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CASE STUDY

Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate

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Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate. G.R.G. Todd, C.L. Acerini, J.J. Buck, N.P. Murphy, R. Ross-Russell, J.T. Warner, D.R. McCance. ©ERS Journals Ltd 2002.

ABSTRACT: Four cases of asthma (one adult, three children) developing acute adrenal crisis after introduction of high-dose inhaled fluticasone proprionate are presented. The three children, aged 7–9 yrs, had been prescribed inhaled fluticasone, dosage 500–2,000 μg·day^{-1} and duration 5 months–5 yrs. All presented with convulsions due to hypoglycaemia (blood glucose 1.3–1.8 mM). The fourth case was a male of 33 yrs with difficult-to-control asthma and had been taking fluticasone propionate 1,000–2,000 μg·day^{-1} for 3 yrs. He presented with fatigue, lethargy, nausea and postural hypotension.

Acute adrenal crisis in each case was confirmed by investigations which included measurement of acute phase cortisol levels, short and long Synacthen stimulation tests and glucagon stimulation tests. Other cases of hypthoalamic-pituitary-adrenal axis suppression were excluded.

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Biochemically detectable suppression of the hypothalamic-pituitary-adrenal axis (HPA) in patients taking inhaled corticosteroids (ICSs) is common but acute adrenal crisis is very rare with only two cases having been reported in nearly 30 yrs of clinical usage of beclomethasone and budesonide [1]. Fluticasone propionate was introduced in the UK in 1993 as a potentially safer ICS than those already in use. It undergoes very high first-pass hepatic metabolism (99.9%) and its efficacy and safety have been established in children at doses of 200 μg·day^{-1} [2], but not at the higher dosages that are often used in more severe cases.

Case reports

Patient 1

A male of 33 yrs presented with fatigue, sweating and decreased exercise tolerance. His difficult-to-control asthma had been treated over the previous 3 yrs with fluticasone (Diskhaler; Allen & Hanbury, Uxbridge, UK) 1,000–2,000 μg·day^{-1}. No oral corticosteroids had been prescribed during this time. An athlete, his peak flow ranged 500–720 L·min^{-1}, and he was unable to train or perform at lower flows. A short Synacthen stimulation test (SSST) (250 μg tetracosactide intramuscularly) showed basal cortisol levels of 69 nM rising to 256 nM (normal increases are $\geqslant$200 nM, peaking at $\geqslant$500 nM). His medication was changed to budesonide 800 μg·day^{-1} (dry powder). Three weeks later, he presented acutely ill with nausea, vomiting, abdominal pain, fatigue and dizziness. His blood pressure was 90/50 mmHg. He commenced hydrocortisone therapy 20 mg·day^{-1}. Marked symptomatic improvement appeared within a few hours and his blood pressure rose to 120/80 mmHg. Adrenal autoantibodies were negative and there was no evidence of hypopituitarism. Fifteen months later, there was no cortisol response to the SSST, but, during prolonged Synacthen stimulation (1 mg tetracosactide intramuscularly daily for 3 days), serum cortisol levels increased from 30 nM at baseline to 806 nM on day 3, suggesting adrenal suppression due to exogenous steroid administration.

In this patient, the systemic effect of budesonide 800 μg·day^{-1} was less than that of fluticasone propionate 1,000–2,000 μg·day^{-1}, to the extent that acute adrenal crisis was precipitated by the change of inhaled steroid.

Patient 2

A male child aged 7 yrs with moderately severe asthma presented following a grand mal seizure. On admission, his Glasgow Coma Score was 10 and he was hypoglycaemic (blood glucose 1.4 mM) with evidence of metabolic acidosis (pH 7.27) and mild hyponatraemia (sodium 131 mM). He was resuscitated with intravenous glucose and fluids with rapid improvement in his condition. A random serum cortisol level measurement (169 nM) was very low

given his clinical presentation (cortisol response to critical illness should exceed 700–830 nM) [3], whereas normal plasma free insulin, serum lactate, plasma amino acid and urinary organic acid estimates excluded hyperinsulinism and inborn errors of metabolism. An SSST later confirmed the presence of hypoadrenalism. Subsequently, a prolonged Synacthen stimulation test showed a rise in serum cortisol levels on day 3 to 380 nM, suggesting hypoadrenalism due to secondary adrenal suppression.

His asthma had been difficult to control and 3 yrs previously beclomethasone 2000 $\mu g \cdot day^{-1}$ (spacer) had been changed to fluticasone propionate 1,000 $\mu g \cdot day^{-1}$ (spacer), stepping down to 500 $\mu g \cdot day^{-1}$ occasionally. He had also required 15 days of oral prednisolone 20 $mg \cdot day^{-1}$ in the previous year. His growth velocity had been normal.

Patient 3

A 9-yr-old female child with moderately severe asthma presented with a grand mal seizure. On admission, her blood glucose level was 1.8 mM and serum cortisol level 156 nM, both inappropriately low [3]. She was treated with intravenous dextrose 10% and 2 mg dexamethasone and made a full recovery. An extensive metabolic, infectious and neurological screen, including magnetic resonance imaging of the brain, gave normal results. Anterior pituitary function testing with glucagon stimulation (500 μg intramuscularly) demonstrated a very poor cortisol response to stress; baseline was <70 nM with no subsequent rise (a response of >580 nM is normal). Baseline adrenocorticotrophic hormone levels were low (<6 $ng \cdot L^{-1}$, normal range 10–80 $ng \cdot L^{-1}$) and there was a normal growth hormone response with a maximum level of 49.3 $mU \cdot L^{-1}$ (normal >20 $mU \cdot L^{-1}$), suggesting HPA suppression secondary to exogenous steroid administration.

She had been treated with fluticasone 1,000 $\mu g \cdot day^{-1}$ (spacer), occasionally stepping down to 500 $\mu g \cdot day^{-1}$, for 5 yrs, and had not received any oral steroids in the preceding 12 months. She had been complaining of general malaise and lethargy over the previous 6 months. Her growth velocity was poor over the previous 4 yrs and her height had fallen from the 25th to the 3rd percentile.

Patient 4

A 7-yr-old female child with moderate asthma presented with status epilepticus. She had been well until a few days previously when she had developed a respiratory tract infection and subsequently vomiting. She was admitted directly to an intensive care unit with continuous grand mal seizures lasting for >30 min and respiratory arrest. She required intubation and ventilation. Her plasma glucose level was 1.3 mM. An SSST carried out within several hours of admission showed an inappropriately low resting cortisol level [3] of 575 nM, rising to only 600 nM. She failed to recover with correction of plasma glucose levels and only improved some hours later after intravenous hydrocortisone was given. A computed tomographic scan of the brain gave normal results. Hyperinsulinism and inborn errors of metabolism were excluded. A glucagon stimulation test excluded hypopituitarism.

She had a history of asthma which had been difficult to control over the previous year. Five months previously budesonide 1600 $\mu g \cdot day^{-1}$ (dry powder) had been changed to fluticasone propionate 1,000 $\mu g \cdot day^{-1}$ (Accuhaler; Allen & Hanbury) increasing to 2,000 $\mu g \cdot day^{-1}$, and, shortly after this, her growth velocity had markedly decreased. She had not received any oral steroids in the previous year. She was discharged on budesonide 800 $\mu g \cdot day^{-1}$ and has remained well with normal growth during 4 yrs follow-up.

Discussion

Asymptomatic secondary adrenal suppression due to ICS is common and not thought to be of clinical significance. Growth retardation and adrenal suppression have been decribed in children and are more likely with high doses, *i.e.* >400 $\mu g \cdot day^{-1}$ beclomethasone or budesonide [4]. Other side-effects of ICS, *e.g.* Cushing's syndrome, can also occur [5, 6]. However, in ~30 yrs of asthma treatment with beclomethasone and budesonide, acute adrenal crisis has only been reported on two occasions [1]. Fluticasone propionate was introduced in the UK in 1993 as a potentially safer ICS, due to its very high first-pass hepatic metabolism (99.9%). The safety of fluticasone at lower dosages is well established [2]; however, growth retardation and severe but asymptomatic adrenal suppression in children receiving high-dose fluticasone have previously been reported [7]. In the present case reports, one adult and three children with acute adrenal crisis due to high-dose fluticasone are described (table 1).

The three children in this series presented with hypoglycaemic convulsions. The mechanism of hypoglycaemia in hypoadrenalism is complex. Adrenocortical deficiency is associated with reduced hepatic glycogen stores, and also the ability of glucagon and adrenalin to increase intrahepatic cyclic adenosine monophosphate levels and mobilize glycogen is impaired by cortisol deficiency. Further, cortisol is one of the counter-regulatory hormones which oppose the hypoglycaemic effects of insulin, and its concentration should rise as blood glucose levels fall.

Fluticasone undergoes very high first-pass hepatic metabolism (99.9%), and is also very lipophilic (~300-times more so than beclomethasone or budesonide), resulting in much higher tissue levels, longer plasma half-life and greater glucocorticoid receptor affinity than beclomethasone or budesonide [8]. A recent meta-analysis of 22 studies [9] showed steeper dose-related adrenal suppression with fluticasone compared to beclomethasone (2.1-fold) [4] or budesonide (2.5-fold). Taken together, these data may account for the severity of adrenal suppression in the presented cases.

Treatment of children with severe asthma with

Table 1. – Acute adrenal crisis: patient data

Patient No.	Age yrs	Sex	Clinical presentation	Blood glucose mM	Fluticasone		Duration of treatment yrs	Cortisol base/peak nM
					Amount μg·day^{-1}	Device		
1	33	M	Vomiting, abdominal pain, hypotension	4.5	1000–2000	Dry powder	3	69/256[#]
2	7	M	Grand mal seizure	1.4	500–1000	MDI+spacer	3	<30/41[#]
3	9	F	Grand mal seizure	1.8	500–1000	MDI+spacer	5	<70/<70[¶]
4	7	F	Status epilepticus, respiratory arrest	1.3	1000–2000	Dry powder	0.5	575/600[¶]

M: male; F: female; MDI: metered-dose inhaler. [#]: short Synacthen stimulation test (250 μg adrenocorticotropic hormone); [¶]: glucagon stimulation test (500 μg *i.m.*) (hypothalamic-pituitary-adrenal axis tests).

dosages of fluticasone >1,000 μg·day^{-1} is permitted by international guidelines [10], and it is also licensed for use at up to 2,000 μg·day^{-1} in adults in the UK. Fluticasone has been preferred for many patients requiring higher dosages of ICS because of a claimed better therapeutic efficacy/safety ratio [11], although this claim has been challenged [12].

Adrenal crisis has occurred rarely in asthmatics treated with inhaled corticosteroids; however, doctors treating patients with severe asthma need to be aware that the almost complete first-pass hepatic metabolism of fluticasone may not protect against severe systemic side-effects. Current advice is that high doses of very lipophilic inhaled corticosteroids such as fluticasone should only be used with extreme caution in adult and child asthmatics. Furthermore, following withdrawal of high-dose fluticasone, or change to a different inhaled corticosteroid of lower overall potency, patients should be monitored closely for evidence of adrenal insufficiency.

References

1. Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. *BMJ* 1992; 304: 1414.
2. MacKenzie CA, Weinberg EC, Tabachnik E, Taylor M, Harpan J, Crescenzi K. A placebo controlled trial of fluticasone propionate in asthmatic children. *Eur J Pediatr* 1993; 152: 856–860.
3. Zologa GP. Sepsis induced adrenal deficiency syndrome. *Crit Care Med* 2001; 29: 688–689.
4. Russell G. Inhaled corticosteroid therapy in children: an assessment of the potential for side effects. *Thorax* 1994; 49: 1185–1188.
5. Priftis K, Averard ML, Millner AD. Unexpected side-effects of inhaled steroids: a case report. *Eur J Pediatr* 1991; 150: 448–449.
6. Wilson AM, Blumsohn A, Jung RT, Lipworth BJ. Asthma and Cushing's syndrome. *Chest* 2000; 117: 593–594.
7. 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: 27–29.
8. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997; 52: Suppl. 39, 1–34.
9. Lipworth BJ, Wilson AM. Dose response to inhaled corticosteroids: benefit and risks. *Semin Respir Crit Care Med* 1998; 19: 625–646.
10. Anonymous. A Six-part Asthma Management Program. Global Strategy for Asthma Management and Prevention NHLBI/WHO Workshop. NIH Publication No. 95-3659, 92. 1995.
11. Fuller R, Johnson M, Bye A. Fluticasone propionate – an update on preclinical and clinical experience. *Respir Med* 1995; 89: Suppl. A, 3–18.
12. Clark DJ, Grove A, Cargill RI, Lipworth P. Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients. *Thorax* 1996; 51: 262–266.