Lesson of the week

Symptomatic adrenal insufficiency presenting with hypoglycaemia in children with asthma receiving high dose inhaled fluticasone propionate

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Children taking high dose fluticasone propionate may present with hypoglycaemia secondary to iatrogenic adrenal suppression

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Inhaled corticosteroids are central to the successful long term management of asthma and are generally regarded as safe.[1] Systemic adverse effects have been described in children but are thought to be rare.[2] High dose inhaled corticosteroids are used in the step-up phase of treatment to optimise the control of asthma. Fluticasone propionate may be prescribed at higher doses to relieve respiratory symptoms in the belief that it generates fewer side effects than other inhaled steroids. Some studies have shown that fluticasone is safer than beclomethasone or budesonide, with limited oral absorption and extensive hepatic first pass metabolism leading to a lower systemic bioavailability.[3] Others have shown that appreciable amounts of inhaled fluticasone are absorbed from the lung[4]; fluticasone has also been associated with growth retardation and adrenal suppression in children.[5] Reports of adrenal insufficiency in childhood secondary to inhaled steroids have not described hypoglycaemia as a presenting feature.[5–7] We report on four children with asthma presenting with acute hypoglycaemia secondary to adrenal suppression caused by inhaled fluticasone propionate.

Case reports

Case 1—An 8 year old boy was investigated for a three year history of seizures during intercurrent illnesses, associated with hypoglycaemia (glucose 0.6-1.8 mmol/l; normal range 2.8-6.5 mmol/l). His height was on the second centile, below that predicted from parental heights. He had no cushingoid features. His asthma had been controlled with inhaled fluticasone 1000 μg daily for 5 years. A standard short Synacthen test (Alliance Pharmaceuticals, Wiltshire) showed a peak serum cortisol concentration of less than 20 nmol/l (expected >550 nmol/l). The baseline concentration of adrenocorticotrophic hormone was 6.2 μg/l (normal range less than 25 μg/l).

Case 2—An 8 year old boy became unresponsive, having been unwell with vomiting for 24 hours. He had been receiving inhaled fluticasone 1000 μg daily for 2 years. He had no cushingoid features. His height and weight were on the 2nd centile, below that predicted from parental heights, but his rate of growth was normal. At presentation his blood glucose concentration was 1.7 mmol/l and serum cortisol concentration 384 nmol/l. The peak cortisol concentration during the Synacthen test was 198 nmol/l.

Case 3—A 4 year old boy was admitted with an impaired level of consciousness during an acute exacerbation of asthma. He had been receiving inhaled fluticasone 500-1000 μg daily for 16 months. His growth was linear and his height was on the 75th centile. He had no cushingoid features. At presentation his blood glucose concentration was 0.7 mmol/l and serum cortisol concentration less than 5.5 nmol/l. The peak cortisol response to the Synacthen test was 20 nmol/l. Hydrocortisone replacement was started; the patient was weaned off the treatment over 4 months. A repeat Synacthen test showed recovery of the hypothalamic-pituitary-adrenal axis.

Case 4—An 8 year old boy with asthma presented with a decreased level of consciousness. He had had a severe headache and had vomited the previous day. He was receiving inhaled fluticasone 1500 μg daily. He had no cushingoid features. His growth was linear along the 0.4th centile, below that predicted from parental heights. At presentation his blood glucose concentration was 1.1 mmol/l and serum cortisol concentration 28 nmol/l. The peak cortisol response during the Synacthen test was 336 nmol/l.

Investigations

All the children were thoroughly investigated for causes of hypoglycaemia. Insulin concentrations at the time of hypoglycaemia in cases 1, 2, and 4 were appropriately undetectable; growth hormone concentrations were normal. Further investigations in case 1 included a prolonged fast, which showed no hypoglycaemia, and measurement of plasma lactate concentrations, which were normal. Cases 1, 2, and 3 had normal concentrations of plasma and urine amino acids and organic acids. Although insulin concentration was not tested in case 3, it is unlikely that hyperinsulinaemia would present as an isolated episode of hypoglycaemia in an 8 year old. Additionally, since the oral steroids were stopped there has been no recurrence of hypoglycaemia. All the cases were managed with oral hydrocortisone and by reducing the doses of inhaled steroid. In case 1 fluticasone was gradually withdrawn; there has been recovery in the response to the Synacthen test and no further hypoglycaemia.

Discussion

Children receiving high dose inhaled steroids may present with symptomatic hypoglycaemia secondary to adrenal suppression. Adrenal insufficiency is an uncommon cause of hypoglycaemia in childhood but should be considered in the differential diagnosis, especially in children regularly receiving steroids. Hypoglycaemia is more likely to occur at times of metabolic stress, particularly during infection, and results from impaired gluconeogenesis. Cortisol opposes the actions of insulin, enhances the availability of hepatic gluconeogenic enzymes, and stimulates the secretion of glucagon. Cortisol deficiency thereby limits the availability of glucose during starvation.

Exogenous steroids exert negative feedback on central glucocorticoid receptors, suppressing the secretion of corticotrophic hormone and adrenocorticotrophic hormone and reducing cortisol secretion from the adrenal. Prolonged adrenal suppression results in atrophy of the adrenal cortex. Exogenous glucocorticoid may compensate for the reduced concentrations of cortisol, except at times of metabolic stress, when the extra demand for cortisol cannot be met by the atrophied adrenal glands. Abrupt withdrawal of exogenous glucocorticoids may precipitate an adrenal crisis.[7] Children receiving high dose treatment who have a suppressed hypothalamic-pituitary-adrenal axis and who may also be poorly compliant during intercurrent illness are particularly at risk of hypoglycaemia.

Although fluticasone is widely used as an alternative to established inhaled steroids, it is not exempt from systemic side effects. Whereas a recent meta-analysis found that fluticasone was no more effective than other inhaled steroids, fluticasone had greater dose related adrenal suppression.[8] This effect cannot be accounted for by enhanced potency alone and is most noticeable with doses above 800 μg/day.[9] The considerable susceptibility between individuals to the effects of inhaled corticosteroids, however, makes the prediction of systemic side effects difficult.[8 9]

The investigation of suspected adrenal suppression should include measurement of the serum adrenocorticotrophic hormone concentration, which, in the presence of hypocortisolaemia should be within or below the normal range. Aldosterone production is preserved in secondary adrenal failure; renin concentrations will therefore be normal, and Synacthen tests will show a subnormal response to cortisol. The low dose Synacthen test may be used to show mild adrenal insufficiency not detected by the standard short Synacthen test, although this remains controversial.[10 11] As the responses to the Synacthen tests in our patients were clearly abnormal, low dose tests were unnecessary. Recovery of adrenal function usually follows that of the hypothalamus and pituitary; this is shown by improved results in response to Synacthen testing. Other causes of hypoglycaemia should be excluded; serum and urine samples must be taken at the time of hypoglycaemia for relevant investigations, in particular to exclude hyperinsulinaemia and inborn errors of metabolism.

Although inhaled corticosteroids remain a cornerstone of asthma management, the potential for serious side effects remains, particularly with high doses. This is notably the case for fluticasone in relation to adrenal suppression in children. Alternative treatments, such as long acting β_2 agonists and leukotriene receptor antagonists, should be considered for children in whom asthma is not controlled with fluticasone 200 μg daily (the maximum licensed dose for children), before giving high dose inhaled steroids. Children should not be prescribed more than the maximum licensed dose of fluticasone in general practice without specialist advice; those requiring high doses should be referred to a respiratory specialist. Using the lowest effective dose practitioners should "step-down" the doses of inhaled steroid in accordance with the guidelines of the Medicines Control Agency for those children in whom asthma is well controlled.

These cases show that the hypothalamic-pituitary-adrenal axis can be seriously suppressed even in the absence of abnormal growth or cushingoid features in children receiving high dose inhaled steroids. In such cases replacement with hydrocortisone is necessary until supervised adjustment of treatment allows gradual reduction of the inhaled steroid dose and recovery of the hypothalamic-pituitary-adrenal axis. The hypothalamic-pituitary-adrenal axis should be assessed in all children taking high dose inhaled steroids (for example, greater than >400 μg/day) long term. Children receiving doses in excess of those recommended should carry a steroid card. Carers and health professionals should be advised about hydrocortisone cover for intercurrent illnesses and the use of parenteral hydrocortisone in emergencies. Although adrenal suppression leading to hypoglycaemia or coma is likely to be uncommon, the hypothalamic-pituitary-adrenal axis must be investigated appropriately if patients taking high dose inhaled steroids present in this way. This, in addition to full metabolic screening, should exclude other potential causes of hypoglycaemia.

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Endpiece

The hardest worker?

The lawyer may take days to look up an important problem on which he is called to give advice. The engineer figures stresses, strains and gradients with the aid of a slide rule and reference tables. But, the doctor is called in the dead of night, aroused from a sound sleep and confronted with an emergency, in which immediate action must be taken and highly specialised knowledge is applied. The doctor has to carry his knowledge on his finger tips.

Erle Stanley Gardner

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Commentary: Exogenous glucocorticoids influence adrenal function, but assessment can be difficult

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Inhaled glucocorticoids are considered the most effective anti-inflammatory drugs for patients with asthma.[1] Adrenal insufficiency has been documented in children with asthma receiving high dose inhaled glucocorticoids.[2–4] Drake et al's report raises several issues about clinical management of hypoglycaemia. The first is how a child presenting to an emergency unit with hypoglycaemia should be managed. It is important to realise that hypoglycaemia is not in itself a diagnosis, and a low blood glucose concentration should trigger further rapid biochemical evaluation before being corrected. A minimum biochemical profile should include growth hormone, cortisol, insulin, lactate, and pyruvate, measured in a blood sample drawn at the time of hypoglycaemia.[5]

The second issue is specifically related to treatment with inhaled glucocorticoids. All the children in Drake et al's report received high dose inhaled glucocorticoids. These show dose dependent suppression of adrenal function.[6–8] In such a situation it could be argued that exogenous glucocorticoids are simply replacing endogenous production. If that is so, how did the children in this report become hypoglycaemic? One possibility is that the hypoglycaemia resulted from another disease process. Alternatively the duration of action of the inhaled glucocorticoid in these patients is less than expected. Generally an evening dose of inhaled glucocorticoid suppresses the endogenous secretion of cortisol until any time after 6 am, although there is great variation.[9] Whether such suppression reflects adequate circulating concentrations of inhaled glucocorticoid is unclear, but there is the distinct possibility that at certain times of the early morning or at least before the next dose is due people lack endogenous or exogenous glucocorticoid. Furthermore, occasional non-compliance in patients receiving excessive glucocorticoids should be considered, as any non-compliance with treatment compromises them. Consideration also needs to be given to how patients receiving high dose inhaled glucocorticoids deal with situations such as intercurrent infections or trauma. In patients with adrenal insufficiency the replacement dose of glucocorticoid is doubled, and similar advice may pertain to those receiving high dose inhaled glucocorticoids.

The third issue is how individuals receiving inhaled glucocorticoids should be monitored for hypothalamic-pituitary-adrenal activity. Urinary free cortisol concentrations have been measured to this end, but they are poor discriminators of adrenal underactivity. Cortisol appears in the urine only when the circulating carrier proteins are saturated, which requires high circulating cortisol concentrations, as in Cushing's disease. As such adrenal status should not be monitored on the basis of urinary cortisol concentrations in patients receiving inhaled glucocorticoids. A better approach is to estimate 24 hour secretion rates of total cortisol and cortisol metabolites as derived from gas chromatography-mass spectroscopy.[10]

Another approach has been to assess morning serum cortisol concentrations, usually by obtaining a blood sample at either 8 am or 9 am. Such measurements are also poor discriminators, although when values are undetectable cortisol can be considered absent. Low values do not necessarily indicate insufficiency. This is because cortisol secretion is pulsatile and superimposed on the circadian rhythm. The increase in serum cortisol concentrations in the morning can take place at any time between 4 am and 6 am, so that the morning peak may be detected in normal individuals between 6 am and 9 am. This means that in normal individuals the serum cortisol concentrations at 8 am or 9 am may be low as they are on the descending limb of what was a much higher pulse of cortisol in the circulation. Rather than list other estimates of cortisol secretion it is perhaps better to consider the two pieces of information required by clinicians. Firstly, what is the day to day production rate of endogenous glucocorticoids? This can best be measured by evaluating the cortisol and cortisol metabolites in the urine with gas chromatography-mass spectroscopy. Secondly, what is the response of the hypothalamic-pituitary-adrenal axis in periods of stress? The answer can be obtained either from tests such as insulin induced hypoglycaemia, which is problematic in children, or from a low dose Synacthen test.[11 12]

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