Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma

Joseph S Macdessi, Tabitha L Randell, Kim C Donaghue, Geoffrey R Ambler, Peter P van Asperen and Craig M Mellis

Three children presented with adrenal crises, manifested by vomiting and hypoglycaemia, after protracted courses of high-dose inhaled corticosteroids for asthma. Significant dose reduction was possible in all three without loss of asthma control, emphasising the importance of back-titration to minimise dose. Parents of children taking high doses of inhaled corticosteroids should be alerted to the clinical features of adrenal insufficiency. If suspected, prompt medical assessment should be arranged, including serum glucose and cortisol measurement. ***(MJA 2003; 178: 214-216)***

THE EFFECTIVENESS of prophylactic inhaled corticosteroids (ICS) in childhood asthma is well established[1] and these drugs are recommended as a safe, first-line preventive therapy.[2-4] Dose-dependent biochemical adrenal suppression with ICS has been well documented,[3-5] although, until recently, reports of frank adrenal insufficiency in children have been rare.[6-9] We present the first documented Australian report of three children who presented with adrenal crises while being treated with ICS for asthma. Each had a history of an intercurrent illness during which they were unable to mount a stress-response rise in cortisol level.

Clinical records

Patient 1

Presentation: A seven-year-old boy presented with hypoglycaemia associated with vomiting, abdominal pain and drowsiness preceded by two days of fever, rhinorrhoea and fatigue. He had had a previous episode of hyponatraemia and vomiting, but his blood glucose level was not documented at the time. Although he had been noted to have a cushingoid appearance in the past, he was normal on physical examination, his height and weight were on the 3rd percentile, and his growth velocity was normal. He was found to be hypoglycaemic and hyponatraemic, with a low serum cortisol level (Box 1). A short Synacthen test confirmed adrenal insufficiency (Box 2).

Asthma history: The patient had a history of "poorly controlled" asthma, but his wheeze was minimal and not associated with increased work of breathing. He undertook normal physical activity and was rarely absent from school. Spirometry findings in the past had been normal.

Medications: He was taking fluticasone propionate (1500 μg daily), nebulised budesonide (1000 μg daily till three weeks before presentation), salmeterol (50 μg twice daily), nebulised salbutamol (5 mg four times daily) and ipratropium (250 μg four times daily) and montelukast (5 mg daily). From the age of two years his ICS doses had been progressively increased and had been at these levels for 10 months before this presentation. He had received frequent doses of oral prednisolone from the age of four years, but had had none for the past eight months.

Treatment and clinical course: Immediate treatment included a glucose bolus, fluid replacement and hydrocortisone. Ongoing treatment involved giving regular hydrocortisone while reducing the dose of ICS, with no deterioration of asthma control. Four months after his presentation he was taking 500 μg fluticasone daily and being weaned off hydrocortisone.

Patient 2

Presentation: A four-year-old boy was referred for investigation of two episodes of hypoglycaemia associated with vomiting and lethargy. There was a third episode of vomiting and lethargy; his blood glucose level was normal on this occasion (his mother had treated him with glucose before presentation at hospital). The patient was normal on physical examination, with height and weight between the 10th and 25th percentiles and with normal growth velocity. He was not cushingoid in appearance and had no abnormal pigmentation. Results of available baseline investigations during the hypoglycaemic episodes are shown in Box 1. A short Synacthen test confirmed secondary adrenal insufficiency (Box 2).

See also page 223

Department of Respiratory Medicine, The Children's Hospital at Westmead, Westmead, NSW, Australia.

Joseph S Macdessi, MB BS, DCH, Paediatric Fellow; **Peter P van Asperen,** MD, FRACP, Head, Department of Respiratory Medicine, and Clinical Associate Professor, The Children's Hospital at Westmead Clinical School, University of Sydney.

Department of Endocrinology, The Children's Hospital at Westmead, Westmead, NSW, Australia.

Tabitha L Randell, MB ChB, MRCP, MRCPCH, Paediatric Fellow; **Kim C Donaghue,** MB BS, PhD, FRACP, Endocrinologist, and Senior Lecturer, University of Sydney; **Geoffrey R Ambler,** MD, FRACP, Endocrinologist.

Discipline of Paediatrics and Child Health, The Children's Hospital at Westmead Clinical School, The University of Sydney, Westmead, NSW, Australia.

Craig M Mellis, MD, MPH, FRACP, Head, Discipline of Paediatrics and Child Health, and Sub-Dean, The Children's Hospital at Westmead Clinical School, University of Sydney.

Reprints will not be available from the authors. Correspondence: Dr Joseph S Macdessi, Department of Respiratory Medicine, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145. josephm@chw.edu.au

1: Baseline investigations

	Daily dose of fluticasone propionate	Blood glucose level (normal, > 3.5 mmol/L)	Sodium level (normal, 135–145 mmol/L)	Urinary sodium concentration (normal, < 20 mmol/L)
Patient 1	1500 μg	1.3 mmol/L	130 mmol/L*	88 mmol/L
Patient 2	500–1000 μg	2.2 mmol/L <1.2 mmol/L	Not available 135 mmol/L	Not available Not available
Patient 3	1000 μg	<1.0 mmol/L	126 mmol/L†	Not available

*Specimen collected before glucose bolus. †Specimen collected after glucose bolus.

2: Adrenal investigations

	Stimulated cortisol level (normal, > 600 nmol/L)	Adrenocorticotropic hormone level (normal, 2–10 pmol/L)	Adrenal antibodies (normal, negative)	Very long chain fatty acids (normal, negative)
Patient 1	108 nmol/L*	Not available	Negative	Negative
Patient 2	44 nmol/L†	< 1 pmol/L	Negative	Negative
Patient 3	129 nmol/L†	< 1 pmol/L	Negative	Negative

*At time of presentation with hypoglycaemia (blood glucose level, 1.3 mmol/L). †During short Synacthen test (60 minutes after an injection of 250 μg Synacthen).

Asthma history: The patient had had a history of episodic cough and wheeze since the age of four months, but had good exercise tolerance and minimal nocturnal symptoms between episodes. Past spirometry findings were normal. He had started taking ICS at 18 months of age, with progressively increasing doses in an attempt to control acute episodes.

Medications: His medications were 1–2 puffs of 250 μg fluticasone propionate with 25 μg salmeterol (Seretide 250/25; Allen & Hanburys) twice daily (giving a daily fluticasone dose of 500–1000 μg), and salbutamol and ipratropium as required. He had never previously required oral steroids.

Treatment and clinical course: With each hypoglycaemic episode he was treated with intravenous fluids, with good clinical response, but on one occasion he also received a short course of prednisolone for a "mild exacerbation of asthma". With the normoglycaemic episode he was treated with intravenous fluids and hydrocortisone for two days. After adrenal insufficiency was confirmed (Box 2), therapy with replacement hydrocortisone was commenced and he was weaned from his ICS dose. He currently takes 100 μg fluticasone and 4 mg montelukast daily, with no significant symptoms. He takes hydrocortisone as needed in times of stress, such as during infections. The patient was also subsequently found to have normal spirometry results, even during acute episodes of asthma.

Patient 3

Presentation: A 10-year-old boy presented after a hypoglycaemic seizure preceded by 24 hours of vomiting. He was normal on physical examination. His height was on the 90th percentile, weight between the 25th and 50th percentiles, and his growth velocity was normal. He was not of cushingoid appearance and had no abnormal pigmentation. He was found to have hypoglycaemia (Box 1), and hyponatraemia was also detected, but was possibly dilutional, as it was collected from the same intravenous cannula through which the dextrose bolus was given. A short Synacthen test confirmed secondary adrenal insufficiency (Box 2).

Asthma history: The patient had a history of frequent episodic wheeze and breathlessness during early childhood, and had been admitted to a rural intensive care unit for asthma exacerbation at the age of five years. Past spirometry findings had been normal. He had been taking his current ICS dose for the previous two years, despite having no acute episodes of asthma or interval symptoms.

Medications: He was taking Seretide 500/50 twice daily (giving 1000 μg fluticasone propionate daily) and salbutamol as needed.

Treatment and clinical course: Therapy with replacement hydrocortisone was begun while the ICS dose was gradually decreased to two puffs of Seretide 50/25 twice daily (giving 200 μg fluticasone daily); hydrocortisone therapy was continued for four months and is now taken as stress cover for intercurrent illness.

Discussion

Our case series further highlights the potential for the systemic activity of ICS to manifest as an acute adrenal crisis. These children, as well as patients in previously reported cases,[6-9] all had biochemical evidence of adrenal insufficiency in the absence of other causes (normal long-chain fatty acids, excluding adrenoleukodystrophy, and normal adrenal antibodies, excluding autoimmune adrenalitis [Box 2]). The vomiting associated with hypoglycaemia seen in the three children has been previously described,[6-9] as have seizures[7-9] seen in our Patient 3. The hyponatraemia found in two of our patients is an unexpected feature, but mild hyponatraemia with normokalaemia has been documented in secondary adrenal insufficiency and postulated to be the result of inappropriate vasopressin secretion[10] or subnormal aldosterone secretion in response to severe sodium restriction.[11] Hydrocortisone has some mineralocorticoid action, and its use as sole replacement therapy was

sufficient to restore electrolyte balance in these instances. While growth suppression was noted in one case series,[6] and has been reported in association with asymptomatic adrenal suppression,[12,13] it was not a feature in our patients, or in other reports.[7,8] This suggests that adrenal suppression may manifest differently, perhaps related to differing patient susceptibility, or dose or duration of ICS use.

Our patients and most children in previous reports[6-9,12,13] were taking high doses of fluticasone. This may reflect current prescribing habits. While fluticasone may be more likely to cause severe adrenal suppression owing to its higher potency compared with other ICSs,[7-9,12,13] all ICS medications have been shown to produce dose-dependent adrenal suppression in children.[3-5] The low doses used in some reported cases[6] again suggest varying patient susceptibility.

Screening for asymptomatic adrenal insufficiency in children receiving high doses of ICS is problematic, particularly as abnormal results do not accurately predict clinically meaningful adrenal-axis suppression.[4] Clinical indicators of systemic effects, such as poor growth or cushingoid features, were not seen in our patients or in previously reported cases.[6-9] Results of tests such as 24-hour urinary free cortisol excretion and random serum or salivary cortisol levels are often indeterminate.[14] Early-morning levels of serum or salivary cortisol which are at the high end of the normal range reassure that there is no serious adrenal suppression, but lower levels can be indeterminate.[15] "Gold standard" tests, such as insulin-induced hypoglycaemia or metyrapone suppression, carry significant risks and are difficult to justify in this situation. The standard dose (250 μg) short Synacthen test is generally reliable, but may give false normal results in some instances where central hypothalamic–pituitary–adrenal-axis suppression predominates. The low-dose (0.5 μg/1.73m^2) short synacthen test has been proposed as being less prone to such errors,[14] but abnormal test results do not always have clinical significance.

A more pragmatic approach would be to warn the parents of children taking high dose ICS of the potential for adrenal suppression so that they seek medical advice during an intercurrent illness associated with unexpected lethargy, vomiting, abdominal pains or seizures. Such "non-respiratory" presentations warrant urgent assessment and tests for baseline blood glucose level (for hypoglycaemia) and serum cortisol level (which may be inappropriately low). Prompt recognition and treatment with hydrocortisone and intravenous fluids containing glucose may be life saving in the event of an adrenal crisis. In less acute presentations, suspected adrenal suppression warrants referral for endocrine assessment and adrenal testing, although there is considerable debate as to the best method for doing this.[16,17] If significant adrenal suppression is evident by either a low cortisol level at the time of hypoglycaemia or an extremely low response to cortisol stimulation, then maintenance hydrocortisone should be used in the short term to facilitate safe weaning of the child from ICS. However, it is important to remember that some degree of adrenal suppression and risk of adrenal crisis may persist in such children if any steroid therapy continues, or for up to 12 months after steroid therapy is ceased.

Two other important messages arise out of these case reports. Firstly, it is important to ensure that ICS therapy is appropriate for the child. The United Kingdom national survey indicated that around 20% of patients presenting with adrenal crisis were later shown not to have asthma.[9] Other areas where ICS have no proven benefit are children presenting with recurrent cough[18] or episodic viral wheeze.[19] Secondly, in children with asthma receiving ICS therapy, it is important to minimise the dose by "back-titration" or by adding long-acting β-agonists (or both), as highlighted in recent guidelines.[2,3] All our patients were taking more than 500 μg per day of fluticasone, which is currently the upper limit of the recommended dose for children.[2] Further, significant dose reduction was possible without loss of asthma control, suggesting that these children were being overtreated. This report also serves to reinforce the recent guideline recommendation for specialist referral for children requiring high doses of ICS.[2,3]

Competing interests

None identified.

References

1. Calpin C, Macarthur C, Stephens D, et al. Effectiveness of prophylactic inhaled steroids in childhood asthma: a systematic review of the literature. *J Allergy Clin Immunol* 1997; 100: 452-457.
2. Asthma Management Handbook 2002. National Asthma Council. Available at: http://www.NationalAsthma.org.au (accessed December 2002).
3. Van Asperen P, Mellis C, Sly P. The role of corticosteroids in the management of childhood asthma. *Med J Aust* 2002; 176: 168-173.
4. Allen DB. Safety of inhaled corticosteroids in children. *Pediatr Pulmonol* 2002; 33: 208-220.
5. Fitzgerald D, Van Asperen P, Mellis C, et al. Fluticasone propionate 750 μg/day versus beclomethasone dipropionate 1500 μg/day: comparison of efficacy and adrenal function in paediatric asthma. *Thorax* 1998; 53: 656-661.
6. Patel L, Wales J, Kibirige M, et al. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. *Arch Dis Child* 2001; 85: 330-334.
7. Drake AJ, Howells RJ, Shield JPH, et al. Symptomatic adrenal insufficiency presenting with hypoglycaemia in asthmatic children with asthma receiving high dose inhaled fluticasone propionate. *BMJ* 2002; 324: 1081-1083.
8. Todd GRG, Acerini CL, Buck JJ, et al. Acute adrenal crisis in asthmatics treated with high dose fluticasone propionate. *Eur Respir J* 2002; 19: 1207-1209.
9. Todd GRG, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; 87: 457-461.
10. Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 1989; 321: 492-496.
11. Williams GH, Dluhy RG. Secondary adrenocortical insufficiency. *Harrison's Online* 2002; Chapter 331.
12. Todd G, Dunlop K, McNaboe J, et al. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; 348: 27-29.
13. Wong JYW, Zacharin MR, Hocking N, Robinson PJ. Growth and adrenal suppression in asthmatic children on moderate to high doses of fluticasone propionate. *J Paediatr Child Health* 2002; 38: 59-62.
14. Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996; 335: 1206-1212.
15. Erturk E, Jaffe CA, Barkan A. Evaluation of the integrity of the hypothalamic–pituitary–adrenal axis by insulin hypoglycaemia test. *J Clin Endocrinol Metab* 1998; 83: 2350-2354.
16. Suliman AM, Smith TP, Labib M, et al. The low dose ACTH test does not provide a useful assessment of the hypothalamic–pituitary–adrenal axis in secondary adrenal insufficiency. *Clin Endocrinol* 2002; 56: 533-539.
17. Gonzalez-Gonzalez JG, De la Garza-Hernandez NE, Mancillas-Adame LG, et al. A high sensitivity test in the assessment of adrenocortical insufficiency: 10 microgram vs 250 microgram cosyntropin dose assessment of adrenocortical insufficiency. *J Endocrinol* 1998; 159: 275-280.
18. Chang AB, Phelan PD, Carlin JB, et al. A randomised, placebo-controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch Dis Child* 1998; 79: 6-11.
19. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software CD 001107.

(Received 6 Sep, accepted 5 Dec 2002)