro Medical Ltd, Kent, UK). Forced expi-

ratory volume in one second (FEV₁) was used as an index of change in airway calibre. Forced expiratory manoeuvres were repeated until two readings of FEV₁ within 100 ml of each other were obtained, the higher of which was used in analyses. Values for FEV₁ and FVC were recorded as a percentage of the predicted values of Knudson *et al.* [15].

Nitric oxide measurement

Mixed expired nitric oxide (eNO) was measured using a modification of the method of Massaro *et al.* [16]. The measurement was performed with the subject standing without a noseclip. The subject took a deep breath and exhaled over 5–15 seconds to residual volume into an NO impermeable polyethylene bag (Scholle Industries Pty Ltd, Elizabeth West, Australia). The exhaled flow, measured by a rotameter (Dwyer Flowmeter Model VFASS-25, AMBIT Instruments Pty Ltd, Parramatta, Australia), was 10 litres/min at a mouth pressure >20 cm H₂O. The exhaled gas from a single breath was analysed within an hour using a chemiluminescence analyser (Thermo Environmental Instruments Model 42C), which has a lower limit of detection of 1 ppb. Ambient NO in the laboratory was measured at the time of testing.

Peak expiratory flow home monitoring

For the whole study period subjects measured peak expiratory flow (PEF) twice a day before inhaling their medication. The subjects blew three times into the PEF meter (Mini-Wright, Clement Clarke International Ltd, Essex, UK) while standing and the best of three values was recorded. The lowest reading for each week was calculated as a percentage of the best peak flow value achieved during the four weeks of the run-in period [17–20].

Symptom score

Subjects completed a diary card and scored their asthma symptoms twice daily. Morning and evening symptom scores were combined to produce a score between 0 and 8, with 0 being symptom free and 8 having maximum symptoms. This score has been adapted from Reddel *et al.* [21].

Statistical analysis

Analysis of eNO was carried out on log transformed data, and the summary values were geometric means with 95% confidence intervals. Summary values for the other measurements were arithmetic means with 95% confidence intervals. Paired t-tests were used to compare the outcome measurements (eNO, FEV₁ % pred, FVC % pred, PEF % pred, PEF lowest % best) between the exacerbation period and 4 weeks post exacerbation. Unpaired t-tests were used for comparison between groups. Fisher Exact test was used to assess for differences in the proportions of subjects who had a symptom free day during the first week.

Results

At recruitment into the ICS dose reduction study there were no significant differences between the budesonide and placebo treatment groups (table 1). All subjects were atopic and all used short acting beta agonists when needed.

Lung function and exhaled nitric oxide values

at four weeks pre-exacerbation, at the time of asthma exacerbation and four weeks post exacerbation are summarised in table 2. Although there was a significant difference in FEV₁ values at the time of asthma exacerbation, there were no significant differences in lung function values or asthma

Table 1

Subject characteristics of the 19 subjects.

		budesonide	placebo	p-value
N		8	11	
Age (years) (range)		44.9 (33.8–53.9)	43.5 (33.8–53.9)	0.79
Gender (m/f)		3/5	5/6	
Asthma severity (2)	severe (n) (FEV ₁ /PEF ≤60% predicted)	0	1	
	moderate (n) (FEV ₁ /PEF >60%–<80 % predicted)	2	1	
	mild (n) (FEV ₁ /PEF ≥80% predicted)	6	9	
Days from last ICS dose reduction to exacerbation (95%CI)		25.4 (13.7–37)	24.9 (15.9–33.9)	0.89
Mean ICS dose (µg beclomethasone equivalent dose)	at exacerbation (95%CI)	269 (136–401)	314 (151–476)	0.74
	4 weeks post exacerbation (95%CI)	831 (547–1115)	750 (273–1226)	0.85

Table 2

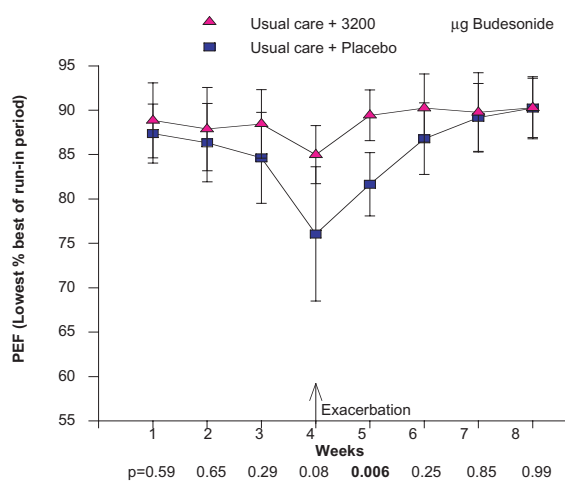
Values for 19 subjects, showing FEV₁, % predicted and eNO at exacerbation and 4 weeks post exacerbation.

		mean values (95% confidence interval)		p-value
		budesonide	placebo	
FEV ₁ predicted (%)	4 weeks pre-exacerbation	98.7 (83–114)	84.2 (76–92.4)	0.11
	at exacerbation	99.7 (82.2–117.3)	79.5 (71.8–87.2)	0.04
	4 weeks post exacerbation	96.7 (81.3–112.1)	83.7 (76.5–90.9)	0.35
PEF predicted (%)	4 weeks pre-exacerbation	93.4 (86.4–96.2)	87.5 (74.4–91.5)	0.13
	at exacerbation	87.1 (83.5–100.6)	77.1 (67–87.3)	0.08
	4 weeks post exacerbation	90 (79.8–100.3)	81.8 (71.5–92.1)	0.09
Exhaled NO (ppb)	4 weeks pre-exacerbation	15.0 (95%CI: 8.2–27.5)	13.6 (6.1–30.5)	0.86
	at exacerbation	18.8 (12.1–29.3)	19.3 (11.4–32.8)	0.76
	4 weeks post exacerbation	14.4 (11.4–18)	20.1 (14.4–28)	0.15

FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; NO: nitric oxide

Figure 1

Weekly peak expiratory flow % best of run-in period pre- and post exacerbation.



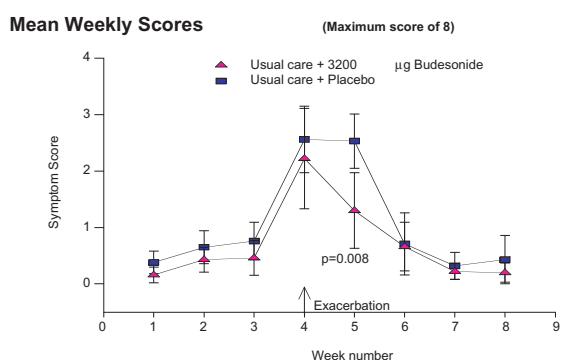
severity between the groups. Further after adjusting for base line data, there was no significant difference in improvement of PEF values between groups. In neither group did exhaled NO increase significantly during the exacerbation or decrease significantly after treatment.

Both groups showed a significant decrease in PEF (lowest % best) in the week of exacerbation compared to the week pre-exacerbation (88.2 ± 5.2 vs. 85.0 ± 3.3 ; $p = 0.04$ for the budesonide group and 84.3 ± 8.6 vs. 76.1 ± 7.6 ; $p = 0.025$ for the placebo group). The mean PEF (lowest % best) at exacerbation appeared to be lower in the placebo group than in the budesonide group but the difference was not statistically significant (76.1 ± 7.6 vs. 85.0 ± 3.3 ; $p = 0.08$). However PEF (lowest % best) differed significantly between the two groups one week post exacerbation (81.7 ± 3.6 vs. 89.4 ± 2.9 ; $p = 0.006$). Subjects in the budesonide group reached their peak recovery in PEF by one week post exacerbation (fig. 1).

Both groups had a significant decrease in symptom score at exacerbation compared to the week pre-exacerbation. The changes in the symptom scores are shown in figure 2. In the placebo group, 2 out of 11 subjects experienced a symptom free day within the first 5 days following exacerbation, whereas all eight subjects in the budesonide group experienced a symptom free day within the first 5 days following exacerbation. This difference was highly significant ($p = 0.0012$).

Figure 2

Symptom scores pre- and post exacerbation.



Discussion

In our patients although the exacerbations were mild, recovery with usual care was slow as it took 14 days for symptom scores and more than 20 days for PEF to return to pre-exacerbation values. The addition of a single dose of 3200 µg budesonide, administered in the laboratory at the time the subjects attended for assessment of their exacerbation shortened this recovery time significantly. The results suggest that the addition of a single high dose of ICS to a subject's usual care can give patients symptom free days in the first week of recovery from an asthma exacerbation.

Unfortunately our randomisation resulted in significant differences in the severity of the exacerbation between the two groups; thus the FEV₁ was significantly greater in the budesonide group compared to the placebo group at the time of asthma exacerbation. This might have influenced our results. There was no significant improvement in FEV₁ in either the placebo or budesonide group. This is in contrast with other published data, where treatment with ICS improved lung function and discontinuation of treatment was often accompanied by exacerbation of the disease and decline in lung function [22]. However our study population showed lung function values close to the normal range. Therefore a further improvement in lung function may not have been possible.

The group with a single high dose of budesonide had returned to their pre-exacerbation PEF values by week one whereas this was not achieved until week 4 in the placebo group. In the budesonide group all subjects experienced a symptom free day within the first 5 days following an asthma exacerbation which was the case in only 2 of 11 subjects in the placebo group. Nana et al. [11] found that subjects receiving 3200 µg budesonide per day had a similar improvement in FEV₁ and PEF after 8 days compared to subjects receiving a tapered dose of prednisone. All these subjects had received an initial dose of 60 mg prednisone at the time of exacerbation. A recently published placebo controlled study has also shown that a single dose of 2400 µg budesonide significantly reduces sputum eosinophils and increases airway responsiveness as early as six hours after dosing [10]. In our

study there were more subjects in the placebo group with severe exacerbations as measured by PEF (lowest % best) than in the budesonide group. This difference as well as the difference in FEV₁ may have contributed to the findings of the study. Asthmatic patients treated with a short course of high dose corticosteroids recover from their asthma exacerbations in a median time of three days [6] which seems to be a faster recovery than in our study with a single high dose of ICS. Therefore a future study comparing a single high dose of ICS with an oral prednisone therapy is needed.

In both groups exhaled NO neither increased significantly during the exacerbation nor decreased significantly after treatment. This is supported by our own previous study in which eNO had no predictive value for asthma exacerbation at any time point [11]. However, the study of Jatakanon et al. [23] found dose dependent changes in eNO levels with the maximum reduction evident at moderate doses of budesonide (400 µg). Although eNO might be expected to be a good predictor of response to steroid reduction, it did not change significantly during exacerbation and after four weeks of increased ICS treatment. It could be hypothesised that because these subjects were on long term ICS treatment their inducible NO synthase was persistently inhibited [24] so that eNO would neither increase during exacerbations nor decrease under increased ICS treatment.

In conclusion our study has shown that addition of a single high dose of ICS to a patient's usual care can improve symptoms and PEF in the first week of recovery from an asthma exacerbation. However larger studies with better randomisation are required.

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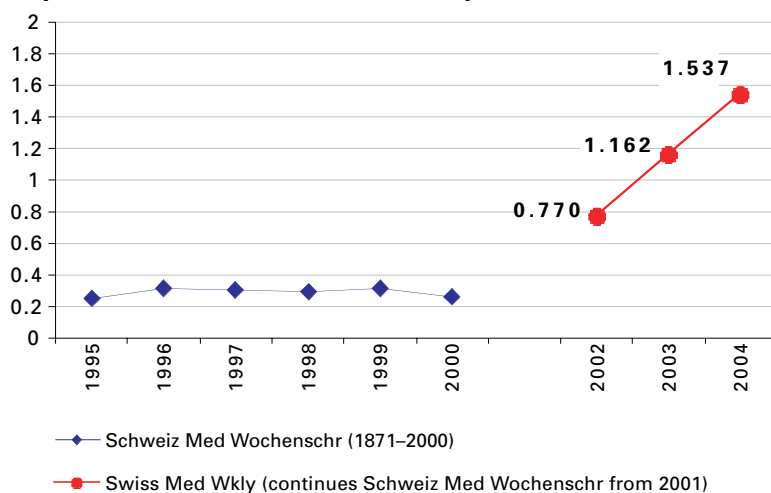
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