ORIGINAL ARTICLE

Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom

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Background: Until recently, only two cases of acute adrenal crisis associated with inhaled corticosteroids (ICS) had been reported worldwide. We identified four additional cases and sought to survey the frequency of this side effect in the United Kingdom.
Methods: Questionnaires were sent to all consultant paediatricians and adult endocrinologists registered in a UK medical directory, asking whether they had encountered asthmatic patients with acute adrenal crisis associated with ICS. Those responding positively completed a more detailed questionnaire. Diagnosis was confirmed by symptoms/signs and abnormal hypothalamic-pituitary-adrenal axis function test results.
Results: From an initial 2912 questionnaires, 33 patients met the diagnostic criteria (28 children, five adults). Twenty-three children had acute hypoglycaemia (13 with decreased levels of consciousness or coma; nine with coma and convulsions; one with coma, convulsions and death); five had insidious onset of symptoms. Four adults had insidious onset of symptoms; one had hypoglycaemia and convulsions. Of the 33 patients treated with 500–2000 µg/day ICS, 30 (91%) had received fluticasone, one (3%) fluticasone and budesonide, and two (6%) beclomethasone.
Conclusions: The frequency of acute adrenal crisis was greater than expected as the majority of these patients were treated with ICS doses supported by British Guidelines on Asthma Management. Despite being the least prescribed and most recently introduced ICS, fluticasone was associated with 94% of the cases. We therefore advise that the licensed dosage of fluticasone for children, 400 µg/day, should not be exceeded unless the patient is being supervised by a physician with experience in problematic asthma. We would also emphasise that until adrenal function has been assessed patients receiving high dose ICS should not have this therapy abruptly terminated as this could precipitate adrenal crisis.

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Corticosteroids are highly effective therapy for persistent asthma due to their anti-inflammatory activity. Inhaled corticosteroids (ICS) were developed to reduce the possibility of side effects associated with oral corticosteroids. Side effects are unlikely with beclomethasone (BDP) and budesonide (BUD) using doses of up to 400 µg/day[1] and with fluticasone (FP) in doses of up to 200 µg/day.[1 2] In severe asthma, the benefits of controlling symptoms often outweigh the risk of side effects and, in these circumstances, use of ICSs in higher daily dosages is recognised.[3] Although recently it has been suggested that the maximum clinical effect of inhaled FP is achieved in adolescents and adults in a dose of around 500 µg/day,[4] others have suggested benefits of FP in severe asthma at higher dosages[5 6] even up to 1500 or 2000 µg/day.[7] Although both British and international guidelines recommend up to 1000 µg/day in severe cases in children,[3] there are no long term studies to support this. Despite the use of these high doses, serious systemic effects in patients receiving ICS are extremely rare. There are, however, a few reports of severe growth retardation and adrenal suppression in children taking ICS doses ≥1000 µg/day.[8 9]

Fluticasone was introduced in the UK in 1993 as a potentially safer ICS than those already in use.[10] Oral systemic availability of FP was low because of the almost complete first pass hepatic metabolism (about 99%)[10] of the swallowed fraction (usually at least 70% of the emitted dose) after oral inhalation. However, significant amounts of ICS is also absorbed systemically through the lung, escaping hepatic first-pass metabolism.[1] At high doses (≥1000 µg/day) severe growth retardation and adrenal suppression have been attributed to systemic activity of FP.[8 9] We recently described four cases of acute adrenal crisis associated with inhaled FP, including three children presenting with hypoglycaemic coma and convulsions.[12]

Until 1999 there were only two published case reports of acute adrenal crisis associated with ICSs in more than 30 years' use. One case was an adult receiving 6400 µg/day BUD,[13] and the other was a child receiving 500 µg/day BUD.[14] However, given our experience of adrenal insufficiency in patients on ICS[12] together with our awareness of other colleagues who were encountering the same problem, we decided to conduct a national survey to investigate the frequency of acute adrenal crisis associated with all ICS. Eleven of the cases identified in our survey have also been published as case reports elsewhere.[12 15–17]

METHODS

An initial questionnaire was sent to all consultant paediatricians and adult endocrinologists registered in a UK medical directory in which tertiary care physicians were specifically identified. The questionnaire inquired whether they had ever encountered cases of acute adrenal crisis thought to be associated with the use of ICSs in patients with asthma, including those presenting with hypoglycaemic coma and/or convulsions. Those who responded positively were contacted again (by mail or telephone) and asked to complete a more detailed questionnaire. Information requested included patient age at presentation, sex, height, growth, weight, details of clinical presentation, acute presentation serum cortisol concentration,

Abbreviations: ICS, inhaled corticosteroids; BDP, beclomethasone; BUD, budesonide; FP, fluticasone; HPA, hypothalamic-pituitary-adrenal

and results of hypothalamic-pituitary-adrenal (HPA) axis function tests and other relevant investigations. Information was also obtained regarding the specific ICS with range of daily dose, duration of treatment, inhaling device, approximate number of days of prednisolone use in the previous year, and assessment of asthma severity (using the grading described in the 1995 British Guidelines on Asthma Management).[3] Finally, respondents were asked to indicate whether, in retrospect, they were certain that the patients' symptoms were due to asthma.

To confirm a diagnosis of acute adrenal crisis, both of the following criteria were required:

(1) At least one of the following symptoms or signs: lethargy, nausea or vomiting, diarrhoea, hypotension, abdominal pain, unexplained hypoglycaemia, convulsion.

(2) At least one of the following indications of abnormal HPA axis function: acute presentation serum cortisol response to critical illness <500 nmol/L, peak cortisol response <500 nmol/L to a short synacthen stimulation test (SSST; 250 μg tetracosactrin intramuscularly) or a failure to increase >200 nmol/L from baseline, peak cortisol response <500 nmol/L to glucagon stimulation test (500 μg glucagon intramuscularly).

For calculations of mean cortisol concentration, when concentrations of cortisol were undetectable, they were entered at a value equal to the sensitivity of the assay and not as zero. Growth retardation and poor weight gain are seen commonly in patients with asthma, and these signs alone were not considered sufficient to represent adrenal insufficiency. Patients were excluded if they had also been on long term oral corticosteroids or had been regularly using high potency topical corticosteroids—for example, betametasone for eczema—if they were adrenal antibody-positive, or if they had abnormal anterior pituitary function tests.

Role of the funding source

This study was funded by the Regional Multi-professional Audit Group (Department of Health, Northern Ireland), which had no involvement in study design; collection,

analysis, and interpretation of data; in the writing of the report; and in decision to submit the paper for publication.

RESULTS

Initial questionnaires were sent to 2912 doctors. Responses were received from 709 (24%), of which 55 (1.9% of those mailed) indicated one or more possible cases of acute adrenal crisis. Thirty-three patients met the criteria for acute adrenal crisis (table 1). Twenty-eight cases were children and 5 were adults. Patient demographics are shown in table 1. All cases had been extensively investigated for other causes of hypoglycaemia.

Clinical presentations
Children
Twenty-two cases presented with acute hypoglycaemia (mean glucose concentration, 1.5 mmol/L; range, 0.7–2.5 mmol/L; normal values, 4.0–6.9 mmol/L). All of these cases presented with decreased levels of consciousness, coma, or coma and convulsions (table 1). One of these children presented with status epilepticus and required intubation and intensive care. In this group acute adrenal insufficiency was believed to have contributed to the death of a child with cushingoid appearance and abdominal striae who presented with fulminant pneumococcal septicaemia. Postmortem examination in this case also revealed adrenal haemorrhages, which may have exacerbated adrenal hypofunction. The remaining cases presented with more insidious onset of symptoms (table 1), mainly lassitude, weakness, nausea, and dizziness.

Adults
The majority of adult patients presented with insidious onset of symptoms (table 1), mainly lethargy and nausea. One adult patient (aged 18 years) presented with hypoglycaemia and convulsions.

Precipitating factors
There were 37 patient episodes of adrenal crisis. In 24 (65%) there was no obvious precipitating cause, in eight (21%) there was evidence of infection (mostly respiratory), in four (11%)

Table 1 Patient demographics

	Children	Adults
Males/females (n)	17/11	3/2
Mean age (range) in years	6.4 (3.3–10)	41 (18–80)
Presentation (n)		
Acute hypoglycaemia	23	1
Decreased levels of conciousness or coma	13	0
Coma and convulsions	10	1
Insidious	5	4
Mean cortisol at acute presentation (range) in nmol/L	165 (6–575)* n = 11	– n = 0
Mean peak cortisol response to SSST (range) in nmol/L	163 (14–600)* n = 20	221 (80–318) n = 4
Mean peak cortisol response to GST (range) in nmol/L	134 (20–312) n = 27	– n = 0
Duration of ICS treatment (years)	1.7 n = 22	3.3 n = 5
Mean dose (range) of FP in μg/day	980 (500–2000) n = 27	1380 (1000–2000) n = 4
Inhaler use (n)		
MDI plus spacer	18†	0
MDI	0	4
Nebuliser	2†	0
DPI	4	1
Unknown	5	0
OCS use in previous 12 months (n)		
≤21 days	27	5
Between 21 and 72 days	1	0

GST, glucagon stimulation test; HPA, hypothalamic-pituitary-adrenal; SSST, short synacthen stimulation test; MDI, metered dose inhaler; DPI, dry powder inhaler; OCS, oral corticosteroid.
*One patient had a baseline cortisol of 575 nmol/L with an increase from baseline in the SSST to 600nmol/L (ie, <200nmol/L).
†One patient was using an MDI plus spacer for FP and a nebuliser for BUD.

the ICS had been stopped, reduced or changed to a different ICS of overall lower potency and finally, one episode (3%) occurred post operatively.

Delay in diagnosis
Four children (three males, one female, age range 4.0–8.7 years, mean 5.7 years) presented with acute hypoglycaemia but no causation was identified. They then re-presented with acute hypoglycaemia after intervals ranging from 3 months to 2 years (mean 0.9 years) and subsequently acute adrenal crisis was diagnosed.

Hypothalamic-pituitary-adrenal axis function
Twenty-five children and five adults were judged to be abnormal by the SSST, either by a peak cortisol response <500 nmol/L (29 cases) or failure to increase >200 nmol/L from baseline (one child). Actual cortisol values were provided for 20 children and four adults (table 1) and were simply indicated as "low" for five additional children and one adult. An additional three children were judged to be abnormal by other criteria stated in methods.

Inhaled corticosteroids
Thirty cases had been treated with FP, one child with both FP and BUD, and one adult and one child with BDP (fig 1). The percentage of prescriptions in the United Kingdom in 1998 is also indicated for each ICS in figure 1 for comparative purposes.

Information on the approximate duration of treatment with the specific ICS was available in 27 cases (table 1). At the time of diagnosis of acute adrenal crisis, treatment duration was equal to or greater than three years in three adults and two children, more than one year and less than two years in two adults and 12 children, and less than one year in six children. The daily dose varied from 500 to 2000 µg/day (table 1). The daily dosage per unit body surface area ranged from 660 to 2460 µg/m2/day with a mean of 1280 µg/m2/day for the 13 children for which this value could be calculated. For two adults this value was 720 and 760 µg/m2/day. The most common inhaling device used was metered-dose inhaler with spacer, accounting for more than 75% of use by children in which the inhaler device was known (table 1).

Height, weight, and body mass index
Data for height and weight at the time of presentation were available in 12 children. Mean height standard deviation score was −1.82 (range, −3.43 to −0.27). Mean weight standard deviation score was −0.76 (range, −3.07 to −0.09). Mean body mass index standard deviation score was 0.6 (range, −1.1 to 2.63). There was insufficient growth velocity data for meaningful analysis.

Diagnosis and severity of asthma
In retrospect, three respondents felt that their patients probably did not have asthma. An additional five patients had probable asthma, but were overtreated with ICS due to other concurrent lung diseases simulating asthma symptoms—for example, bronchiectasis, recurrent chest infections. The breakdown by asthma severity, based on the British Guidelines on Asthma Management,[3] was two adults and four children rated at Step 3 and one adult and 13 children at Step 4 or 5. Information was not available regarding the remaining patients.

Oral corticosteroids
Respondents were asked to estimate the approximate duration of oral corticosteroid therapy in the previous 12 months. In all but one case it was estimated to be ≤21 days (table 1).

DISCUSSION
It is clear that the frequency of acute adrenal crisis associated with ICS is greater than previously assumed. Given that the patients identified in our survey had to fulfil recognised diagnostic criteria, we are confident that our figures do not overestimate the frequency of this adverse event. Indeed, given the somewhat low response rate (24%) to our survey, the results are likely to underestimate the frequency of this serious systemic side effect.

All ICS have dose related systemic effects that can be measured by endocrine tests of adrenal function.[1 18 19] Although the clinical significance is unclear in most cases, adrenal suppression may be taken as a surrogate marker for possible adverse effects in other tissues.[1 18 19] The most widely accepted test of adrenal reserve is the synthetic ACTH (synathen) stimulation test. In recent years the low dose synathen test as described by Crowley et al[19] has been prefered since this gives a more physiological stimulus to the adrenal gland and is thus more sensitive in detecting adrenal impairment.

Acute adrenal crisis may occur when there is marked suppression of endogenous cortisol production caused by administration of exogenous corticosteroids and adrenal reserve is insufficient to respond to stressful stimuli—for example, respiratory infection. This situation is well described with oral or topical corticosteroid therapy. However, in 65% of our cases there was no obvious precipitating factor. One possible explanation is that the human body has a basal need for corticosteroids and that if adrenal function is severely suppressed, this basal need can no longer be satisfied. A background of chronic adrenal insufficiency is supported by the available growth data which shows both height and weight standard deviation scores less than the mean. Events that are normally not regarded as stressful—for example, a few hours of fasting—may then precipitate an adrenal crisis. Another explanation is that occasional non compliance with high dose ICS, in the presence of chronically suppressed adrenal function, results in an acute and critical deficiency of circulating glucocorticoid. Whatever the mechanism, it is clear that the sudden withdrawal of inhaled steroids due to fears as to their safety could precipitate an adrenal crisis with very serious consequences.

Clinically significant side effects due to ICS, such as a cushingoid appearance, are uncommon, and until recently there had only been two reports of acute adrenal crisis.[13 14] We now report 33 cases of acute adrenal crisis associated with ICS. In none of the cases could the findings be attributed to oral or topical corticosteroid use. All but five cases occurred in children, possibly because of the higher doses per unit body surface area in children compared with adults. The majority of cases presented as acute hypoglycaemia with coma and/or convulsions. Acute adrenal crisis is a rare event in the emergency department, and in nearly 11% of cases reported to us, the correct diagnosis was not made at the first presentation. As Russell has written previously, paediatricians, especially, need to be "vigilant investigating asthmatic children with disturbed consciousness, unusual behaviour, or autonomic symptoms suggestive of hypoglycaemia".[21] Investigations should include serum cortisol at acute presentation, followed by dynamic studies of adrenal function, preferably in the form of a low dose Synacthen stimulation test at a later date.[22]

Although almost all of the cases of acute adrenal crisis involved high doses of ICS, most were within accepted treatment guidelines for cases of severe persistent asthma. Treatment of children aged 5 years and older with dosages of FP up to 1000 µg/day (as used by 78% of children in the present study) is permitted according to the British Guidelines on Asthma Management,[3] although FP is only licensed up to 400 µg/day in the UK. FP is also licensed for use up to 2000 µg/day in adults in the UK, although recently the Medicines Control Agency issued a specific warning about using daily doses of FP >1000 µg due to the risk of systemic adverse effects.[23] As indicated above, sudden cessation of high dose ICS could be very hazardous and the patient's family need to
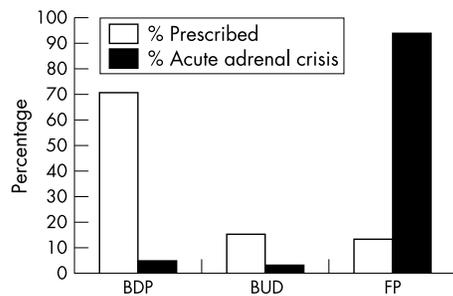
Figure 1 Percentage of prescriptions in the UK compared with percentage of cases of acute adrenal crisis reported in a UK survey.

understand the importance of gradual reduction in dosage. The present findings support titration of the ICS to the lowest effective maintenance dosage to reduce the likelihood of severe adverse events.

It was not anticipated that FP would account for the vast majority of cases of acute adrenal crisis, yet all but two cases had been treated with FP 500 to 2000 µg/day. FP has been preferred for many patients requiring higher doses of ICS because of a claimed better benefit/risk ratio compared with other ICS.[10] Pharmacokinetically, FP might be expected to be the safest of the ICS because of its very high first-pass hepatic metabolism (about 99%)[10] compared with BUD (about 90%).[24] BDP is metabolised in the lung to a more active metabolite, beclomethasone monopropionate. BDP and beclomethasone monopropionate together are estimated to be two to four times less susceptible to first-pass metabolism than BUD.

The association of FP with acute adrenal crisis in most cases is all the more surprising considering that FP accounts for the smallest proportion of prescriptions for ICS (fig 1) In England in 1998, there were only 1.54 million prescriptions for FP compared with 1.88 million for BUD and 8.43 million for BDP.[25] Furthermore, in the UK, BDP has been prescribed for more than 30 years and BUD for more than 20 years, whereas FP has been prescribed for only eight years. In addition, both BDP and BUD can be easily prescribed at high doses (Pulmicort 400 Turbohaler (AstraZeneca, Draco, Sweden), 400 µg per actuation; BDP metered-dose inhaler (generic or branded), 250 µg per actuation). Therefore, the high association with acute adrenal crisis observed with FP relative to other ICS cannot be explained by prescription patterns, and this is supported by a meta-analysis of 27 studies[18] showing that FP had a steeper gradient for dose-related adrenal suppression as measured by 8 am cortisol compared with BUD (3.4-fold) or triamcinolone acetonide (4.2-fold).

We suggest that the greater frequency of adrenal insufficiency may relate to the high lipophilicity of FP. An important source of systemic ICS after inhalation is entry into the blood via the lungs, for which there is no first-pass inactivation. FP is 200–300 times more lipophilic than BUD[26] and beclomethasone monophosphate (the active metabolite of BDP), and this results in a much higher volume of distribution, which is an indication of nonspecific uptake of a drug in peripheral tissue.[20] This binding to peripheral tissues results in a longer elimination half life and the risk of accumulation kinetics.[11] Thus during twice daily inhalation of FP (plasma half life 14.4 hours[11]) there is continuous suppression of adrenal function but flunisolide, a much less lipophilic ICS with a shorter plasma half life (1.6 hours) causes only intermittent suppression throughout a 24 hour period.[27] A combination of various pharmacokinetic factors influenced by the high lipophilicity of FP[18] may then account for the frequency of serious adrenal suppression observed with doses ≥500 µg/day.

In patients with acute adrenal crisis, the greater frequency of metered-dose inhaler use, with or without a spacer, relative to dry-powder inhaler use is consistent with a long term study that found that 36% of children taking FP (≥176 µg/day) by metered-dose inhaler with a spacer device had abnormally low morning cortisol concentrations.[28] In contrast, only minimal adrenal suppression has been detected in studies assessing low to medium doses (200–400 µg/day) given via dry-powder inhalers (Diskus or Diskhaler, Allen and Hanbury, Uxbridge, UK).[1][29] Since systemic availability of inhaled FP is negligible via the oral (gastrointestinal) absorption route, the blood concentration of FP is determined totally by absorption from the lung. Absorption from the lung is influenced by inhaler dependent factors, such as particle size,[30][31] and this may account for the large proportion of patients with acute adrenal insufficiency who were using a metered-dose inhaler with or without a large-volume spacer in the present study.

It is important that the diagnosis of asthma be accurate when increasing ICS to greater-than-recommended doses. Although persistent cough is an important symptom of asthma,[32] it has many other causes,[33] and of the children identified in this study, eight had persistent cough due to causes other than asthma; in the five who also had asthma, it is likely that the cough led to overtreatment. Lack of clinical response to ICS probably led to increasing dosages in these patients, and it has been shown that the risk of systemic effects with FP is greater in patients with normal airways than in patients with asthma,[34] thus explaining the apparent vulnerability of this group when treated with this particular ICS. This finding emphasises the importance of confirming the diagnosis of asthma with respiratory function tests where possible and reconsidering the diagnosis of asthma in patients not responding to increasing dosages of ICS.

In conclusion, the low systemic bioavailability of FP at licensed doses does not translate into enhanced safety when higher doses are used. In view of the number and severity of cases of acute adrenal crisis associated with higher doses of FP reported to us, we advise great caution in using dosages of FP >400 µg/day in children and >1000 µg/day in adults. Also, physicians prescribing high dose ICS must be certain that patient symptoms are due to asthma and if so that alternative therapeutic avenues—for example, identification of environmental trigger factors, use of leukotriene receptor antagonists, and long acting inhaled bronchodilators—have been explored. As the majority (76%) of cases occurred when high dose ICS had been prescribed for more than one year, we recommend that all such patients even if assymptomatic should be considered for investigation of adrenal function with a low dose Synacthen stimulation test. More commonly used tests such as urinary free cortisol, 8am cortisol and conventional dose (250 µg) Synathen stimulation test are poor discriminators of adrenal hypofunction.[35] Finally, although acute adrenal crisis associated with BDP and BUD appears considerably less common, all ICS dosages should be titrated downward to achieve the lowest effective maintenance dosage.

CONFLICT OF INTEREST STATEMENT

ACKNOWLEDGEMENT

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