

Acute adrenal insufficiency in a patient with asthma after changing from fluticasone propionate to budesonide

Geoffrey R. G. Todd, MRCP(UK), David Wright, FIBMS, and Mike Ryan, MRCP(I)

Antrim, United Kingdom

High-dose inhaled corticosteroids have been associated with basal adrenocortical suppression, but usually without clinical consequences.¹ Clinically significant adrenal insufficiency in patients receiving inhaled corticosteroids is extremely rare; only 1 adult (receiving 6400 µg budesonide/day)² and 1 child (receiving 500 µg budesonide/day)³ have been previously reported. We describe a patient who experienced acute adrenal insufficiency when her inhaled steroid was changed from fluticasone propionate 1000 µg/day (administered by means of a spacer) to budesonide 800 µg/day (administered by means of the Turbohaler).

A 6-year-old girl had been referred for investigation of short stature. She had severe asthma from the age of 2 years, which was eventually controlled at the age of 3.5 years by treatment with fluticasone 1000 µg/day (250 µg/inhalation, 2 inhalations twice daily) administered by means of a spacer (Volumatic, Glaxo-Wellcome UK) together with nebulized salbutamol, salmeterol 50 µg twice daily, and slow-release theophylline 120 mg twice daily. Repeated attempts to reduce her fluticasone dose resulted in clinical relapse. Her height subsequently fell from the tenth percentile at the age of 3.5 years to below the third percentile at the age of 6.5 years, and her shoe size had not changed in the previous 2.5 years. Growth over the previous 6 months was only 2 cm. She had not received any oral steroids in the previous 2 years. Inves-

tigations showed normal full blood examination results, renal function, thyroid function, growth hormone measurements, chromosomes, and sweat test results. Bone age was 2.5 years less than chronologic age. Serum cortisol at 11 AM was less than 20 nmol/L (reference, 140 to 700 nmol/L). A low-dose short cosyntropin test result (0.5 µg/1.73 m²) was abnormal, showing serum cortisol at baseline of 65 nmol/L, rising to 127 nmol/L (reference, ≥500 nmol/L) at 30 minutes and a peak of 270 nmol/L after 1 hour, which was consistent with secondary adrenal hypofunction. The inhaled steroid was changed from fluticasone 1000 µg/day (Spacer) to budesonide 800 µg/day (Turbohaler, Astra Draco; 200 µg per inhalation, 2 inhalations twice daily), and all other medications remained unchanged.

A few days later she experienced continuous nausea, bouts of vomiting, severe fatigue, and upper abdominal pain. She was acutely ill on admission, with an increase in these symptoms after an upper respiratory tract infection. Her symptoms resolved within a few hours of receiving oral prednisolone. The oral steroid was discontinued after 15 days, and all her symptoms returned within 48 hours. Serum cortisol on admission was 60 nmol/L. Symptoms resolved again a few hours after the reintroduction of oral steroid (hydrocortisone 20 mg/day). This was reduced gradually, and 9 months later, a repeat low-dose short cosyntropin test result 48 hours after stopping hydrocortisone was normal at 2.5 mg/day, showing a baseline cortisol level of 137 nmol/L rising to 921 nmol/L. One year after stopping fluticasone and continuing budesonide 800 µg/day, growth velocity has shown evidence of acceleration (ie, 4.5 cm in the previous 6 months).

In this patient the systemic effect of budesonide 800 µg/day (Turbohaler) was less than that of fluticasone 1000 µg/day administered by means of a spacer to the

From Antrim Area Hospital, Antrim.

Reprint requests: Geoffrey R. G. Todd, MRCP, Antrim Area Hospital, 45 Bush Rd, Antrim, BT41 2RL, United Kingdom.

J Allergy Clin Immunol 1999;103:956-7.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/54/96026

extent that an acute adrenal crisis was precipitated by the change of inhaled steroid. Subsequently, the systemic effect of budesonide 800 µg/day (Turbohaler) plus oral hydrocortisone (20 mg/day decreasing to 2.5 mg/day) was sufficiently low to allow severely suppressed adrenal function to recover completely. We have already reported 6 other cases of growth retardation and severe adrenal suppression in children receiving high-dose fluticasone (≥ 1000 µg/day),⁴ but none had proven adrenal crisis. All these cases demonstrate that a very high first-pass hepatic metabolism (99.9%) for fluticasone does not prevent the occurrence of serious systemic effects at high doses (≥ 1000 µg/day). This is probably due to fluticasone's very high lipophilicity (300 times greater than that of budesonide), which results in a much higher tissue distribution, longer plasma half-life, and greater glucocorticoid receptor affinity than budesonide.⁵ Fluticasone is the only inhaled steroid reported to accumulate with repeated dosing (≥ 1000 µg/day) in adults,⁶⁻¹¹ although no accumulation effect has been detected in dosages of 400 µg/day in children.¹² The safety of fluticasone in studies with dosages of 200 µg/day in children is well established, although there has been an exceptional report recently of adrenal suppression and growth retardation in an asthmatic child inhaling 250 µg/day.¹³

Fluticasone in doses of 1000 µg/day in asthmatic children the age of our patient (6 years) is allowed by the British Thoracic Society Guidelines¹⁴ in severe cases, and it has been suggested that fluticasone should be used in preference to other inhaled corticosteroids in children and in those patients requiring higher doses of inhaled corticosteroids because of a "better therapeutic efficacy/safety ratio." However, doctors treating subjects with severe asthma with higher doses of fluticasone need to be aware that almost complete first-pass hepatic metabolism does not protect against severe systemic effects.

REFERENCES

1. Brown PH, Blundell G, Greening AP, Crompton GK. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Respir Med* 1991;85:501-10.
2. Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. *BMJ* 1992;304:1415.
3. Zwaan CM, Odink RJH, Delemarre-van de Waal, Dankert-Roelse JE, Bokma JA. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy. *Lancet* 1992;340:1289.
4. Todd G, Dunlop K, McNaboe J, Ryan MF, Carson D, Shields MD. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996;348:27-9.
5. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997;52(suppl 39):1-34.
6. Grahnen A, Eckermas SA, Brundin RM, Ling-Andersson A. An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994;38:521-5.
7. Lonnebo A, Connelo A, Grahnen A, Jansson B, Brundin RM, Ling-Andersson A, et al. 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.
8. Corren J, Rachelefsky G. A five-way randomised study to compare the safety profile of beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP), and triamcinolone (TA) in healthy male volunteers. *Chest* 1996;110(Suppl):835.
9. Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997;52:55-8.
10. Falcoz C, Mackie AE, Moss J, Horton J, Ventresca GP, Brown A, et al. Pharmacokinetics of fluticasone propionate inhaled from the Diskhaler and the Diskus after repeat doses in healthy subjects and asthmatic patients [abstract]. *J Allergy Clin Immunol* 1997;99(Suppl):S505.
11. Thorsson L, Dahlstrom K, Edsbacker S, Kallen A, Paulson J, Wirer J-E. Pharmacokinetics and systemic effects of inhaled fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1997;43:155-61.
12. Lipworth BJ, Clark DJ, McFarlane LC. Adrenocortical activity with repeated twice daily dosing of fluticasone propionate and budesonide given via a large volume spacer to asthmatic school-children. *Thorax* 1997;52:686-9.
13. Zimmerman B, Gold M, Wherrett D, Hanna AK. Adrenal suppression in two patients with asthma treated with low doses of the inhaled steroid fluticasone propionate. *J Allergy Clin Immunol* 1998;101:425-6.
14. The British guidelines on asthma management, 1995: review and position statement. *Thorax* 1997;52(Suppl 1):S1.