Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis

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ABSTRACT: The aim of this study was to examine the dose-response relationship of inhaled budesonide in adolescents and adults with asthma.

A meta-analysis was carried out on placebo-controlled, randomised clinical trials, presenting data on at least one outcome measure of asthma and using at least two doses of budesonide, delivered by turbuhaler or metered-dose inhaler + spacer twice daily.

A total of six studies of 1,435 adolescents and adults, with mild to moderately severe asthma, met the inclusion criteria for the meta-analysis. A negative exponential model indicated that 80% of the benefit at 1,600 μg day⁻¹ was achieved at doses of 200–400 μg day⁻¹ and 90% by 300–600 μg day⁻¹. Meta-regression with a quadratic term in dose showed that the maximum effect was obtained with doses of ~1,000 μg day⁻¹.

In conclusion, the available published data indicate that, in adolescents and adults with mild to moderate asthma, most of the therapeutic benefit of budesonide delivered by turbuhaler or metered-dose inhaler + spacer is achieved with a dose of ~400 μg day⁻¹ and the maximum effect is achieved at ~1,000 μg day⁻¹. This conclusion is qualified by the recognition that there is considerable individual variability in the response to inhaled corticosteroids and that the subjects included in this meta-analysis had predominantly mild to moderate asthma.

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In a recent meta-analysis of the dose-response relationship of fluticasone, it was shown that most of the therapeutic benefit is achieved with doses of 100–250 μg day⁻¹ and that the maximum effect is obtained at ~500 μg day⁻¹ in adolescents and adults with asthma [1]. This therapeutic dose range is two-fold lower than that recommended in the international and national consensus guidelines and formularies, and the dose commonly prescribed in clinical practice [2–4]. In view of this disparity and in response to the recommendations of the Cochrane Centre [5], the current authors have further investigated the therapeutic dose range of inhaled corticosteroids by undertaking a similar meta-analysis of the dose-response relationship of budesonide.

Methods

A search of Medline was conducted from Jan 1966 to Jan 2003 and of Embase from Jan 1980 to Jan 2003. On Medline, studies were searched using a combination of the keywords "budesonide" and "dose" or "dosage". AstraZeneca, the manufacturer of budesonide, was also asked for details of all relevant studies; no additional studies were identified. No relevant studies published in other languages were found on Medline or Embase. Finally, the reference lists of relevant studies were examined and no other studies were found.

Inclusion criteria

Two people examined each paper’s title and abstract, and then the full paper if necessary. To be included in the primary meta-analysis, studies had to meet all of the following criteria: a double-blind, placebo-controlled, randomised trial involving two or more doses of budesonide, delivered by turbuhaler or metered-dose inhaler (MDI) + spacer device twice daily, in adolescents (aged >12 yrs) or adults with asthma, of at least 4 weeks in duration. The decision to include studies using the turbuhaler and MDI + spacer was based on evidence that both delivery systems achieved similar lung deposition, greater than that with the MDI alone [6, 7], although it is noted that a formal dose-response comparison between the two devices was not undertaken. The search strategy recommended by the QUORUM statement is shown in figure 1. Letters were sent to the authors of three out of six studies included in the meta-analysis to obtain the data in the format required.

Data extraction

Extraction of data was based on reported summary statistics (mean, SD, SEM) for the intention-to-treat population. The outcome measures assessed were forced expiratory volume in one second (FEV1) measured at the clinic, peak expiratory flow (PEF; both morning and evening), use of β-agonists, total withdrawals and exacerbations of asthma leading to withdrawal.

Data analysis

For each outcome measure, the mean change reported in each study was plotted against the total daily dose of...
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Results

Description of the studies

Six studies met the criteria for inclusion in this analysis [11–16]. These studies were published between 1990 and 2000 and were of 4–16 weeks in duration (table 1). A total of 1,435 adolescents and adults with asthma were included in the studies, with a mean age (range) of 41 yrs (12–70). In most studies, the patients had mild to moderately severe asthma, with a mean FEV1 of 69% pred at enrolment. The doses of budesonide ranged 200–1,600 μg·day⁻¹; only one study used a dose of budesonide >800 μg·day⁻¹. The funnel plots (data not shown) did not suggest publication bias, although it is acknowledged that with only six studies, this provides only limited support.

Plots of mean change in outcome measures at different doses

Plotting the raw data for each outcome measure against the dose of budesonide showed most of the benefit was achieved at a dose of 200–500 μg·day⁻¹, with little further improvement at higher doses.

Determination of the dose at which 80 and 90% of the effect obtained with 1,600 μg·day⁻¹ is achieved

From the negative exponential line of best-fit derived from the weighted means of the effect at each dose, it was calculated that 80% of the benefit obtained with 1,600 μg·day⁻¹ was achieved at doses of 200–400 μg·day⁻¹ and 90% at doses of 300–600 μg·day⁻¹, depending on the outcome measure (table 2). The plot of the per cent predicted maximum effect based on the negative exponential model for all four major clinical outcome measures is shown in figure 2.

Determination of the dose at which the maximum response is achieved

The dose of the peak effect ranged 881–1,090 μg·day⁻¹ for the different outcome variables (table 3). The maximum increase in FEV1 was 0.32 L, utilising the fixed-effects model.

Effect on FEV1 of a dose of 400 μg·day⁻¹ budesonide, as compared with higher doses

The meta-analysis of the standardised difference in FEV1 at a dose of 400 μg·day⁻¹ compared with higher doses showed a difference in FEV1 of 0.05 SD, with a CI that included zero (-0.12–0.22). The pooled sds for the three studies reporting FEV1 ranged -0.083–0.1141. The homogeneity statistic was not significant. Forest plots of FEV1 did not suggest that a dose of 400 μg·day⁻¹ produced an inferior response as compared to ≥800 μg·day⁻¹ (fig. 3).

Effect on peak expiratory flow of a dose of 400 μg·day⁻¹ budesonide, as compared with higher doses

The meta-analysis of the standardised difference in PEF at a dose of 400 μg·day⁻¹ as compared with higher doses showed a difference in PEF of 3.7 L·min⁻¹ (-5.8–13.2). Forest plots of

budenedione. A negative exponential curve of the mean relative percentage change from baseline for each outcome measure was modelled, weighted by the number of participants in the study. From this graph, the doses at which 80 and 90% of the effect obtained with 1,600 μg·day⁻¹ were determined. The effect obtained with 1,600 μg·day⁻¹ was considered to be the “maximum effect” for the purposes of this analysis. The confidence intervals of the outcome measures of this model could not be estimated from the published data.

Meta-regression was used to compare the effect of change in dose of budesonide on the asthma response variables. A general linear model, weighted by the inverse of the calculated variance for each variable, was used [8, 9]. Scatter plots of the response and explanatory variable (the total daily dose of inhaled budesonide) suggested a curved relationship, therefore, a quadratic model was used for this measure. The variance for each response variable was calculated from the SD or SE cited in the extra data from the authors, by using the initial number of patients for each treatment category. Analysis of residuals indicated that normality and other assumptions were met. The peak dose effect for the quadratic model was calculated by the following equation:

\[ \beta_1/(2 \times \beta_2) \]  

where \( \beta_1 \) is the parameter for the dose of budesonide and \( \beta_2 \) the parameter for the square of the dose. The weighted model variance was used to calculate 95% confidence intervals (CI) for the predicted peak dose. Both fixed-effects and random-effects models were used.

A meta-analysis was undertaken to establish the difference in effect on FEV1 and PEF of an inhaled dose of 400 μg·day⁻¹ budesonide, as compared with higher doses, based on the standardised difference in FEV1 and PEF for the studies in which these data were available [10]. The standardised difference represented the differences in the means, divided by the pooled within-groups SD. Both fixed- and random-effects models were fitted.

Due to heterogeneity between studies and the low numbers involved, it was not possible to perform a meaningful statistical analysis of the data for withdrawals due to exacerbations of asthma. Likewise, the relatively high frequency of withdrawals due to events other than an exacerbation of asthma in two of the four studies that reported these data also meant that the total withdrawal data could not be analysed.
PEF did not suggest that a dose of 400 mg\textsuperscript{-day\textsuperscript{-1}} gave an inferior response as compared to 800 mg\textsuperscript{-day\textsuperscript{-1}} (fig. 4).

Withdrawals due to asthma

The data for total withdrawals or for exacerbations of asthma leading to withdrawal could not be analysed, due to heterogeneity between studies, zero cell counts in different dose groups and the relatively high frequency of withdrawals due to events other than exacerbations of asthma (table 4).

Examination of the individual study data indicate that most of the benefit with respect to the reduction in asthma exacerbations leading to withdrawal was achieved with a dose of 400 mg\textsuperscript{-day\textsuperscript{-1}}.

Discussion

This meta-analysis has shown that, in adolescents and adults with mild to moderate asthma, most of the therapeutic benefit of budesonide is achieved with a total daily dose of \(400\) mg and that the maximum achievable benefit occurs with a dose of \(800\) mg. Given that \textit{in vitro} and clinical studies have indicated a 2:1 potency ratio of fluticasone to budesonide and beclomethasone dipropionate (BDP) [17–19], these findings are strongly consistent with the previous fluticasone meta-analysis, which showed that 90\% of clinical benefit was achieved with doses in the range of 150–250 mg\textsuperscript{-day\textsuperscript{-1}} and the peak effect with a dose of \(500\) mg\textsuperscript{-day\textsuperscript{-1}} [1].

These findings are also consistent with the recent large dose-response study of BDP administered via MDI, which reported that the top of the dose-response curve in terms of efficacy was between 400–800 mg\textsuperscript{-day\textsuperscript{-1}}, depending on the outcome measure examined [20]. Together, these findings allow determination of the therapeutic dose-response relationship of the different inhaled corticosteroids used in clinical practice, depending on their relative potencies.

Limitations of the study

The major limitation of this meta-analysis was the paucity of studies using high doses of budesonide; only one study examined a dose >800 mg\textsuperscript{-day\textsuperscript{-1}}. Consequently, one of the findings is that data in the published literature on which to confidently determine the dose relationship of budesonide at high doses is limited. The authors are confident that all available studies were included in the analysis because of the comprehensive search that was undertaken.

The authors were concerned that the requirement for the studies to be placebo-controlled may have led to the exclusion of a number of large dose-response studies examining doses of
budesonide >800 µg·day⁻¹ and that their inclusion would have enabled the dose-response to be determined at the higher level. However, this was not the case, as only two nonplacebo-controlled studies identified examined doses of >800 µg·day⁻¹ [21, 22] and these studies indicated that there was a minimal additional benefit of using doses up to 3,200 µg·day⁻¹.

For reasons stated previously, the authors were unable to undertake a meaningful statistical analysis of withdrawals due to worsening asthma. However, examination of data from individual studies suggested that most of the benefit is achieved with a dose of 400 µg·day⁻¹. For example, in the large study of Busse et al. [11], budesonide at a dose of 400 µg·day⁻¹ led to a reduction in withdrawals from asthma from 57 to 10%, with the 1,600 µg·day⁻¹ dose causing a minimal further reduction to 7%.

It is also acknowledged that the greater number of withdrawals on placebo may have led to an underestimation of the magnitude of the difference in lung function and symptoms between placebo and budesonide. This consideration did not apply to the comparisons between the 400, 800 and 1,600 µg doses of budesonide, in which the proportion of withdrawals was similar.

Another issue is the intersubject variation in response to inhaled corticosteroid therapy, which is likely to result in a proportion of patients requiring doses higher than the observed mean dose to achieve the maximum effect, just as a proportion may well require lower doses. Regrettably the authors were unable to quantify this variability in response, as AstraZeneca were unable to make the individual patient data available and the interpretation of the study findings is limited in this respect.

Table 3. – Estimates of dose of budesonide (µg·day⁻¹) giving peak effect and effect on mean change in outcome measure

| Outcome measure          | R² % | Fixed-effects model | Random-effects model |
|--------------------------|------|---------------------|---------------------|
|                          |      | Dose of peak effect | Mean change (95% CI) | Dose of peak effect | Mean change (95% CI) |
| FEV₁ L                   | 39   | 1084                | 0.29 (0.19–0.40)     | 1090              | 0.30 (0.15–0.45)     |
| Morning PEF L·min⁻¹      | 39   | 881                 | 58.2 (45–72)         | 976               | 61.8 (35.4–88.1)     |
| Evening PEF L·min⁻¹      | 50   | 926                 | 36.6 (25–48.2)       | 1050              | 40.2 (11.7–68.8)     |
| β-agonist use puffs·day⁻¹| 52   | 965                 | -2.54 (-0.78–-4.35)  | 1038              | -2.76 (-6.33–-0.81)  |

CI: confidence interval; FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow.
Key findings

There was consistency in the findings from the different methods of analysis; the majority of the clinical effect of inhaled budesonide is achieved at a dose of 250–500 μg·day⁻¹, with higher doses providing little further benefit. As with the previous meta-analysis of fluticasone [1], similar dose-response relationships were observed for the different outcome measures, including lung function, symptoms and exacerbations.

The findings are also consistent with other dose-response studies of budesonide that did not include a placebo arm and as a result could not be included in this meta-analysis [21–28]. For example, similar results were found in the studies by Chanez et al. [22] and Tuuviainen et al. [23], which showed no difference between initial treatment with 400 or 1,600 μg·day⁻¹ budesonide after 4 weeks, or with 200 or 800 μg·day⁻¹ after 12 weeks, respectively. In the FACET study [25], there were clinically significant improvements in asthma control with budesonide taken over a 12-month period at 800 as compared to 200 μg·day⁻¹. In contrast, in the 4-week study by Van der Molen et al. [28], initial treatment with 200 or 800 μg·day⁻¹ budesonide did not result in statistically significant differences for any of the clinical outcome measures. In the only randomised, double-blind study that compared doses of budesonide >1,600 μg·day⁻¹, there was no therapeutic difference between 8 weeks of treatment with 3,200 and 1,600 μg·day⁻¹, confirming the lack of further benefit at very high doses [21].

Cases when higher doses may be warranted

The asthmatic subjects recruited in the studies that were included in the meta-analysis can be considered to have had predominantly mild to moderate asthma, on the basis of a mean FEV1 69% pred. As a result, although some subjects with severe asthma were included in the studies (lower range in FEV1 40% pred), the findings may not necessarily apply to more severe asthmatics. As has been noted previously, due to individual variability, a proportion of asthmatics may require doses greater than the peak of the dose response observed in this meta-analysis to achieve maximal clinical benefit, just as a proportion may require lower doses.

Furthermore, the current findings do not exclude the

### Table 4 – The number of withdrawals and withdrawals due to asthma according to budesonide dose in the three studies

| First author [ref.] | Dose       | Subjects n | Total withdrawals n (%) | Withdrawals due to asthma n (%) |
|---------------------|------------|------------|-------------------------|---------------------------------|
| BUSSE [11]          | Placebo    | 92         | 55 (60)                 | 52 (56)                         |
|                     | 200 μg     | 91         | 24 (26)                 | 16 (18)                         |
|                     | 400 μg     | 93         | 17 (18)                 | 10 (11)                         |
|                     | 800 μg     | 99         | 16 (16)                 | 9 (9)                           |
| KEMP [12]           | Placebo    | 89         | 13 (13)                 | 7 (7)                           |
|                     | 400 μg     | 93         | 9 (10)                  | 5 (5)                           |
|                     | 800 μg     | 91         | 5 (6)                   | 0 (0)                           |
| MIYAMOTO [13]       | Placebo    | 70         | 18 (26)                 | 3 (4)                           |
|                     | 200 μg     | 63         | 7 (11)                  | 0 (0)                           |
|                     | 400 μg     | 67         | 12 (18)                 | 1 (2)                           |
|                     | 800 μg     | 67         | 6 (9)                   | 1 (2)                           |
| O’BYRNE [15]        | Placebo    | 20         | 6 (30)                  | 2 (10)                          |
|                     | 400 μg     | 17         | 4 (24)                  | 0 (0)                           |
|                     | 800 μg     | 20         | 8 (40)                  | 0 (0)                           |

*: the withdrawal data from this study was measured from the graph of discontinuations from the study (fig. 1); this data does not correspond to that stated in the text (withdrawal due to worsening asthma: 61% of placebo group; 20% of 200 μg·day⁻¹ group; 11% of 400 μg·day⁻¹ group; 8% of 800 μg·day⁻¹ group; and 7% of 1,600 μg·day⁻¹ group).
possibility that there may be certain circumstances when higher doses of budesonide may be useful. There is some evidence that budesonide at 3,200 µg·day$^{-1}$ may be as effective as oral corticosteroid therapy in follow-up treatment after an acute asthma attack [29]. However, a recent meta-analysis by the Cochrane Collaboration suggests that further research is needed to clarify this and that insufficient evidence exists at present for such an inhaled regimen to be implemented [30].

Another clinical situation is the use of high doses of budesonide in oral steroid-dependent asthmatics to enable a reduction in oral steroid dose. Most studies have shown that a significant reduction in oral steroid dose can be achieved with high doses of inhaled corticosteroid therapy, although whether 1,600 µg·day$^{-1}$ of budesonide is superior to 800 µg·day$^{-1}$ is inconclusive [31–33].

**Contrasting dose-response relationship of systemic effects**

In contrast to the dose-response with efficacy, adverse systemic effects exhibit a more linear relationship with no evidence of a plateau in response. The two main adverse effects of concern with long-term use of inhaled corticosteroids in adults are adrenal suppression and reduced bone mineral density, with bruising, cataracts and glaucoma also being associated with their use. Studies have shown that doses >1,000 µg·day$^{-1}$ of budesonide can produce significant suppression of the hypothalamic-pituitary-adrenal axis [34–36]. Indeed, 6 weeks of budesonide treatment at a dose of 3,200 µg·day$^{-1}$ may lead to suppression of adrenal cortisol production of a magnitude similar to that observed with 10 mg of oral prednisone [36].

The cumulative doses of inhaled corticosteroids are particularly important when the adverse effects on bone density are considered in relation to the requirement for lifelong therapy. This is illustrated by Wong et al. [37], who calculated that the use of 2,000 µg·day$^{-1}$ of budesonide or equivalent for 7 yrs results in a reduction of bone mineral density in the lumbar spine of at least 1 sd. In postmenopausal females, an effect of this magnitude is associated with a two-fold increase in fracture risk. As a result, patients currently treated with high doses of inhaled corticosteroids may well enter later life with reduced bone mineral density, as well as a degree of adrenal insufficiency. It is, therefore, important to consider the therapeutic index of inhaled corticosteroids, incorporating both the dose-response relationship for efficacy and systemic effects.

**Comparison with guidelines and clinical practice**

It is of concern to contrast the present findings with the therapeutic dose range recommended in national and international guidelines and formularies. For example, the recent British Guideline on the Management of Asthma recommends the use of inhaled corticosteroid with dose increments on the basis of clinical need, with provision for the dose of budesonide to be increased up to 2,000 µg·day$^{-1}$ to obtain adequate control if this is not achieved at lower doses [2]. Likewise, the British National Formulary gives a dose range for budesonide of 200–2,000 µg·day$^{-1}$ for adults [4]. Reducing the dose within the therapeutic dose range would not only result in major financial savings, but also improve the risk-to-benefit ratio.

**Therapeutic implications**

One of the major therapeutic implications of these findings is at what dose of budesonide should a long-acting β-agonist (LABA) be added if the patient has inadequately controlled asthma. The FACET study found that a four-fold increase in the dose of budesonide from 200 to 800 µg·day$^{-1}$ was more effective than adding formoterol to budesonide 200 µg·day$^{-1}$ for reducing severe exacerbations, which was the primary outcome variable [25]. In contrast, the addition of formoterol to low-dose budesonide resulted in a greater reduction in symptoms and improvement in lung function. In the OPTIMA study of subjects with mild asthma, the addition of formoterol to 200 µg·day$^{-1}$ of budesonide resulted in significantly greater efficacy for all outcome measures, including severe exacerbations, than increasing the dose of budesonide from 200 to 400 µg·day$^{-1}$ [26].

These studies indicate that considerable benefit can be achieved with the addition of a LABA to budesonide within the 200–800 µg·day$^{-1}$ dose range and suggests that such an approach is preferable to increasing the dose of budesonide to a range beyond the dose-response profile observed in the present study.

**Conclusions**

This study provides more evidence that inhaled corticosteroids exhibit a flat dose-response at higher doses with most of the therapeutic benefit being achieved with a dose of ~400 µg·day$^{-1}$ budesonide or equivalent. Prescribing within the established therapeutic dose range for inhaled corticosteroids has an optimal risk-to-benefit ratio, whereas doses beyond the peak of the dose-response curve need to be prescribed with caution, as patients will be exposed to the potential adverse systemic effects of inhaled steroids with minimal further gain in terms of efficacy.

**Conflicts of interest**

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