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Inhaled corticosteroids and HPA axis suppression: how important is it and how should it be managed?

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Summary

Inhaled corticosteroids (ICS) are established as a cornerstone of management for patients with bronchoconstrictive lung disease. However, systemic absorption may lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis in a significant minority of patients. This is more likely in 'higher risk' patients exposed to high cumulative ICS doses, and in those treated with frequent oral corticosteroids or drugs which inhibit cytochrome p450 3A4. HPA axis suppression is frequently unrecognised, such that some patients, notably children, only come to light when an adrenal crisis is precipitated by physical stress. In order to minimise this risk, 'higher risk' patients and those with previously identified suppressed cortisol responses to Synacthen testing should undergo an education programme to inform them about sick day rules. A review of ICS therapy should also be undertaken to ensure that the dose administered is the minimum required to control symptoms.

Introduction

Corticosteroids have been established as an important treatment for bronchoconstrictive lung disorders ever since the first successful use of cortisone in asthma in 1950.¹ The subsequent development of inhaled corticosteroid (ICS) preparations in the 1970s² revolutionised therapy as it enabled local delivery to the lung in high concentrations and limited exposure to other organs. ICS are now firmly established as an important treatment

for chronic asthma and chronic obstructive pulmonary disease.³⁻⁶ However, whilst the clinical effectiveness of ICS is clear, the development of more potent preparations with significant absorption across the lungs has led to recognition of hypothalamic-pituitary-adrenal (HPA) axis suppression as a clinical challenge. Here, we review the extent of this problem, and recommend strategies for its assessment, prevention and treatment.

Mode of action and relative potency

Five ICS preparations are currently in use in the UK: beclometasone dipropionate (BDP), budesonide, ciclesonide, fluticasone propionate and mometasone furoate. These share a common mode of action by binding to the glucocorticoid receptor, although preparations differ in their pharmacodynamic and pharmacokinetic properties. ICS receptor binding can be quantified as relative receptor affinity (RRA) with reference to dexamethasone whose affinity is set at 100.⁷ The RRA of ICS in current use is set out in table 1. Those with the highest RRA include fluticasone propionate and mometasone furoate. BDP and ciclesonide have lower RRA, but are converted to their active metabolites beclometasone monopropionate and desisobutyryl ciclesonide by pulmonary epithelial enzymes. *In vitro* binding of ICS at the glucocorticoid receptor is broadly predictive of *in vivo* potency, such that BDP and budesonide have approximately equal activity, whilst fluticasone is equally active at half the microgram dose.^{3,8} Mometasone is estimated to have equal potency to fluticasone whereas ciclesonide has a potency in between BDP and fluticasone.

Factors affecting absorption and systemic concentrations

Approximately 10 to 60% of ICS administered via a metered dose inhaler enters the lung, where it exerts its therapeutic effects. The remainder of the drug is deposited in the oropharynx and swallowed. This portion is subsequently absorbed in the gastrointestinal tract but undergoes first pass metabolism in the liver by cytochrome p450 3A4 (CYP450 3A4) and is converted to inactive metabolites. Ciclesonide, fluticasone and mometasone are almost completely metabolised, whereas 11% budesonide and 20-40% BDP escapes first pass metabolism (table 1).⁹ Circulating drug concentrations are thus predominantly dependent on lung absorption. Although CYP450 3A5 efficiently metabolises glucocorticoids in the lungs¹⁰, up to 20% of inhaled fluticasone, for example, is still systemically available.¹¹

Systemic side-effects are also affected by plasma protein binding, half-life and systemic clearance (table 1). Binding of an ICS to plasma protein (albumin) renders it pharmacologically inactive. ICS preparations with high protein binding, such as ciclesonide

and its active metabolite desisobutyryl ciclesonide (both >99% bound), may thus be less likely to induce cortisol suppression than those with lower protein binding. Preparations with short half-lives and high clearance rates may also reduce exposure to the systemic circulation. ICS elimination half-lives range from 14 hours for fluticasone to as little as 0.5 hours for ciclesonide (table 1)¹². Metabolism occurs predominantly in the liver with clearance rates typically similar to the rate of hepatic blood flow, although systemic clearance of desisobutyryl ciclesonide is considerably greater¹³.

Absorption of ICS also appears to be affected by lung function. Fluticasone absorption is higher in healthy subjects than in those with airflow obstruction¹⁴, an effect which may be less apparent for patients taking budesonide or ciclesonide.^{15,16} This has clinical relevance since the absorption of fluticasone increases with improvement in airflow obstruction, an observation that should prompt a dose reduction once asthma is controlled.

Inhibitors of CYP450 3A4 may also affect systemic concentrations of ICS. Reports of interactions of itraconazole and ritonavir, both potent inhibitors of CYP450 3A4, with budesonide¹⁷ or more commonly fluticasone¹⁸ confirm the pathological relevance of these drug interactions on induction of Cushing's syndrome and HPA axis suppression. Other drugs which act as inhibitors of this enzyme system might be expected to similarly increase circulating ICS concentrations (Table 2).¹⁹

HPA axis suppression: how common is it?

Systemic absorption of ICS leads to ACTH suppression and down-regulation of the HPA axis, such that the subject's overall steroid exposure is adjusted to remain within the normal range. Whilst clinical signs of Cushing's syndrome may not be apparent unless high doses are administered, even low doses can lead to suppression of the HPA axis. Indeed, the relationship between ICS dose and HPA axis suppression is linear, such that no dose is completely without risk.²⁰

The prevalence of HPA axis suppression in patients taking ICS is not entirely clear and not easy to quantify due to the frequent co-administration of oral corticosteroids in this patient group and their potential to suppress the HPA axis in their own right. The prevalence is also likely to be affected by ICS potency, dose, treatment duration, delivery method, drug interactions and the site of drug activation. In a systematic review and meta-analysis of 732 adults and children treated with ICS, HPA axis suppression was observed in 6, 7, 10 and 13

percent of patients taking 500, 1000, 1500 and 2000 micrograms/day of fluticasone respectively.²¹ In keeping with its greater potency, fluticasone is the most common ICS reported to be associated with HPA axis suppression in children and adults^{22,23} although an important caveat is that this may reflect preferential prescribing at high dose in patients with refractory asthma.

Clinical consequences of ICS-induced HPA axis suppression

The most serious complication of ICS use is adrenal crisis consequent upon suppression of the HPA axis and sudden cessation of long-term therapy, or precipitated by trauma, sepsis or surgery. However, adrenal crisis appears to occur only rarely after ICS therapy, and mainly in children, with one UK survey reporting 33 cases (28 children, 5 adults) from 2912 questionnaires. As might be anticipated, crisis was more common in patients taking higher ICS doses (500-2000 micrograms/day), with the majority taking fluticasone alone (91%) or in combination (3%),²⁴ leading the authors to recommend avoidance of doses of fluticasone above the licensed dose of 400 micrograms/day in children unless supervised by a respiratory physician.

Growth suppression is also an important consideration in children, since ICS are recommended for children of all ages with chronic asthma and are likely to be prescribed long-term. Severe asthma may itself impair growth but an effect of ICS on growth suppression is difficult to prove due to the complex influences of genetic background and pubertal factors on height. Some studies have shown short-term growth suppression in response to ICS treatment²⁵ but final adult height does not appear to be affected.²⁶ Childhood is also a critical time for bone development, although the available evidence suggests that reduction in bone mineral density (BMD) is not a significant concern with ICS, at least at low to moderate doses.²⁷ An adverse effect of ICS use on bone health in adults is also unproven, although one study with a 6 year follow-up showed an inverse association between cumulative ICS exposure and BMD at both the lumbar spine and femoral neck.²⁸ Whilst these studies suggest that ICS use may be associated with long-term adverse effects, it should be recognised that any such risks are likely to be outweighed by the ability of ICS to reduce the need for frequent courses of oral corticosteroids, provided the ICS dose is carefully regulated.³

How should patients with ICS-induced HPA axis suppression be managed?

Since clinically relevant HPA axis suppression in patients taking ICS is generally confined to patients exposed to higher cumulative doses, universal screening is neither practical nor justified. We recommend that a case-finding approach be considered such that patients with specific risk factors for HPA axis suppression, signs of Cushing's syndrome or symptoms of adrenal insufficiency be offered testing. Such risk factors would include patients exposed to high cumulative doses of ICS, patients taking more than 800 micrograms/day BDP equivalent, patients with a history of frequent oral corticosteroid therapy for exacerbations, and those receiving concomitant drug therapy with an agent which inhibits CYP450 3A4 (figure 1). A presentation with shock, hypoglycaemia²⁹ or reduced consciousness in a child with a history of high dose ICS exposure should also prompt investigation, as should a presentation with slowed growth. We anticipate that such patients are likely to concentrate in secondary care respiratory clinics, as these are often the patients with the most refractory disease.

One of two potential approaches to management might then be considered. Advocates of endocrine testing would favour a management approach based on biochemical assessment of endogenous cortisol production, which would be required to establish suppression of the HPA axis with diagnostic certainty. A number of endocrine tests might be considered in this context but a reasonable first step would be measurement of an early morning (08:00 a.m) cortisol. This test has high specificity if a low cut-off value (<100 nmol/l) is used. However, sensitivity is poor, and a value within the laboratory reference range does not rule out the presence of adrenal suppression. A dynamic test is required in these circumstances to confirm the integrity or otherwise of the HPA axis. If a testing strategy is to be followed, we would advocate the use of the standard dose (250 micrograms) ACTH (Synacthen) test in adults since data on normative responses are now available for all commonly used cortisol assays in the UK.³⁰ Assay interference does not appear to be a concern,³¹ and false negative results are uncommon provided the usual caveats of interference with oestrogen therapy³⁰ or recent onset axis suppression are recognised. In a recent retrospective analysis of a large cohort of patients on ICS who had undergone standard dose Synacthen testing, Woods *et al* found that a basal cortisol of >348 nmol/l was 100% specific for a 'pass' to Synacthen testing whereas a basal cortisol value of <34 nmol/l gave 100% sensitivity for failure.³² The authors estimated that up to 50% of Synacthen tests might thus be avoided by adopting these basal cortisol cut-offs. In children, the low dose Synacthen test is used in preference by many centres, although considerable variation exists with respect to the dose administered (complicated by the need for dilution), sample timing and diagnostic criteria

applied.³³ Supporters of the low dose test believe that it detects subtle degrees of adrenal insufficiency otherwise missed by the standard dose test, whereas critics argue that this increased sensitivity generates false positive results. A major limitation is the inadequate normative data available for interpretation; centres should be encouraged to develop age- and gender-appropriate reference ranges if they are going to rely on this test for investigation. Other approaches for diagnosis which might avoid dynamic testing have also been considered, including morning ACTH³⁴ and salivary cortisone levels,³⁵ although further studies are needed before these can be considered as potential alternatives, whether for diagnosis or in the assessment of axis recovery.

The clinical consequences, however, of often minor reductions in serum cortisol response to Synacthen in patients established on ICS are not currently known, and the benefits and potential disadvantages of a systematic biochemical testing policy, especially with respect to treatment adherence, remain to be established. Until such data become available, a pragmatic alternative approach could be considered, whereby 'higher risk' patients (figure 1) are presumed to have some degree of HPA axis suppression, and widespread, resource-intensive endocrine testing is avoided. Management should then focus on: (1) careful patient education about the need for steroid supplementation at times of stress (daily oral steroids may not be necessary as overall glucocorticoid exposure is already high), and (2) a review of the ICS preparation and dose (figure 1). These overriding principles would also apply to any patients who have already undergone biochemical testing and been found to have subnormal dynamic test responses.

As with other causes of adrenal insufficiency,^{36, 37} an education programme should train patients in recognising stressful situations (e.g. infection, trauma or surgery) and the importance of additional steroid supplementation at these times to reduce the risk of adrenal crisis. Patients should be provided with specific written advice about steroid replacement in the event of a severe intercurrent illness or surgery.^{3, 36, 37} For minor physical stress, a daily oral hydrocortisone dose of 40mg in adults or 20-30 mg/m² in children is appropriate, increasing to higher intravenous doses in cases of severe physical stress or diarrhoea/vomiting (figure 1).^{36, 37} Patients should also be encouraged to carry a steroid emergency card to include details on their ICS preparation, and the respiratory physician and endocrinologist responsible for their care. Adoption of the new Pan-European emergency card should be encouraged wherever possible.³⁸ Patients may also wish to

consider wearing Medic-Alert jewellery and they should be supplied with a glucocorticoid emergency kit.

Since ICS-induced HPA axis suppression is potentially reversible, clinicians should review the potency and dose of ICS therapy, in parallel with embarking upon a patient education programme. The minimum ICS dose to control symptoms should be used and therapy should be 'stepped down' once asthma is controlled.³ This is an important consideration but is frequently overlooked, leaving patients at risk of over-treatment. A slow reduction, comprising a 25-50% reduction in ICS dose every three months, is appropriate^{3,39} since some patients may deteriorate rapidly. For this reason, dose reductions and/or change in ICS preparation should always be supervised by the respiratory team. Spacer devices may also be useful in increasing airway deposition and reducing oropharyngeal exposure. Concomitant use of fluticasone and ritonavir should be avoided; if ritonavir is needed then this should be used in combination with another ICS such as low dose budesonide or BDP.

In patients who have undergone biochemical testing, recovery of the HPA axis should be tested for with a repeat Synacthen test 3 months after any ICS dose reduction, recognising that recovery may take many months, or, in patients treated with high doses of ICS and/or oral doses for a long period of time, not occur at all. In such circumstances, patients may require lifelong glucocorticoid replacement therapy.

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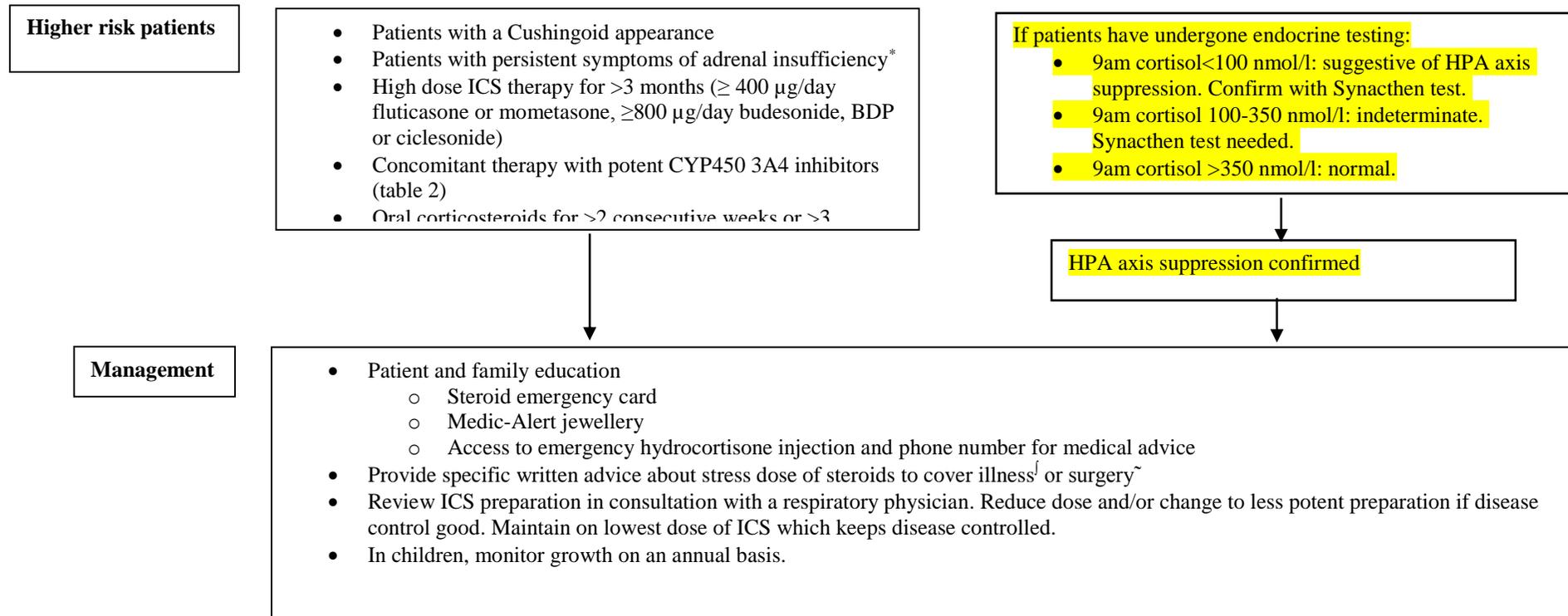
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Figure 1. Recommendations for management of ICS-induced HPA axis suppression



* Emergency management may be required for symptoms of adrenal crisis such as hypoglycaemia or hypotension.

[†] In adults, cover illness or fever with 20mg bd oral hydrocortisone. In children, use 20-30 mg/m²/day oral hydrocortisone in three or four divided doses. Parenteral doses may be needed in cases of diarrhoea/vomiting.³⁷

[~] For detail, see reference³⁷. In adults, cover major surgery with 100mg IV hydrocortisone injection followed by 50mg qds IV hydrocortisone or 200mg IV infusion over first 24 hours³⁷. In children, use 50-mg/m² IV, followed by 50-100 mg/m²/day IV divided in 6-hourly doses.³⁷

Table 1. Pharmacodynamic and pharmacokinetic properties of inhaled corticosteroids (adapted from ⁷ and ¹⁰).

Corticosteroid	Relative receptor affinity^a	Protein binding (%)	Oral bioavailability (%)	Systemic clearance (L/h)	Half-life (h)
Beclomethasone dipropionate/17-monopropionate ^b	53/1345	87	20/40	150/120	UK/2.7
Budesonide	935	88	11	84	2.0
Ciclesonide/desisobutyryl ciclesonide ^b	12/1200	99/99	<1/<1	152/228	0.5/4.8
Fluticasone propionate	1800	90	≤1	66	14.4
Mometasone furoate	2200	99	<1	53	UK

a Relative receptor binding affinities are expressed with reference to dexamethasone whose affinity is set at 100

b Beclomethasone dipropionate and ciclesonide are prodrugs which are activated in the lungs to their active metabolites, beclomethasone 17-monopropionate and desisobutyryl ciclesonide respectively.

UK, unknown.

Table 2. Inhibitors of cytochrome p450 3A4

Strong inhibitors	Moderate inhibitors
Ritonavir	Verapamil
Indinavir	Diltiazem
Nelfinavir	Aprepitant
Saquinavir	Erythromycin
Clarithromycin	Fluconazole
Chloramphenicol	Bergamottin (in grapefruit juice)
Itraconazole	
Ketoconazole	
Nefazodone	