Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations

J M FitzGerald, A Becker, M R Sears, S Mink, K Chung, J Lee, and the Canadian Asthma Exacerbation Study Group

Background: Previous guidelines recommend doubling the daily dose of maintenance inhaled corticosteroid to treat or prevent progression of exacerbations of asthma. Methods: Over a 6 month period a cohort of patients were evaluated prospectively and randomised in a double blind controlled trial to treatment with either a continued maintenance dose (MD) of inhaled corticosteroid or doubling the dose (DD) at the time of an exacerbation. Results: A total of 290 patients were randomised (33% male) and 98 (DD, n = 46) experienced evaluable asthma exacerbations during the study period. Mean (SD) baseline characteristics at randomisation (age 33.5 (14.0) years; forced expiratory volume in 1 second (FEV1) 2.8 (0.7) l; peak expiratory flow (PEF) 422.9 (110.5) l/min) were similar in both groups. In the DD group 41% of patients were considered treatment failures because they either required systemic steroids (n = 12), had an unscheduled visit to a physician (n = 1), or their asthma did not return to baseline (n = 6). This did not differ from the MD group in which 40% were treatment failures (n = 9, 0, and 12, respectively; p = 0.94). Conclusions: In patients who regularly take an inhaled corticosteroid, doubling the maintenance dose may not affect the pattern of the exacerbation.
received a maintenance inhaler of budesonide dispensing committees at each research site and signed written informed potential not using an effective means of birth control were and patients with a smoking history of 10 pack years or more, visit 1 were further reasons for exclusion. Current smokers during the month before visit 1, treatment with long acting ketotifen, disodium cromoglycate and/or nedocromil sodium visit 1 were excluded from the study. Treatment with 3 months before visit 1, and patients who regularly used oral preceded 10 years, hospitalisation due to asthma in the (requiring intubation and mechanical ventilation) in the preceding 10 years, hospitalisation due to asthma in the 3 months before visit 1, and patients who regularly used oral or parenteral glucocorticosteroids during the month before visit 1 were excluded from the study. Treatment with ketotifen, disodium cromoglycate and/or nedocromil sodium during the month before visit 1, treatment with long acting β2 agonists, and respiratory tract infection within 1 month of visit 1 were further reasons for exclusion. Current smokers and patients with a smoking history of 10 pack years or more, pregnant or lactating women, or women of child bearing potential not using an effective means of birth control were also excluded.

The study protocol was approved by the institutional ethics committees at each research site and signed written informed consent was received from all patients prior to enrolment.

**Study procedures**

After the run in period the patients were randomised to one of two treatment arms. The maintenance dose (MD) group received a maintenance inhaler of budesonide dispensing 100, 200, or 400 µg/dose (depending on their maintenance therapy) plus an additional inhaler containing placebo for twice daily use. The double dose (DD) group received the same maintenance inhaler as the first group, but the additional inhaler dispensed 100, 200, or 400 µg/dose of budesonide as well. The additional Turbuhaler was identical in appearance to the maintenance Turbuhaler but was identifiable by a red dot. In both treatment arms the additional inhaler was to be added to the twice daily maintenance inhaler at the time of an asthma exacerbation. The time of the exacerbation was deemed to have begun when the criteria outlined below were present for 48 hours. Thus, upon exacerbation, one group received a doubling dose of ICS while the dose received by patients in the other group remained unchanged.

Patients not currently using budesonide were switched to it at an equivalent dose and placed on a twice daily dosage regimen. The dosage conversion was as close to a 1:1 ratio as possible, based on the investigator’s clinical judgement. All patients received a terbutaline sulphate inhaler (Bricanyl Turbuhaler, 500 µg/inhalation as required) to be used as rescue medication throughout the study. Each patient received a 7 day supply of oral methylprednisolone (MP) totalling 32 mg/day to be used, if needed, to treat an exacerbation.

FEV1 was measured in all patients during the initial clinic visit. PEF data were obtained using the Vitalograph 2110 computerised peak flow meter and recorded in an electronic diary (MiniDoc). These measurements were collected morning and evening during the run in and throughout the study period. The morning value was used to assess for an exacerbation. Diary data were also to be used as criteria in the definition of an exacerbation during the treatment period. Symptoms from the previous 24 hours were used to create a score. The symptoms included chest tightness, breathlessness, coughing, and wheezing. The symptoms were rated each morning according to the following scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. The alert PEF value was 80% of the mean baseline morning PEF. The Vitalograph displayed different colour zones corresponding to percentage ranges of the patient’s baseline PEF value: the green zone represented 81–100%, the yellow represented 61–80%, and the red zone ≤60% of the baseline morning PEF. The mean baseline PEF was calculated from the 7 days immediately preceding visit 2.

Once the MiniDoc indicated to a patient that the criteria for an exacerbation had been fulfilled, the patient reported this to the study nurse or physician and was given instructions to begin taking the additional inhaler. A critical PEF value of 60% of the mean baseline morning PEF—that is, a 40% fall in the mean baseline morning PEF—was also programmed into the MiniDoc. If this lower level was reached, the MiniDoc signalled the patient to begin oral MP. The critical PEF value was derived from patient groups involved in previous action plans used in education intervention studies.

**Outcomes**

The primary outcome variable was defined as the proportion of patients who, after developing an exacerbation of their asthma, failed to regain control after introducing the additional inhaler, as judged by the need for treatment with oral MP or an unscheduled visit to a physician or medical emergency department due to asthma or unstable asthma after 14 days of treatment. The question regarding any unscheduled visit was asked at day 14 after the exacerbation.

For the purpose of this study, stability was defined as a morning PEF of ≥90% of the mean baseline value on either of the previous two days, Bricanyl Turbuhaler <4 inhalations/ day over the previous two days, no nocturnal awakenings due to asthma over the previous two consecutive nights, and a total symptom score not exceeding the mean baseline level by more than two ordinal values over the previous two days. If these criteria were not met the asthma was deemed to be unstable.

During the study period monthly check up visits were scheduled to ensure that no asthma exacerbations were missed and to encourage patient compliance.

**Compliance**

At visit 1 the importance of complying with the dosage regimen was emphasised. Patients were instructed to enter the number of doses taken from their maintenance and additional Turbuhaler into the MiniDoc computerised diary. At each subsequent visit and during any telephone contact, the need for compliance was further reinforced. At all visits subsequent to visit 1, compliance with the maintenance Turbuhaler was checked by collection of self-reported data—that is, the number of doses of ICS entered in the MiniDoc during the treatment period immediately preceding the visit.

**Randomisation procedure**

Patients were randomised to treatment groups at visit 2 according to a blocked computer generated randomisation list for each centre.

**Other treatment**

Theophylline, anticholinergics, and nasal steroids were allowed throughout the study.

**Asthma exacerbation during treatment period**

An exacerbation during the treatment period—that is, an indication to introduce the additional inhaler—was defined as a combination of two of the following criteria, provided that at least one of the two was the first, second, or third criterion:
best PEF test falls to ≤80% of the mean baseline morning value on two consecutive readings or two consecutive morning readings;
• bronchodilator use ≥4 inhalations/day on two consecutive days;
• nocturnal awakenings due to asthma on two consecutive nights;
• total asthma symptom score for the combined symptoms of chest tightness, breathlessness, coughing, and wheezing increases by ≥3 ordinal values from the mean baseline value on two consecutive days;
• inability to go to school or work due to asthma for two consecutive days; and
• unscheduled physician visit due to asthma during the time period when the concomitant criterion/criteria started to be fulfilled.

Three month surveillance period
Patients who had an asthma exacerbation during the study period and who were assessed as stable at the end of the 14 day additional treatment course were followed for a 3 month surveillance period to monitor their asthma control. This surveillance period was primarily to ensure that there were no late differences shown between the groups.

Data analysis
The primary objective of this study was to determine whether doubling the dose of budesonide early in the course of an asthma exacerbation is an appropriate strategy for preventing worsening of the exacerbation. The primary efficacy variable was treatment failure—that is, the proportion of patients who, after developing an exacerbation, needed at least one course of oral MP or an unscheduled visit to a physician or medical emergency department due to asthma or who had unstable asthma after 14 days of treatment. It was assumed that the rates of exacerbation would be the same in the two treatment groups. For morning PEF and total asthma symptom score, a mean baseline value was calculated for each patient. The data from the 7 days immediately preceding randomisation (visit 2) were used to make this calculation.

Statistical analysis used the “all patients treated” (APT) approach. Since patients were “treated” only if they had an exacerbation, all patients who had at least one asthma exacerbation after randomisation and were treated with at least one dose of additional study drug are included. The reason for adjusting for the baseline dose of ICS, which was done by post-stratification, was to see the impact of asthma severity on outcomes. The primary variable was analysed using a logistic regression model with adjustments for centre and strata (≤400 μg ICS v. >400 μg ICS) effects. The Cochran-Mantel-Haenszel (CMH) test adjusted for centre was used for analysis of the secondary variable, which was the number of asthma exacerbations during the 3 month surveillance period after the initial exacerbation. SAS version 6.12 running under Windows NT was used for analysis.

Sample size determination
The sample size was based on two assumptions. Firstly, based on previous studies, it was assumed that 25% of patients in each treatment group would suffer an exacerbation after randomisation.18 Secondly, it was assumed that the proportion of patients suffering an exacerbation who would need a course of oral steroids would be 50% in the MD group and 20% in the DD group.

Based on these figures, it was estimated that 38 exacerbations would be needed in each group for a statistical analysis with a significance level of 5% (two sided) and power of 80% to show a difference between the two treatment groups. Since the number of exacerbations was a random variable in each group and because imbalance causes a decrease in power, a 5% increase in the estimated number of exacerbations was considered necessary. This led to an estimated requirement of 160 patients randomised into each treatment group. The 5% increase was deemed sufficient to compensate for an imbalance of exacerbations in the two groups of 40/60%.

Interim analysis
A review of the exacerbation rate without breaking the treatment code was planned when data for approximately 25% of the patients were available. If exacerbations were found to be occurring at a sufficient rate, the study was to continue. If not, the protocol was to be amended to increase the sample size and/or lengthen the enrolment period. At the time of the interim analysis it was deemed that an adequate number of exacerbations were occurring.

RESULTS
The scheme for patient recruitment and randomisation is shown in fig 1. Sixteen patients discontinued other than for exacerbations (nine from the placebo group). There were no differences in patient characteristics between those who experienced an exacerbation and those who did not (data not shown). Characteristics at randomisation of patients who had an exacerbation of their asthma are shown in table 1. Two of the 52 patients in the MD group were on theophylline and 13 were on constant doses of nasal steroids, while 12 of the 46 patients in the DD group were on similar stable doses of nasal steroids. No patients were taking long acting β2 agonists during the study period.

Table 2 shows the results for the primary outcome variable (treatment failure). No difference was found between treatments (p = 0.94). Furthermore, of those patients who completed the 3 month surveillance period following their asthma exacerbation, there was no difference between groups in the mean number of exacerbations (six of 35 in the MD group v five of 34 in the DD group, p = 0.92). The median time from the use of additional Turbuhaler—that is, the time from asthma exacerbation to the start of oral MP treatment—was 3 days in both the MD and DD groups.

The pattern of β2 agonist use, mean symptom scores, and nocturnal awakenings were similar in both arms of the study at the time that patients had an exacerbation (fig 2A–C). There were no significant differences in the three major criteria for triggering an asthma exacerbation (changes in PEF, increased bronchodilator use, nocturnal awakenings). Because of a technical fault in the recovery of the raw PEF data at the end of the study, the PEF data were flawed and too inconsistent to be analysed at the data centre. These data were, however, available to individual patients to enter into their Mini-Docs throughout the study.

There was no difference in outcome between patients who were switched from other ICS to budesonide (n = 40) compared with patients who were already taking budesonide (n = 58) when recruited into the study. There were also no differences between centres. Patients receiving ICS in a dose of ≤400 μg/day were less likely to have treatment failure after exacerbation than those receiving ICS in a dose of >400 μg/day in both treatment groups (table 3). There was no difference in outcome related to age (adolescents versus adults). The difference with 95% confidence intervals between treatments in proportions (DD – MD) was 0.9% (95%CI –17.9 to 19.8).

Compliance with inhaled treatment before an exacerbation, based only on reported use, was high in both groups.
Within 48 hours of the onset of an exacerbation did not change the outcome and the need for further intervention compared with patients who continued on their usual maintenance dose.

Patients in the study clearly experienced exacerbations of asthma, evident in changes in symptoms, nocturnal awakenings, and use of short acting β2 agonists. Changes in the symptoms score associated with an exacerbation and other markers of instability were equal to or even more pronounced than in other studies. Unfortunately, for technical reasons, PEF data were not available for the final analysis. With that exception, the outcome measurements used in this study were equivalent to other exacerbation studies and to common routine clinical practice. The distinction between poor asthma control and asthma exacerbations has been defined. In this study some patients may have been deemed to have poor asthma control rather than an exacerbation but, given the consistent pattern of increased symptoms, the need for short acting β2 agonists, and the fall in PEF, we are confident our patients did experience exacerbations. The study had adequate power to detect a difference of 30% in the proportion of patients experiencing a treatment failure between the two study arms. Although we anticipated a

**DISCUSSION**

It is common practice to recommend doubling the dose of ICS at the onset of an exacerbation of asthma. Many national and international guidelines for asthma management have previously strongly endorsed this recommendation, but recent guidelines have been more cautious. Our study has shown that, in patients using regular ICS, doubling the dose within 48 hours of the onset of an exacerbation did not elsewhere.

**Table 1** Characteristics of patients who had an exacerbation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MD group (n = 52)</th>
<th>DD group (n = 46)</th>
<th>Total (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>32.7 (11.9)</td>
<td>31.6 (14.6)</td>
<td>32.2 (13.2)</td>
</tr>
<tr>
<td>No (%) male</td>
<td>13 (25%)</td>
<td>14 (30%)</td>
<td>27 (28%)</td>
</tr>
<tr>
<td>Mean FEV1 (L)</td>
<td>2.8 (0.6)</td>
<td>2.9 (0.8)</td>
<td>2.8 (0.7)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>43 (83%)</td>
<td>41 (89%)</td>
<td>84 (86%)</td>
</tr>
<tr>
<td>Asthma first diagnosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year ago</td>
<td>47 (90%)</td>
<td>43 (93%)</td>
<td>90 (92%)</td>
</tr>
<tr>
<td>&lt; 1 year ago</td>
<td>5 (10%)</td>
<td>3 (7%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Mean (SD) days from recent exacerbation to visit 1</td>
<td>123.6 (74.1)</td>
<td>123.7 (80.1)</td>
<td>130.6 (74.8)</td>
</tr>
<tr>
<td>Mean (SD) dose of budesonide at baseline</td>
<td>630.8 (297.4)</td>
<td>639.1 (255.1)</td>
<td>634.7 (277.0)</td>
</tr>
</tbody>
</table>

MD = maintenance dose group; DD = double dose group.
higher overall rate of exacerbations than was reported, in the end the total number of exacerbations (n = 98) exceeded our planned number (n = 80).

In a smaller paediatric study of similar design, Garrett et al also found no benefit to doubling the dose of ICS at the time of an exacerbation. However, the authors cautioned that, because of their sample size, they did not have adequate power to detect a significant difference.

On the other hand, there is some evidence for the potential benefit of a more substantial increase in the dose of ICS such as tripling or quadrupling the maintenance dose. Foresi et al studied patients stabilised on 800 μg budesonide twice daily who were then randomised to receive 100 μg or 400 μg budesonide twice a day plus additional treatment in case of exacerbation (group 1, 400 μg twice daily + placebo; group 2, 100 μg twice daily + 200 μg four times daily; group 3, 100 μg twice daily + placebo). Patients in group 2 who had a quadrupling of their ICS at the onset of an exacerbation had significantly better outcomes. The study by Foresi et al is not strictly comparable with ours because patients were stabilised on a high dose of budesonide before randomisation, which is not usual clinical practice. In a further study of mild exacerbations, 19 patients were randomised to either doubling the dose of ICS or addition of a single dose of 3200 μg budesonide. Those receiving the high single dose treatment initially improved more, with a greater increase in PEF in the first week (87.4 (4.7) l/min v 76.7 (5.3) l/min, p = 0.029), but at 3 weeks there was no difference between the groups. A priori, we anticipated that there might be an effect on outcome based on the baseline dose of ICS. This, in fact, was true (table 3), with treatment failure being higher in subjects who were in the higher dose range at baseline. As might be expected, the results of this subgroup analysis were not statistically significant.

Treatment with high dose ICS has been shown to be equivalent in some studies to the administration of systemic steroids. In one study patients discharged from the emergency department on budesonide 600 μg four times daily had comparable relapse rates to patients given prednisone 40 mg orally daily. In a similar study involving patients with milder asthma exacerbations, Levy et al showed that fluticasone 1000 μg was equivalent to prednisone 40 mg orally daily. A further paediatric study confirmed equivalence between high dose budesonide and oral prednisone. A synergistic effect of inhaled and oral corticosteroid was demonstrated by Rowe et al in acute asthma. In this study of patients discharged from the emergency department, those receiving a combination of budesonide 1600 μg daily with prednisone 40 mg daily had fewer relapses than patients receiving oral corticosteroids alone (12.8% v 24.5%, p = 0.049). An early effect of ICS was demonstrated by Gibson et al in patients withdrawn from ICS and then randomised to a single dose of budesonide 2400 μg or placebo. As early as 6 hours later there was less sputum eosinophilia and reduced airway hyperresponsiveness. All of these data suggest that higher doses of ICS may be more effective in the management of exacerbations than simply doubling the maintenance dose.

There are a number of other reasons why doubling the dose of ICS may have been ineffective in our study. Firstly, there was close monitoring and excellent compliance of the patients, although reported compliance may have overestimated actual compliance. In an effectiveness study of an action plan in a family practice setting where patients were less closely monitored, less than 40% implemented their action plan. On the other hand, in this study patients were alerted electronically by the MiniDoc and initiated physician contact within 48 hours of the commencement of an exacerbation. This excellent compliance in making contact

<table>
<thead>
<tr>
<th>Table 2 Primary outcome (treatment failure) in patients randomised to the two study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD group (n = 52)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Asthma instability</td>
</tr>
<tr>
<td>Oral CS</td>
</tr>
<tr>
<td>Oral CS and instability</td>
</tr>
<tr>
<td>Oral CS, visit and instability</td>
</tr>
<tr>
<td>Oral CS and unscheduled visit</td>
</tr>
<tr>
<td>Unscheduled visit</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

MD = maintenance dose group; DD = double dose group; CS = corticosteroid.
with their physician was also reflected in their high compliance in taking maintenance ICS. The fact that the patients in the maintenance arm of the study actually took their prescribed doses of ICS may have had a significant protective effect. In a previous study of hospitalised patients, those with near fatal asthma took only 50% of their prescribed ICS, as did the control group with less severe asthma.22

Secondly, doubling the dose was associated with only twice daily administration. Previous studies have shown that a four times a day dosing regime provides greater efficacy in an acute situation or with severely uncontrolled asthma.23 However, our study was designed to assess the validity of the usual clinical recommendation, which is doubling of the daily maintenance dose and continuing the twice daily regime.

A third potential confounding factor is that patients increased their ICS up to 48 hours after the onset of the exacerbation. In clinical practice patients may increase their ICS earlier, particularly within the first 12–24 hours after the onset of increased symptoms. In some studies of exacerbations increased symptoms preceded a fall in PEF,24 while in others the changes occur concurrently.25 It is unlikely that access to study personnel was a barrier to changes in treatment as research nurses and investigators were available on a 24 hour basis throughout the study.

There are methodological reasons which may explain our negative results. In our initial pre-study estimates, based on an earlier study,26 we estimated that 50% of patients in the MD arm would require oral corticosteroids for an exacerbation. In fact, only 17% of patients required oral steroids. This again suggests that, in an efficacy study with higher compliance with medication, regular treatment may be the most critical factor in limiting the need for augmented therapy. Although the overall result was that doubling the dose of ICS did not reduce the number of patients requiring oral corticosteroid compared with the MD group, the number of patients with unstable asthma at 14 days in the MD group (23%) was almost double that in the DD group (13%). An additional reason could be that only certain exacerbations respond to an increased dose of ICS. It is well documented that viral infections are responsible for many asthma exacerbations27 and that ICS may not be effective in this type of exacerbation.

The implications of our study are that, if patients routinely comply with maintenance ICS, then doubling the dose of ICS may not alter the course of an asthma exacerbation. Our study also shows that such patients have relatively short lived exacerbations which do not require a major change in treatment. We cannot comment on the use of larger doses of ICS for patients who do not regularly use their preventer or controller medication, or if better results might have been achieved if the dose of ICS was increased earlier. For patients experiencing an exacerbation, the clinician may choose one of several approaches including: continued close observation of the exacerbation, an empirical decision to increase the dose of maintenance ICS to doses recently studied in more severe exacerbations (for example, >2000 μg beclometasone equivalent), or the use of a short course of prednisone. Future prospective studies using the same methodology as outlined in this study should address the issue of the optimal increase in the dose of ICS that may be needed to prevent the development of an exacerbation or progression to a more severe exacerbation needing oral corticosteroid. A recent publication also confirms the lack of effect of doubling the dose of inhaled corticosteroids.27

ACKNOWLEDGEMENTS

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Table 3 Treatment failure associated with initial ICS dose

<table>
<thead>
<tr>
<th>ICS dose</th>
<th>MD group (n = 52)</th>
<th>DD group (n = 46)</th>
<th>Total (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;400 μg</td>
<td>18 Yes 7 No 21%</td>
<td>12 No 5 12%</td>
<td>30 No 12 28%</td>
</tr>
<tr>
<td>&gt;400 μg</td>
<td>13 No 10 21%</td>
<td>15 Yes 14 29%</td>
<td>28 Yes 28 50%</td>
</tr>
</tbody>
</table>

MD = maintenance dose group; DD = double dose group.
LUNG ALERT

Digital cameras are reliable in teleradiology

Teledicine, and particularly teleradiology, can be very useful in developing countries where skilled radiological expertise is not freely available. “Store and forward teleradiology”, where digitised images are electronically sent after image compression to reduce file sizes (for easier internet transfer), will be particularly useful. In this article the authors assess the adequacy of such a system using a freely available digital camera and various image compression algorithms.

Ninety one erect chest radiographs, most of which had one or more features of tuberculosis (consolidation, cavitation, effusion, pneumothorax, lymphadenopathy, calcification, scarring, etc), were photographed using a 5 megapixel Olympus 3000Z digital camera and were converted to gray scale and electronically modified using Adobe Photoshop software. Twenty two radiographs were normal. Four blinded independent observers (three radiologists and one pulmonologist) read three versions of the same image: (1) the original analogue image, (2) the standard JPEG image (compressed to 400 MB), and (3) a JPEG 2000 image which involves 60:1 wavelet image compression (compressed to 120 MB).

Software developed by the authors (available from http://www.sourceforge.net/projects/telemedmail) helped in image viewing.

Receiver operating characteristic curve analysis of the data showed no significant difference between the interpretation of features of tuberculosis in the three groups apart from calcification which was better detected on the standard JPEG images than on the analogue images. This study shows that low cost, small file size teleradiology allows readings of sufficient quality to make a diagnosis of tuberculosis and can be of benefit to physicians in developing countries with slow dial-up internet connections.

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