

Relative safety and efficacy of inhaled corticosteroids

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Inhaled corticosteroids are the main treatment for controlling asthma in adults and children. However, there is still some concern over the safety of these drugs when used at high doses and for long periods of time. Hence issues relating to the efficacy and safety of inhaled corticosteroids have been extensively researched over the past 5 years. General considerations, such as use of an appropriate dose of inhaled corticosteroid in an appropriate asthma population, are discussed. Studies comparing the efficacy and safety of fluticasone propionate, beclomethasone dipropionate, and budesonide are highlighted, and a systematic review of these studies suggests that fluticasone propionate has a better efficacy:safety therapeutic ratio than either beclomethasone dipropionate or budesonide. (J Allergy Clin Immunol 1998; 101:S460-4.)

Key words: *Inhaled corticosteroids, asthma, safety, efficacy*

Inhaled corticosteroids are the mainstay of anti-inflammatory treatment for the majority of adult patients with asthma and an increasing number of children.¹⁻³ In comparison to oral corticosteroids, inhaled corticosteroids clearly have a superior safety profile. However, there is concern among some clinicians that their use at higher doses for more prolonged periods of time in the young and in the elderly may cause problems.⁴ For example, a small effect on bone metabolism may not be relevant if treatment is for a short period of time, but if treatment is for more than 20 or 30 years, it may cause problems. In addition, the dose-response curve of a patient to an inhaled corticosteroid depends on a number of factors, such as the response being studied, asthma severity, and the steroid used. Issues relating to the relative efficacy and safety of inhaled corticosteroids, particularly when used at higher doses and in children, have been extensively researched and discussed in the past 5 years.^{5,6}

It is important that safety and efficacy are investigated in the same studies. If efficacy is to be investigated, this must be performed in patients whose asthma is of appropriate severity. As shown in the theoretical dose-response curves in Fig. 1, different individuals will show different responses to inhaled steroids. Because of these varying responses it is of little use to try and compare the efficacy of high- and low-dose inhaled corticosteroids in patients with mild asthma because the majority will have

Abbreviations used

BDP:	Beclomethasone dipropionate
17-BMP:	Beclomethasone-17-monopropionate
21-BMP:	Beclomethasone-21-monopropionate
CI:	Confidence interval
FP:	Fluticasone propionate

normal or best achievable lung function and well-controlled asthma with low-dose inhaled corticosteroids. The side effects being measured are also important. The most clinically relevant side effects of inhaled corticosteroids are probably long-term effects on bone metabolism in adults and effects on growth in children. However, because these side effects require trials with large numbers of patients being studied over prolonged periods of time, there is a paucity of such investigations and hence most studies have concentrated on measuring adrenocortical function in the short term. Although adrenocortical function can be readily and reproducibly measured, whether it correlates with the risk of long-term side effects is not clear.⁷ Furthermore, many different measures of adrenocortical function are possible and there is not universal agreement about which of these is the most clinically relevant. This review will discuss clinical studies performed in asthmatic patients in which efficacy and safety, as assessed by adrenocortical function, have been determined together in the same study.

Steroid receptor binding

Present evidence suggests that there is only one type of glucocorticoid receptor in human beings, with no evidence of receptor subtypes.⁸ Partly as a consequence of this, receptor binding characteristics of different steroids does, therefore, have some correlation with their clinical efficacy. This correlation is less robust for inhaled than for systemic steroids because other characteristics such as particle size and lipophilicity may strongly influence the inhaled steroid action in vivo. Furthermore, while most inhaled steroids act directly, there is evidence that beclomethasone dipropionate (BDP) is metabolized to form beclomethasone-17-monopropionate (17-BMP) and beclomethasone-21-monopropionate (21-BMP).⁹ This is an activation step for BDP, with the majority of its activity thought to be the result of the more potent metabolite, 17-BMP. The most commonly used inhaled corticosteroids, BDP and budesonide, are considerably more potent than reference steroids such as dexamethasone. Taking into ac-

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count the metabolism of BDP to 17-BMP, it would appear that BDP and budesonide are approximately equipotent.⁹ Fluticasone propionate (FP) is more active at steroid receptor binding than either BDP or budesonide.¹⁰

Cellular responses in vitro

Many of the cells thought to play an important role in asthma are affected by corticosteroids. For example, T-cell proliferation is inhibited by steroids at pharmacologically relevant doses. The effects of the different inhaled corticosteroids have been investigated with these techniques; in keeping with the steroid receptor binding studies, both BDP and budesonide are more active than the reference steroid, dexamethasone, with FP being even more active than BDP or budesonide at preventing T-cell proliferation¹¹ and decreasing eosinophil survival.¹²

MacKenzie skin blanching test

The MacKenzie skin blanching (or vasoconstrictor) test was initially developed to evaluate the potency of dermatologic steroids but has also been found useful for assessing the potency of other topical steroids, including inhaled corticosteroids. Because the skin provides a much thicker physical barrier than the bronchial epithelium, the response of the MacKenzie skin blanching test is influenced by the ability of the steroid to penetrate the dermis. With this technique, budesonide is more potent than BDP, but metabolism of BDP to the active 17-BMP does not appear to occur in the skin. In some studies, FP has been equal in potency to budesonide,¹³ whereas in other studies it has proved more potent.¹¹

Studies in human beings: General considerations

Studies in human beings, and in particular in patients with asthma, are the most important means of assessing the relative efficacy and safety of inhaled corticosteroids. There are, however, many factors that need to be taken into account when interpreting the results of the studies. Studies in which efficacy is investigated will not show any difference between high- and low-dose inhaled corticosteroids if the majority of patients recruited have mild asthma, show normal lung function, and have well-controlled asthma when using low-dose inhaled corticosteroids (see Fig. 1). The type of delivery device may also have a major effect on both efficacy and safety. If one delivery device is more efficient than another, the actuated dose leaving both devices may be the same but the amount reaching the lungs may be quite different. If lung absorption is the major route for systemic absorption and thus determines systemic activity, an increase in lung deposition may result in an improvement in efficacy but also a worsening of safety. The amount of drug reaching the stomach also may be an important factor in the safety of many drugs, especially if they are absorbed from the stomach and not completely metabolized by the liver.

Studies in healthy volunteers and volunteers with mild

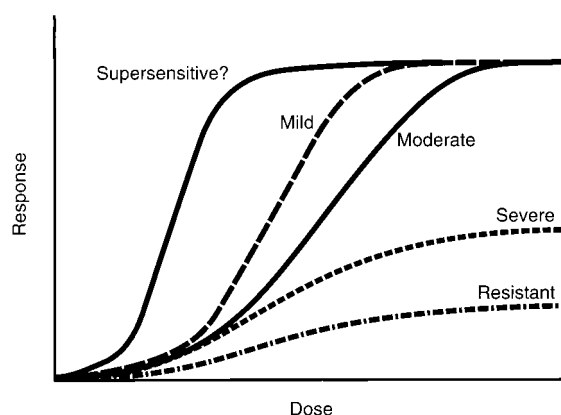


FIG. 1. Different theoretical dose-response curves to inhaled corticosteroids.

asthma, as opposed to patients with inadequately controlled asthma who require additional treatment, have generally shown larger changes in adrenocortical function in response to inhaled corticosteroids. There may be several factors that account for this. Patients with asthma may have different absorption rates of inhaled corticosteroids or may be more resistant to the adrenocortical suppressive effects compared with volunteers. The dose of inhaled corticosteroid reaching the systemic circulation of patients with asthma may be less than that received by healthy volunteers because the disease itself may reduce inspiratory volume and hence alveolar drug deposition. Studies performed in controlled clinical pharmacology units may also cause greater adrenocortical suppression than studies performed in the community.

Studies in volunteers and volunteers with asthma

Studies in volunteers have shown no difference in adrenocortical suppression between equal or approximately equal doses of FP and budesonide.¹⁴⁻¹⁶ Multiple dosing does increase adrenocortical suppression with both FP and budesonide.^{15, 17} Bootsma et al.¹⁷ showed greater adrenocortical suppression with FP than budesonide at approximately equal doses in volunteers when the 24-hour pooled cortisol levels were assessed. However, there was almost no difference in peak cortisol levels, and greater suppression was seen after chronic dosing with both drugs. Clark and Lipworth¹⁸ have shown greater adrenocortical suppression with FP doses greater than 1000 µg/day than budesonide in patients with mild asthma. However, no measurement of efficacy was undertaken because the patients' asthma was too mild to show any benefit.¹⁸ Pharmacokinetic studies of FP in healthy volunteers¹⁹ and patients with asthma²⁰ have reported that the steady-state plasma concentrations were lower in healthy volunteers, after adjustment for dose, than in patients with asthma.

In a study by Meibohm et al.,²¹ a pharmacokinetic/

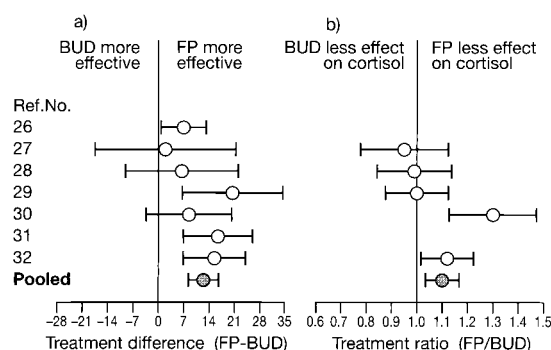


FIG. 2. a, Treatment differences [fluticasone propionate (FP) – budesonide (BUD)] with 95% confidence intervals in improvement in morning peak expiratory flow rate (L/min) for FP and BUD at a dose ratio of at least 1:2. **b,** Treatment ratios (FP/BUD) with 95% confidence intervals for the ratio of mean plasma cortisol levels at baseline and at the end of therapy between FP and BUD at a dose ratio of at least 1:2. Data from Reference 25.

pharmacodynamic approach was used to evaluate the influence of administration time on the cumulative cortisol suppression in healthy volunteers after single doses of inhaled FP and flunisolide. Both corticosteroids showed similar diurnal variation in cumulative cortisol suppression, dependent on administration time, with maximum suppression when administered at 3 AM. The optimal time for minimal cumulative cortisol suppression was at 3 PM for FP and 7 PM for flunisolide, probably because of the shorter terminal half-life for flunisolide. Thus administration time must be considered as a pivotal influential factor in clinical studies comparing cumulative cortisol suppression among different inhaled corticosteroids.

Studies in patients with asthma

Many studies have now compared the relative efficacy and safety of budesonide, BDP, and FP. The studies comparing BDP and budesonide were performed in small numbers of patients, and in retrospect it is clear the studies were of insufficient power to resolve any possible differences between the drugs. However, an overview of these studies suggests there is little difference either in efficacy or safety between the two drugs.²²

Studies have compared FP with BDP across a range of doses. In general these studies have either been performed at equal doses in micrograms or at an FP:BDP dose ratio of 1:2. When used in equal dosages, FP showed greater efficacy than BDP, with no difference in morning cortisol levels. When used in a 1:2 dose ratio, FP has shown equal efficacy with fewer side effects; however, this difference is only apparent when the drugs are used at higher doses (but still within the recommended dose range) when changes in adrenocortical function can be detected.

Studies have also investigated the relative efficacy and potency of FP and budesonide. Ayres et al.²³ showed that both FP dosages of 1000 and 2000 $\mu\text{g/day}$ were more effective than 1600 $\mu\text{g/day}$ budesonide (the highest

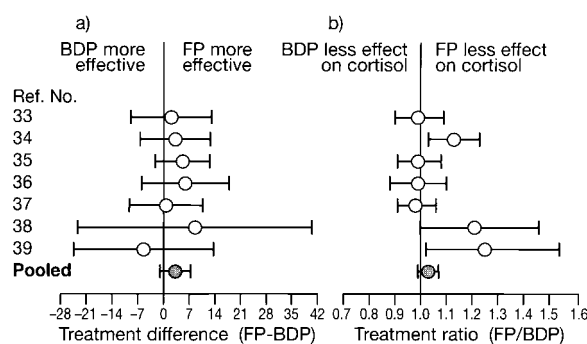


FIG. 3. a, Treatment differences [fluticasone propionate (FP) – beclomethasone dipropionate (BDP)] with 95% confidence intervals in improvement in morning peak expiratory flow rate (L/min) for FP and BDP at a dose ratio of at least 1:2. **b,** Treatment ratios (FP/BDP) with 95% confidence intervals for the ratio of mean plasma cortisol levels at baseline and at the end of therapy between FP and BDP at a dose ratio of at least 1:2. Data from Reference 25.

licensed dose in most countries). None of the doses caused any significant change in mean adrenocortical function; however, the dose ordering in terms of changes in adrenocortical function was 1000 $\mu\text{g/day}$ FP, 1600 $\mu\text{g/day}$ budesonide, and 2000 $\mu\text{g/day}$ FP. A series of studies has looked at budesonide at twice the dose of FP; at lower doses there has been generally no difference in efficacy between the two inhaled corticosteroids, but at higher doses FP has proved more effective. The majority of these studies have used morning peak flow as a primary outcome measure; however, a study in children by Agertoft and Pedersen²⁴ tried to reduce the dose of inhaled corticosteroids while maintaining asthma control. However, methodologic problems with the study, including the fact that patients were not allowed to reduce their inhaled corticosteroids dose to less than 100 $\mu\text{g/day}$, make interpretation difficult.

In an effort to obtain an overview of these studies, a meta-analysis²⁵ of all trials of FP and budesonide²⁶⁻³² and FP and BDP,³³⁻³⁹ in which morning peak flow was an outcome measure and drugs were compared at the 1:2 dose ratio, has been performed. The meta-analysis has shown the pooled value of the mean morning peak expiratory flow to be significantly higher with FP than with a dose of budesonide at least twice the FP dose (difference of +12 L/min; 95% confidence interval [CI] +8 to +17 L/min; $p < 0.001$) (Fig. 2, a).²⁵ At low doses no intergroup differences in mean morning cortisol levels were detected, but at higher doses (FP ≥ 500 $\mu\text{g/day}$, budesonide ≥ 1200 $\mu\text{g/day}$) significant differences in favor of FP (i.e., reduced suppression of morning cortisol levels) were apparent. Across all five studies the pooled value of plasma cortisol ratio after FP was significantly greater than that after budesonide (ratio = 1.1 nmol/L; 95% CI 1.08 to 1.17; $p = 0.005$) (Fig. 2, b).²⁵ In the studies comparing FP at half the dose with BDP, the pooled analysis of improvement in mean morning peak expiratory flow showed a nonsignificant trend in

favor of FP (difference of +3 L/min; 95% CI -3 to +9 L/min) (Fig. 3, *a*).²⁵ In addition, the pooled analysis across all seven studies showed no significant difference between FP and BDP on cortisol ratios (ratio = 1.01 nmol/L; 95% CI 0.99 to 1.08) (Fig. 3, *b*).²⁵ These meta-analyses confirm the original claims made about FP, namely that it has a better efficacy:safety ratio than either BDP or budesonide.

Conclusions

Inhaled corticosteroids at low doses in adults with asthma are effective, and there are few concerns about long-term safety; at higher doses, some concerns about long-term safety remain. Studies in volunteers, or volunteers with mild asthma, are only able to investigate the safety aspect of the drugs and not the efficacy, and there is evidence that the side effects of the drugs are overestimated by these studies. When studies are performed in patients with asthma of the appropriate severity for the dose of the inhaled corticosteroid used, fewer side effects are observed, and these studies suggest that FP has a better efficacy:safety ratio than either BDP or budesonide. These differences are likely to be of importance in patients with asthma that is more difficult to control and requires higher doses of inhaled corticosteroids.

REFERENCES

- British Thoracic Society. Guidelines for the management of asthma in adults, I: chronic persistent asthma. *Br Med J* 1990;301:651-3.
- International Consensus Report on Diagnosis and Management of Asthma. *Clin Exp Allergy* 1992;22(Suppl 1):1-71.
- National Heart, Lung and Blood Institute International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992;5: 601-41.
- Geddes DM. Inhaled corticosteroids: benefits and risks. *Thorax* 1992;47:404-7.
- Boner AL, Piacentini G. Inhaled corticosteroids in children, is there a 'safe' dosage? *Drug Saf* 1993;9:9-20.
- Boyd G. Systemic effects of inhaled corticosteroids in asthma: a comparative risk profile assessment of fluticasone propionate and budesonide. *Inpharma* 1996;Suppl 3:1-11.
- Monson JP. Systemic effects of inhaled steroids. *Thorax* 1993;48: 955-6.
- Muller M, Renkawitz R. The glucocorticoid receptor. *Biochem Biophys Acta* 1991;1088:171-82.
- Wurthwein G, Rohdewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone 17-monopropionate. *Biopharm Drug Dispos* 1990;11:381-94.
- Hogger P, Rohdewald P. Binding kinetics of fluticasone propionate to the human glucocorticoid receptor. *Steroids* 1994;59:597-602.
- English AF, Neate MS, Quist DJ, Sareen M. Biological activities of some steroids used in asthma. *Am J Respir Crit Care Med* 1994; 149(Suppl):Abstract 4.
- Boyce JA, Frazer J, Owen WF. Fluticasone propionate is more potent than dexamethasone in the induction of ciprotopsis of eosinophils. *PNC Asthma*.
- Andersson N, Klint S, Randwall G, Wiren JE. Equipotency of budesonide and FP [abstract]. *Am J Respir Crit Care Med* 1994; 149(Suppl):A467.
- Grahnen A, Eckernas SA, Brundin RM, Ling-Andersson A. An assessment of the systemic activity of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994;38:1-5.
- Lonnebo A, Grahnen A, Jansson B, Brundin RM, Ling-Andersson A, Eckernas SA. An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur J Clin Pharmacol* 1996;49:459-63.
- Grove A, Allam C, McFarlane LC, McPhute G, Jackson CM, Lipworth BJ. A comparison of the systemic bioactivity of inhaled budesonide and fluticasone propionate in normal subjects. *Br J Clin Pharmacol* 1994;38:527-32.
- Bootsma M, Andersson N, Larsson P, Ullman A. Assessment of the relative systemic potency of inhaled fluticasone and budesonide. *Eur Respir J* 1996;9:1427-32.
- Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997;52:55-8.
- Mackie AE, Falcoz C, McDowall JE, Moss J, Ventresca GP, Bye A. Pharmacokinetics of fluticasone propionate inhaled from the Diskhaler and the Diskus powder devices in healthy subjects. *Br J Clin Pharmacol* 1997;43:540P-1P.
- Falcoz C, Mackie AE, Horton J, et al. Pharmacokinetics of fluticasone propionate inhaled from the Diskhaler and the Diskus powder devices in asthmatic patients. *Br J Clin Pharmacol* 1997;43:541P-2P.
- Meibohm B, Hochhaus G, Rohatagi S, et al. Dependency of cortisol suppression on the administration time of inhaled corticosteroids. *J Clin Pharmacol* 1997;37:704-10.
- Barnes NC. The therapeutic efficacy and side effects of inhaled steroids. *Int Mon* 1992;3:1-4.
- Ayres JG, Bateman ED, Lundback B, Harris TAJ. High dose of fluticasone propionate 1 mg daily versus fluticasone propionate 2 mg daily or budesonide 1.6 mg daily in patients with chronic severe asthma. *Eur Respir J* 1995;8:579-86.
- Agertoft L, Pedersen S. A randomized, double-blind dose reduction study to compare the minimal effective dose of budesonide Turbuhaler and fluticasone propionate Diskhaler. *J Allergy Clin Immunol* 1997;99:773-80.
- Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. *Respir Med* 1998;92:95-104.
- Williams J, Richards KA, on behalf of the UK Study Group. Ease of handling and clinical efficacy of fluticasone propionate Accuhaler/Diskus (Rm) inhaler compared with the Turbuhaler (Rm) inhaler in paediatric patients. *Br J Clin Pract* 1997;51:147-53.
- Langdon CG, Thompson J, on behalf of the UK Study Group. A multicentre study to compare the efficacy and safety of inhaled fluticasone propionate and budesonide via metered-dose inhalers in adults with mild-to-moderate asthma. *Br J Clin Res* 1994;5:73-84.
- Connolly A, on behalf of the UK Study Group. A comparison of fluticasone propionate 100 micrograms twice daily with budesonide 200 micrograms twice daily via their respective powder devices in the treatment of mild asthma. *Eur J Clin Res* 1995;7:15-29.
- Langdon CG, Capsey LJ, on behalf of the UK Study Group. Fluticasone propionate and budesonide in adult asthmatics: a comparison using dry-powder inhaler devices. *Br J Clin Res* 1994;5:85-99.
- Backman R, Pickering CAC, Baumgarten C. A comparison of fluticasone propionate via Diskus (Accuhaler) inhaler and budesonide via Turbuhaler inhaler in adult asthmatics. *J Allergy Clin Immunol* 1996;97:249.
- Steinmetz K-O, Trautmann M. Efficacy of fluticasone propionate (0.5 mg daily) via MDI and budesonide (1.2 mg daily) via Turbuhaler in the treatment of steroid-naïve asthmatics. *Am J Respir Crit Care Med* 1996;153:A338.
- Ringdal N, Swinburn P, Backman R, et al. A blinded comparison of fluticasone propionate with budesonide via powder devices in adult patients with moderate-to-severe asthma: a clinical evaluation. *Mediators Inflamm* 1996;5:382-9.
- Dahl R, Lundback B, Malo JL, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. International Study Group. *Chest* 1993;104:1352-8.
- Leblanc P, Mink S, Keistinen T, Saarelainen PA, Ringdal N, Payne SL. A comparison of fluticasone propionate 200 micrograms/day with beclomethasone dipropionate 400 micrograms/day in adult asthma. *Allergy* 1994;49:380-5.
- Gustafsson P, Tsanakas J, Gold M, Primhak R, Radford M, Gillies

- E. Comparison of safety and efficacy of inhaled fluticasone propionate 200 micrograms/day with inhaled beclomethasone dipropionate 400 micrograms/day in mild and moderate asthma. *Arch Dis Child* 1993;69:206-11.
36. Pauwels RA, Demedts MG, Yernault JC, Geusens P, Roosens WA. Comparison of long-term safety and efficacy of fluticasone propionate and beclomethasone dipropionate in combination with salmeterol in patients with moderate to severe asthma. *Am J Respir Crit Care Med* 1995;151:A276.
37. Lundback B, Alexander M, Day J, et al. Evaluation of fluticasone propionate ($500 \mu\text{g day}^{-1}$) administered either as a dry powder via a Diskhaler inhaler or pressurized inhaler and compared with beclomethasone dipropionate ($1000 \mu\text{g day}^{-1}$) administered by pressurized inhaler. *Respir Med* 1993;87:609-20.
38. Bootsma GP, Dekhuijzen PNR, Festen J, van Herwaarden CLA. Comparison of fluticasone propionate and beclomethasone dipropionate on direct and indirect measurements of bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1995;151:A275.
39. 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. International Study Group. *Eur Respir J* 1993;6:877-85.