

## Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis

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### Abstract

**Objective** To examine the dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma.

**Design** Meta-analysis of placebo controlled, randomised clinical trials that presented data on at least one outcome measure of asthma and that used at least two different doses of fluticasone.

**Setting** Medline, Embase, and GlaxoWellcome's internal clinical study registers.

**Main outcome measures** FEV<sub>1</sub>, morning and evening peak expiratory flow, night awakenings,  $\beta$  agonist use, and major exacerbations.

**Results** Eight studies, with 2324 adolescents and adults with asthma, met the inclusion criteria. Data on doses of >500  $\mu\text{g}/\text{day}$  were limited. The dose-response curve for the raw data began to reach a plateau at around 100-200  $\mu\text{g}/\text{day}$  and peaked by 500  $\mu\text{g}/\text{day}$ . A negative exponential model for the data, without meta-analysis, indicated that 80% of the benefit at 1000  $\mu\text{g}/\text{day}$  was achieved at doses of 70-170  $\mu\text{g}/\text{day}$  and 90% by 100-250  $\mu\text{g}/\text{day}$ . A quadratic meta-regression showed that the maximum achievable efficacy was obtained by doses of around 500  $\mu\text{g}/\text{day}$ . The odds ratio for patients remaining in a study at a dose of 200  $\mu\text{g}/\text{day}$ , compared with higher doses, was 0.73 (95% confidence interval 0.49 to 1.08). Comparison of the standardised difference in FEV<sub>1</sub> for an inhaled dose of 200  $\mu\text{g}/\text{day}$  against higher doses showed a difference in FEV<sub>1</sub> of 0.13 of a standard deviation (-0.02 to 0.29).

**Conclusions** In adolescent and adult patients with asthma, most of the therapeutic benefit of inhaled fluticasone is achieved with a total daily dose of 100-250  $\mu\text{g}$ , and the maximum effect is achieved with a dose of around 500  $\mu\text{g}/\text{day}$ . However, these findings were limited by the lack of data on individual patients and by the paucity of dose-response studies that included doses of >500  $\mu\text{g}/\text{day}$ .

### Introduction

Inhaled corticosteroids are the most effective anti-inflammatory drugs for treating asthma and are recommended for most adult patients with symptomatic chronic asthma.<sup>1,2</sup> Since the introduction of the inhaled corticosteroid beclometasone dipropionate in the early 1960s, doses prescribed to patients with asthma have

progressively increased. This is shown in the latest version of the British Thoracic Society's guidelines, in which steps 3 to 5 recommend that adults with chronic asthma should take beclometasone and budesonide in doses of 800-2000  $\mu\text{g}/\text{day}$  in a large volume spacer.<sup>1</sup> Because of its greater potency, fluticasone propionate is recommended in doses of 400-1000  $\mu\text{g}/\text{day}$ . The *British National Formulary* gives a dose range for fluticasone of 200-2000  $\mu\text{g}/\text{day}$  for adults.<sup>3</sup> These recommendations are largely pragmatic and were not based on strong scientific evidence of a clinically important dose-response relation in terms of efficacy at these higher doses.<sup>4</sup> We undertook a meta-analysis of the dose-response relation of the inhaled corticosteroid fluticasone in terms of efficacy in adolescents and adults with asthma.

### Methods

#### Search strategy

We conducted a search of Medline from January 1 1966 to December 1999 and of Embase from 1980 to December 1999. On Medline we combined a search of studies containing the keyword "fluticasone" with a search using the MeSH subject heading "asthma" and "chemical and pharmacologic phenomena" (MeSH) or "dose-response relationship, drug" (MeSH) or the keywords "dose" or "dosage." On Embase we searched for studies containing the keywords "fluticasone" and "dose" or "dosage." When limited to English, the total number of studies was 204. We also asked GlaxoWellcome, the manufacturer of fluticasone, for details of all relevant studies. No additional studies were identified, including studies not published in English. We did not find any relevant studies published in other languages on Medline or Embase. Finally, we examined the reference lists of relevant studies but found no other studies.

#### Inclusion criteria

Two people examined each paper's title and abstract, and then the full paper if necessary. To be included in this meta-analysis, studies had to meet all the following criteria: a double blind, randomised, placebo controlled trial of adolescents ( $\geq 12$  years of age) or adults with asthma; more than one dose of inhaled fluticasone was studied; fluticasone was delivered by one device; and data on measures of clinical efficacy were reported. Studies in which participants were dependent on oral steroids or involved in oral steroid reduction regimes were excluded.

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**Table 1** Summary of studies included in meta-analysis of trials of fluticasone in adults and adolescents with asthma

Study	No of patients	Duration of study (weeks)	Doses of FP (µg/day)	Device	Range (mean) of FEV <sub>1</sub> as % of predicted	Age (mean)	Baseline ICS usage	Outcomes measured					
								FEV <sub>1</sub>	Morning PEF	Evening PEF	β agonist use	Exacerbations	Night awakenings
Chervinsky <sup>8</sup>	331	8	50; 200; 1000	MDI	60-90 (72)	≥18 (38)	8-16 puffs BDP/ day	✓	✓	✓	✓	—	✓
Sheffer <sup>9</sup>	307	12	50; 100; 200	MDI	45-75 (63)	≥12 (30)	0	✓	✓	✓	✓	✓	—
Galant <sup>10</sup>	353	12	100; 200	MDI	45-75 (61)	12-75 (30)	≥0	✓	✓	—	✓	✓	✓
Wolfe <sup>11</sup>	281	12	200; 500; 1000	MDI	(65)	12-87 (34)	>0	✓	✓	—	✓	✓	✓
Lawrence <sup>12</sup>	261	6	200; 1000	Diskhaler	50-80 (66)	≥18	>0	✓	✓	—	✓	✓	✓
Wasserman <sup>13</sup>	321	12	100; 200; 800	Diskhaler	50-80	≥12	≥0	✓	✓	✓	✓	✓	✓
Noonan <sup>14</sup>	105	8	100; 200	MDI	60-85 (74)	12-57 (28)	0	✓	✓	✓	✓	✓	✓
Pearlman <sup>15</sup>	342	12	100; 200; 800	Diskhaler	50-80 (67)	12-72 (35)	>0	✓	✓	✓	✓	✓	✓

FP=fluticasone propionate; FEV<sub>1</sub>=forced expiratory volume in one second; ICS=inhaled corticosteroid; PEF=peak expiratory flow; MDI=metered dose inhaler; BDP=beclometasone dipropionate.

**Data extraction and analysis**

Extraction of data was based on reported summary statistics (means, standard deviations, standard errors of means) for the intention to treat population. The outcome measures assessed were forced expiratory volume in one second (FEV<sub>1</sub>), measured at the clinic, peak expiratory flow (both morning and evening), use of β agonists, night awakening, and exacerbation or withdrawal rate (in all the studies patients withdrew if they experienced a major exacerbation). Other outcome measures were not analysed.

For each outcome measure the mean change reported in each study was plotted against the total daily dose of fluticasone. We then modelled a negative exponential curve of the mean relative percentage change from baseline for each outcome measure, weighted by the number of participants in the study. From this graph the doses at which 80% and 90% of the effect obtained with 1000 µg/day were determined.

We used meta-regression to compare the effect of change in dose of fluticasone on the asthma response variables.<sup>5,6</sup> We pooled the odds ratios according to whether patients taking a dose of fluticasone of 200 µg/day, compared with patients taking higher doses, remained in a particular study.

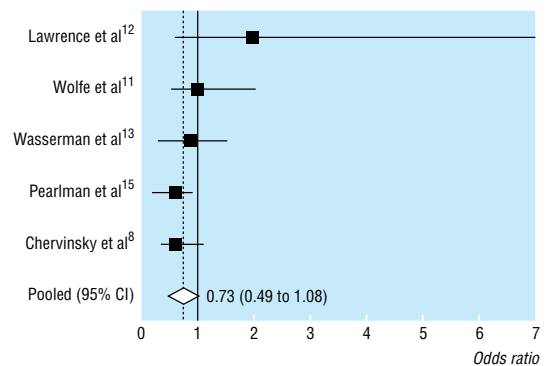
We also undertook a meta-analysis of the difference in effect on FEV<sub>1</sub> of an inhaled dose of 200 µg/day of fluticasone, compared with higher doses, based on the standardised difference in FEV<sub>1</sub> for the four studies from which data could be extracted.<sup>7</sup>

**Table 2** Doses of fluticasone (µg/day) at which 80% and 90% of the maximum effect is achieved, as derived from a negative exponential model\*

Outcome measure	80% of maximum effect achieved	90% of maximum effect achieved
FEV <sub>1</sub>	146	209
Morning PEF	172	247
Evening PEF	175	251
Use of rescue medication	71	102
Major exacerbations	108	155
Night awakenings	135	193

\*The effect obtained with 1000 µg/day of fluticasone was considered to be the "maximum effect" for the purposes of this analysis.

FEV<sub>1</sub>=forced expiratory volume in one second; PEF=peak expiratory flow.



Odds ratio of remaining in a trial at a dose of 200 µg/day of fluticasone, compared with higher doses, in the five trials that compared a dose of 200 µg/day with higher doses (higher ratio=favours lower dose)

**Results**

Eight studies met the criteria for inclusion in this analysis.<sup>8-15</sup> These studies were published between 1994 and 1998 (table 1). In most studies the patients had moderate or severe asthma. (For more details see the full version of this paper on the *BMJ's* website.)

We calculated that 80% of the benefit obtained with 1000 µg/day was achieved at doses of 70-170 µg/day and 90% at doses of 100-250 µg/day, depending on the outcome measure (table 2). For four of the outcome measures it was possible to determine the dose giving the peak effect. This dose ranged from 560 to 660 µg/day.

The pooled odds ratio of patients remaining in a trial at a total dose of inhaled fluticasone of 200 µg/day, compared with higher doses, was 0.73 (0.49 to 1.08) (figure).<sup>8,11-13,15</sup> The random effects pooled odds ratio was 0.70 (0.38 to 1.3).

The meta-analysis of the standardised difference in FEV<sub>1</sub> for the four studies that reported these data and that compared a dose of 200 µg/day with higher doses showed a difference in FEV<sub>1</sub> of 0.13 of a standard deviation, with a confidence interval that included zero (-0.02 to 0.29).<sup>8,12,13,15</sup> The random effects pooled odds ratio was 0.13 (-0.03 to 0.30).

## Discussion

### Limitations of the study

A number of issues need to be addressed in considering the results of this study. We are likely to have identified all the eligible trials of fluticasone because of our comprehensive search, thus publication bias is unlikely. Funnel plots (not shown) did not indicate publication bias. We used five different methods to analyse the published data, each with its own limitations. It was not possible to undertake more detailed analyses as data on individual patients could not be made available to us by GlaxoWellcome.

We identified eight studies involving over 2300 patients with asthma, this number providing considerable power to examine the dose-response relation. However, only five of the studies that were eligible for our analysis used doses greater than 500 µg/day, and so our results at the higher end of the dose-response relation must be considered with this limitation in mind. As a result, one of our findings is that data in the published literature on which to determine confidently the dose-response relation of fluticasone at doses >500 µg/day are limited. However, the available evidence suggests that further efficacy is not obtained with this higher range.

Another consideration is whether a higher dose of fluticasone would have been required to achieve maximum efficacy if patients with more severe asthma were studied. This possibility was not supported by our study, for the studies were mostly of patients with moderate or severe asthma, whose mean pre-bronchodilator FEV<sub>1</sub> was 66% of predicted normal values at enrolment despite the fact that most patients used concurrent inhaled corticosteroids.

### Fluticasone compared with other inhaled corticosteroids

Comparison with the dose-response relation of the inhaled corticosteroids beclometasone dipropionate and budesonide is difficult because of the sparsity of randomised, double blind, placebo controlled dose-response studies in patients with asthma. A dose-response study of beclometasone administered by metered dose inhaler reported that the top of the dose-response curve in terms of efficacy was 400-800 µg/day, depending on the outcome measure.<sup>16</sup> The findings of a large dose-response study of budesonide delivered by Turbuhaler were similar: no significant differences were noted when doses were doubled from 400 to 800 to 1600 µg/day.<sup>17</sup> If it is assumed that the difference in potency between fluticasone and budesonide or beclometasone is about twofold, the findings of these studies of the dose-response relation of the other inhaled corticosteroids are similar to those of this study examining fluticasone.

### Cases when higher doses may be warranted

The findings of this meta-analysis do not exclude the possibility that there may be special circumstances when higher doses are useful. One study has indicated that in cases of severe exacerbations of asthma a high dose of inhaled fluticasone is equivalent in efficacy to oral corticosteroids.<sup>18</sup> Another such clinical situation is the use of fluticasone in patients dependent on oral steroids; Nelson et al found that 1000 µg/day and 2000 µg/day of fluticasone allowed most patients to be

### What is already known on this topic

Inhaled corticosteroids are recommended for most patients with asthma, with the dose being increased as required to obtain control

A therapeutic dose range of fluticasone propionate of 200-2000 µg/day is recommended in the *British National Formulary* for adults with asthma

### What this study adds

Published data are insufficient to determine with confidence the dose-response relation of inhaled fluticasone at doses of >500 µg/day

The dose-response curve for inhaled fluticasone in moderate to severe asthma in adolescents and adults, for all major clinical outcome measures, including exacerbations, begins to plateau at 100-200 µg/day and peaks at around 500 µg/day

This study partially explains why adding a long acting β agonist to inhaled corticosteroids is more efficacious than increasing the dose of inhaled steroid beyond this dose range

weaned off oral corticosteroids.<sup>19</sup> Thus our findings relate only to the long term, regular treatment of patients with mild, moderate, or severe asthma.

### Contrasting dose-response relation of systemic effects

The dose-response relation in terms of efficacy contrasts with that in terms of systemic effects. There is a linear relation between the dose and the effects on the hypothalamic-pituitary-adrenal axis and bone metabolism, with no evidence of a plateau in response for doses up to 2000 µg/day.<sup>4</sup>

### Implications of the findings

National and international guidelines will need to be modified, such that lower doses of fluticasone are recommended for the treatment of asthma in adolescents and adults. The pragmatic approach that has been recommended of starting inhaled corticosteroids at a high dose, then reducing the dose once the patient's asthma is controlled, should be reconsidered.<sup>20</sup> This is also suggested by one major clinical study, which showed that starting with a low dose of budesonide in patients who had not previously used corticosteroids was as effective as the high dose, step down regime.<sup>21</sup> Of the two alternative regimes recommended in the British Thoracic Society's guidelines for when asthma is not controlled with fluticasone at a dose of 200-500 µg/day, adding a long acting β agonist is preferable to increasing fluticasone to a dose of >500 µg/day.

Some of the previous studies that compared the efficacy of different inhaled corticosteroids in patients with asthma will need to be re-examined. Many of these studies compared doses that are at, and in some cases way beyond, the top of the dose-response range, which in the light of our findings is inappropriate.<sup>22</sup>

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- British Asthma Guidelines Coordinating Committee. British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;52(suppl):S1-24.
- National Heart, Lung, and Blood Institute, National Institutes for Health. *Global strategy for asthma management and prevention: NHLBI/WHO workshop report*. Bethesda, Maryland: National Institutes of Health, 1996.
- British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary*. London: BMA, RPS, 2000:147. (No 40).
- Lipworth B. Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-55.
- Johnson ES, Lanes SE, Wentworth CE, Satterfield MH, Abebe BL, Dicker LA. A meta-regression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med* 1999;159:1248-53.
- Smith SJ, Caudill SP, Steinberg KK, Thacker SB. On combining dose response data from epidemiological studies by meta-analysis. *Stat Med* 1995;14:531-44.
- D'Agostino RB, Weintraub M. Meta-analysis: a method for synthesizing research. *Clin Pharmacol Ther* 1995;58:605-16.
- Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, LaForce C, et al. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. Fluticasone Propionate Asthma Study Group. *J Allergy Clin Immunol* 1994;94:676-83.
- Sheffer AL, LaForce C, Chervinsky P, Pearlman D, Schaberg A. Fluticasone propionate aerosol: efficacy in patients with mild to moderate asthma. Fluticasone Propionate Asthma Study Group. *J Fam Pract* 1996;42:369-75.
- Galant SP, Lawrence M, Meltzer EO, Tomasko M, Baker KA, Kellerman DJ. Fluticasone propionate compared with theophylline for mild-to-moderate asthma. *Ann Allergy Asthma Immunol* 1996;77:112-8.
- Wolfe JD, Selner JC, Mendelson LM, Hampel F Jr, Schaberg A. Effectiveness of fluticasone propionate in patients with moderate asthma: a dose-ranging study. *Clin Ther* 1996;18:635-46.
- Lawrence M, Wolfe J, Webb DR, Chervinsky P, Kellerman D, Schaumburg JP, et al. Efficacy of inhaled fluticasone propionate in asthma results from topical and not systemic activity. *Am J Respir Crit Care Med* 1997;156:744-51.
- Wasserman SI, Gross GN, Schoenwetter WF, Munk ZM, Kral KM, Schaberg A, et al. A 12-week dose-ranging study of fluticasone propionate powder in the treatment of asthma. *J Asthma* 1996;33:265-74.
- Noonan MJ, Chervinsky P, Wolfe J, Liddle R, Kellerman DJ, Crescenzi KL. Dose-related response to inhaled fluticasone propionate in patients with methacholine-induced bronchial hyperresponsiveness: a double-blind placebo-controlled study. *J Asthma* 1998;35(2):153-64.
- Pearlman DS, Noonan MJ, Tashkin DP, Goldstein MF, Hamedani AG, Kellerman DJ, et al. Comparative efficacy and safety of twice daily fluticasone propionate powder versus placebo in the treatment of moderate asthma. *Ann Allergy Asthma Immunol* 1997;78:356-62.
- Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104:1215-22.
- Busse WW, Chervinsky P, Condemni J, Lumry WR, Petty TL, Rennard S, et al. Budesonide delivered by Turbuhaler is effective in a dose-dependent fashion when used in the treatment of adult patients with chronic asthma. *J Allergy Clin Immunol* 1998;101:457-63.
- Levy ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. *Thorax* 1996;51:1087-92.
- Nelson HS, Busse WW, de Boisblanc BF, Berger WE, Noonan MJ, Webb DR, et al. Fluticasone propionate powder: oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. *J Allergy Clin Immunol* 1999;103(2 part 1):267-75.
- National Asthma Education and Prevention Program (National Heart, Lung, and Blood Institute). *Guidelines for the diagnosis and management of asthma: expert panel report 2*. Bethesda, MD: National Institutes of Health, 1997.
- Van der Molen T, Meyboom-de Jong B, Mulder HH, Postma DS. Starting with a higher dose of inhaled corticosteroids in primary care asthma treatment. *Am J Respir Crit Care Med* 1998;158:121-5.
- Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. *Eur Respir J* 1993;6:877-84.

## Commentary: Dosage needs systematic and critical review

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The systematic review by Holt and colleagues is in principle simple and straightforward. They would have been able to do an even more thorough job had they been provided with the data on individual patients from the studies, but their conclusion is convincing and important. With any new drug that has therapeutic activity, an appropriate dosage regimen must be worked out from a clear understanding of the pharmacokinetics and the dose-response relation. When these are known, sensible decisions can be made on the starting dosage, the minimum time to allow before increasing the dose, dose increments, and the maximum useful dose. Why did it take until now, from the first marketing of fluticasone in 1993, to discover that the maximum useful dosage for most cases is only about half of that hitherto recommended by guidelines and the manufacturer? How did the data emerge, and why were they not used earlier?

My guess is that the scientists at GlaxoWellcome (sponsor of the trials in the meta-analysis) and at the Medicines Control Agency and the clinicians and academics working on asthma had not appreciated the need for and value of systematic reviews and appropriate meta-analysis. Also, few systematic reviews have yet examined dose-response relations: these are hardly mentioned in the new edition of *Systematic Reviews in Health Care*.<sup>1</sup> Another contributory factor is that clinicians rarely think critically about the dose-response relations of the drugs they use. Many drugs have been introduced at doses that later were found to be too high; and usually years have passed, with unnecessary toxicity, before action was taken.<sup>2</sup> This is not acceptable.

As Holt and colleagues hint, it is time to re-examine the dose-response data for beclomethasone propionate and budesonide, drugs whose maximum dosages also seem to be about twice what they should be. It is likely that the dose-response relations of other drugs should be revisited. We need to identify the most important of them and begin.

A major obstacle is access to the data. In the case of fluticasone "data on individual patients could not be made available" by GlaxoWellcome. Although Sir Richard Sykes commendably committed the company to openness, there are different degrees of openness.<sup>3</sup> It would of course have taken time and money to extract the data, and a reanalysis carries the risk of embarrassing findings<sup>4</sup>—but the Medicines Control Agency always has access to the data. Whether it uses them is another question. Because the Medicines Control Agency is wedded to secrecy, we are unlikely to learn the answer.<sup>5</sup> Making sure that the dosages that are used best serve the patients should be near the top of the agenda for regulators and the prescribing community. Right now this item seems to be nowhere on the agenda—but that needs a separate article.

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- Egger M, Davey Smith G, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001. www.systematicreviews.com (accessed 20 May 2001).
- Herxheimer A. How much drug in the tablet? *Lancet* 1991;337:346-8.
- Sykes R. Being a modern pharmaceutical company. *BMJ* 1998;317:1172.
- Tramer MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ* 1997;315:635-40.
- Roberts I, Li Wan Po A, Chalmers I. Intellectual property, drug licensing, freedom of information and public health. *Lancet* 1998;352:726-9.