

Occasional review

Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids

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Received 3 February 1997
Returned to authors
5 February 1997
Revised version received
7 February 1997
Accepted for publication
10 February 1997

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Topical corticosteroids are now widely accepted for use as first line preventative therapy in the treatment of inflammatory diseases of the lower and upper respiratory tract – namely, asthma and rhinitis. Although there is some disparity in the dose response relationship for anti-asthmatic efficacy and systemic activity of glucocorticoids between individuals, it has been shown that there is a dissociation in the dose response relationship above 400 µg/day in children and 800 µg/day in adults, at which stage the dose response curve for anti-asthmatic activity becomes relatively flat compared with the curve for systemic activity which becomes steep. This results in a U-shaped curve for the therapeutic ratio (benefit to risk) for inhaled

corticosteroids.¹ The factors which determine glucocorticoid response at the receptor and molecular level are complex, and probably explain the individual variation and tissue specificity in systemic response (fig 1).

It is important first of all to consider the factors that determine systemic absorption of inhaled and intranasal corticosteroids.² For inhaled corticosteroids such as budesonide, fluticasone propionate, and triamcinolone acetonide there is a relatively high degree of hepatic first pass inactivation of the swallowed fraction of the inhaled dose, whereas there is no first pass metabolism in the lung. Hence, the lung bioavailability will provide the larger component of overall systemic absorption and will determine the systemic bioactivity profile. It is therefore conceivable that patients with more severe asthma may be protected from systemic effects as a consequence of reduced lung bioavailability of the inhaled fraction. For the intranasal route there is also no first pass effect so absorption of unchanged drug will occur directly into the systemic circulation as with the lung. Whilst there is a high degree of intranasal deposition, it is also important to consider rapid nasociliary clearance into the throat as well as the relative mucosal surface area for absorption (fig 2). The situation for beclomethasone dipropionate is somewhat different in that there is a degree of first pass activation and inactivation for this compound in the lung and nose as well as in the liver. Pharmacological properties such as glucocorticoid receptor potency, affinity, and residency time will in part determine the systemic pharmacodynamic response. In addition, pharmacokinetic factors including plasma elimination half life and volume of distribution (due to lipophilicity) will contribute to effects at steady state in terms of drug accumulation in the blood and retention in systemic tissue.³

The main focus of this review is to evaluate the different measures of systemic bioactivity for inhaled and intranasal corticosteroids in terms of their relative sensitivity and to assess their clinical relevance in everyday practice. A detailed discussion of the evaluation of corticosteroid effects on bone density is beyond the scope of this review article. The pharmacokinetics and dose response relationships for inhaled steroids and differences between drugs will not be discussed in depth as this has been extensively covered elsewhere.¹⁻³

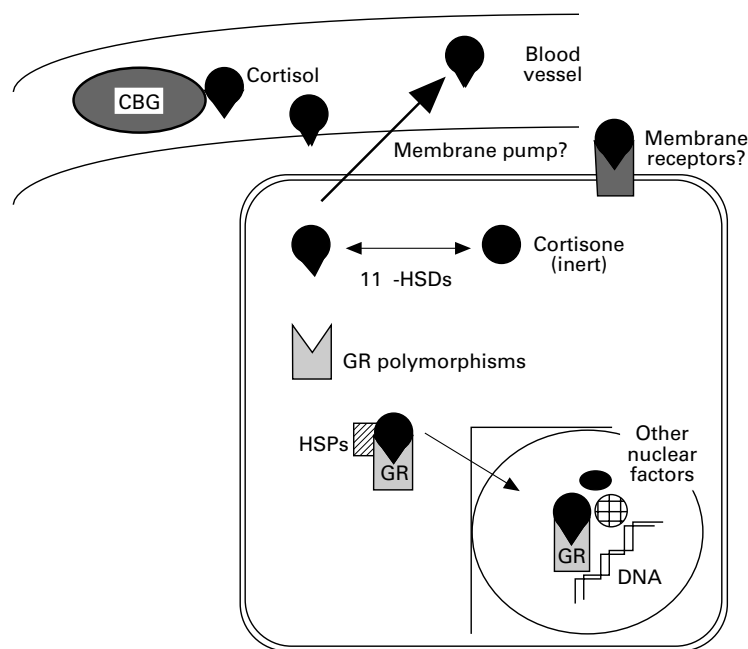


Figure 1 Physiological cortisol circulates largely bound to corticosteroid-binding globulin (CBG) and is thus inactive, whereas most synthetic steroids are free. Lipophilicity ensures ready uptake of free steroids into cells, although there may be membrane receptors in some organs such as the brain and membrane pumps (out) have been mooted for some synthetic steroids. Once within a cell, some corticosteroids are rapidly metabolised by high affinity enzymes systems such as 11 β -hydroxysteroid dehydrogenase (11 β -HSD) to inert forms, whilst other steroids are poor substrates. Some steroids inactivated in one organ may be reactivated by the reverse reaction at other sites. Intracellular action requires both cytoplasmic glucocorticoid receptors (GR), which are genetically polymorphic and thus vary in their affinity for steroids, and accessory "heat shock proteins" (HSPs). GR activated by steroids are transferred to the nucleus where they interact either directly with specific DNA sequences and/or with other nuclear factors to regulate the transcription of target genes. The nuclear mechanisms are highly specific for each tissue and even individual target genes.

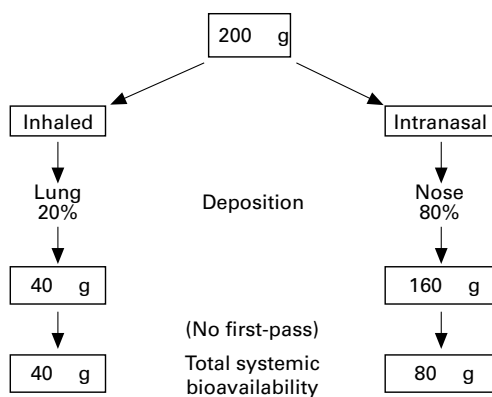


Figure 2 Schematic diagram depicting systemic absorption of a topical corticosteroid for a 200 µg nominal dose given by inhaled and intranasal routes of administration, assuming 20% and 80% deposition, respectively. The total systemic bioavailability for each route will be determined by the deposited dose in the lung and nose, as well as by the relative surface areas available for absorption. The relative figures for lung and nasal absorption have been calculated assuming 100% bioavailability from the lung fraction and 50% bioavailability from the nasal fraction (due to nasociliary clearance and available absorptive surface area).

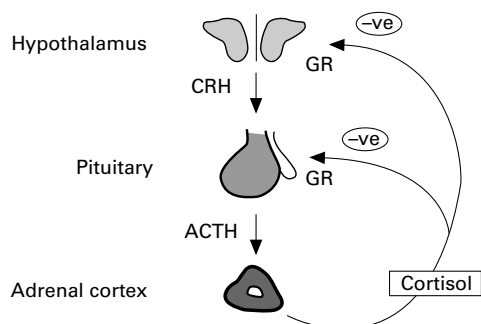


Figure 3 Exogenous glucocorticoids or endogenous cortisol bind to glucocorticoid receptors (GR) in the pituitary, hypothalamus, and some other brain regions where they act to suppress activity of the hypothalamic-pituitary-adrenal (HPA) axis (negative feedback). Tests of HPA axis function include measures of endogenous cortisol production and secretion and tests which stimulate components of the HPA axis using synthetic adrenocorticotropic hormone (ACTH) (adrenal reserve) and corticotrophin releasing hormone (CRH) or insulin induced hypoglycaemia (pituitary responses and adrenal reserve). All may be blunted by exogenous glucocorticoids.

Hypothalamic-pituitary-adrenal (HPA) axis activity

It is well recognised that measures of HPA axis activity can be used to demonstrate the dose response effects of inhaled corticosteroids in terms of their systemic bioactivity. These effects of exogenous corticosteroids occur as a consequence of their negative feedback on the HPA

axis resulting in suppressed levels of corticotrophin releasing hormone (CRH) and adrenocorticotrophin (ACTH) and attenuated cortisol secretion, eventually causing adrenal cortical atrophy (fig 3). Measures of cortisol secretion and elimination have the advantage of being readily available in most laboratories as well as being sensitive and reproducible for use in clinical practice and research. Moreover, they may be clinically relevant since suppression of HPA axis activity implies an inadequate physiological response to stress. In general there are two broad categories for measurements of HPA axis activity – namely, those tests which measure endogenous cortisol secretion and dynamic stimulation tests which measure adrenal cortical reserve (fig 4).

The use of a single morning cortisol measurement is of little value as a screening test for adrenal suppression, particularly if the timing is inconstant – for example, with sample collection between 08.00 and 10.00 hours as is the case in many multicentre studies.⁴⁻⁷ This is because there is marked diurnal variability in plasma cortisol levels with peak levels usually occurring no later than 08.00 hours and up to a threefold difference in levels between 08.00 and 10.00 hours.^{8,9} Even with strict standardisation of the collection time at 08.00 hours there remains a considerable degree of intra-individual and inter-individual variability which makes a single morning plasma cortisol estimate a relatively insensitive end point for detecting suppression of HPA axis activity. The measurement of a single plasma level of ACTH at 08.00 hours is more variable and of even less value than a single measurement of plasma cortisol at 08.00 hours because of the pulsatile nature of the ACTH release throughout the night.

An alternative approach is to measure the integrated 24 hour cortisol profile in either urine or plasma and to express this as an area under the curve. Dose ranging studies with inhaled corticosteroids have shown good agreement for percentage suppression of both 24 hour urine and plasma cortisol measurements.⁸ However, for most clinical studies the measurement of a 24 hour plasma cortisol profile is impractical as this requires frequent venous sampling, whilst the compliance with a 24 hour urine collection is often poor unless the subject is closely supervised during a period of confinement. Neither of these tests is therefore ideal for screening HPA axis activity either for outpatient studies or for everyday clinical practice.

The 24 hour urinary free cortisol excretion has been shown to be more sensitive at detecting adrenal suppression than a single plasma cortisol sample at 09.00 hours and has comparable sensitivity to a 250 µg bolus dose of ACTH stimulation or an insulin stress test.¹⁰ The use of timed fractionated collections to measure urinary free cortisol excretion has been investigated in order to obviate the compliance and variability problems associated with a 24 hour collection. An overnight and first waking collection of urinary free cortisol is simple for the patient to collect and is as sensitive as a

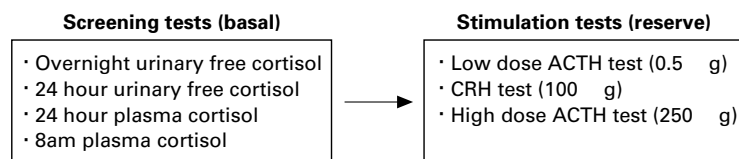


Figure 4 Screening measurements of basal endogenous cortisol secretion/excretion and dynamic stimulation tests to evaluate adrenal reserve shown in order of decreasing sensitivity (from top to bottom).

24 hour collection, particularly when corrected for creatinine excretion.¹¹ In a recent short term, steady state, dose ranging evaluation of inhaled fluticasone propionate and budesonide in adult asthmatic subjects at a dose of 250 µg twice daily there was a mean treatment difference of 50% for suppression of the overnight urinary cortisol/creatinine ratio compared with a 23% difference for suppression of 08.00 hours plasma cortisol level, suggesting that the urinary ratio may be a more sensitive measure.¹² However, the clinical relevance of such differences would require a dynamic test of adrenal reserve during longer term therapy.

In everyday clinical practice the doctor is dealing with an individual rather than an average patient, and it is therefore more relevant to look at individual responses. Thus, in the study by Clark *et al*¹² the number of low overnight urinary cortisol values was 21 out of 36 for fluticasone propionate compared with three out of 36 for budesonide over a dose range of 250 µg, 500 µg, and 1000 µg twice daily. However, it is evident on inspecting these data that there is considerable inter-individual variability in urinary cortisol suppression for a given dose of inhaled corticosteroid. This is particularly the case at lower doses of inhaled corticosteroid, making it very difficult for the clinician to predict whether a given patient will have an abnormal response. Interestingly, studies with inhaled budesonide in children have shown remarkably little evidence of basal cortisol suppression as assessed by overnight urinary cortisol/creatinine excretion.¹³ This probably reflects the shorter half life of budesonide (1.5 hours) and a greater degree of systemic clearance in children.¹⁴ A 24 hour collection for urinary cortisol metabolites may also be used to assess adrenocortical excretion rates,¹⁵ although this test is more difficult and expensive than measurement of urinary free cortisol. Since it is not available in most service laboratories in the United Kingdom, it has therefore not gained widespread acceptance.

The above screening tests may be used to detect endogenous adrenocortical activity and should be used merely as a marker of potential for systemic activity by a given dose of inhaled corticosteroid. Prolonged exposure to exogenous systemic corticosteroid results in suppressed ACTH levels and adrenocortical atrophy. In order to ascertain the clinical relevance of long term adrenal suppression it is necessary to perform a dynamic stimulation test to evaluate adrenal reserve, as this is thought to mimic the physiological response to stress. Conventionally, most clinicians have used the ACTH stimulation test, measuring the cortisol response to a high supraphysiological intravenous dose (250 µg) of synthetic ACTH analogue (tetracosactrin) given as a bolus or a six hour infusion. Unfortunately, at least in the UK, the routine use of this test is questionable as the use of Synacthen (Ciba Pharmaceuticals) is contraindicated on the data sheet for allergic or asthmatic subjects because of occasional case reports of hypersensitivity reactions, including anaphylactic shock. Whilst this is most probably due to sensitisation in individuals re-

peatedly exposed to tetracosactrin, physicians need to be aware of this limitation and have immediate access to resuscitation equipment. It has been shown that the use of much lower doses of tetracosactrin (0.5–1 µg) is as effective in producing a cortisol response, correlating well with an insulin stress test, and it may be superior to the higher dose 250 µg ACTH test in detecting subtle defects of adrenal reserve.^{16–18} Indeed, in a study of asthmatic children and adults receiving long term inhaled beclomethasone dipropionate (median daily dose 482 µg/m²) and budesonide (median daily dose 507 µg/m²) it was found that 24% of cases had an insufficient response to 0.5 µg of tetracosactrin but exhibited a normal response with 250 µg of tetracosactrin.¹⁹ This in turn suggests that, in patients receiving inhaled corticosteroids, the high dose tetracosactrin test may be associated with a substantial rate of false negative results and may be a poor predictor of clinically relevant impaired adrenal reserve. Interestingly, measurements of 24 hour urinary cortisol in the same study¹⁹ also distinguished between responders and non-responders to low dose tetracosactrin stimulation. Although the insulin stress test assesses the integrity of the whole HPA axis, it is rarely used because it is potentially hazardous and unpleasant for patients.

It would therefore appear that the low dose tetracosactrin stimulation test may be a better mimic of a physiological stress response than the high dose test, the latter being more reflective of a pharmacological response. Another way of measuring adrenal reserve is to use CRH which has the advantage of evaluating the status of the anterior pituitary gland as well as the adrenal cortex, whereas tetracosactrin only stimulates the cortex. Synthetic human CRH in a bolus dose of 100 µg has been shown to correlate well with an insulin stress test in discriminating impaired adrenal reserve in patients receiving oral prednisolone.²⁰ In a study of asthmatic patients in which placebo was compared with 1000 µg inhaled budesonide twice daily it was shown that depression of basal 08.00 hours cortisol and ACTH was associated with a comparable degree of blunting of the peak cortisol and ACTH response to stimulation with a 100 µg bolus of human CRH.²¹ The disadvantage of the CRH stimulation test is that it requires more frequent blood sampling over a 120 minute period for both cortisol and ACTH compared with a single 30 minute cortisol sample after stimulation with the short tetracosactrin test. More information is required on the relative sensitivity and reproducibility of the CRH test compared with the low dose tetracosactrin test and the insulin stress test in patients receiving long term inhaled corticosteroids, before its use can be advocated for routine clinical practice.

Another relevant question is whether the degree of HPA axis suppression wanes with time during repeated exposure to inhaled corticosteroid as a result of receptor down-regulation at the level of the hypothalamus or pituitary. In the short term, exposure to intranasal fluticasone (200 µg/day) or budeson-

ide (400 µg/day) for one week resulted in a significant reduction in serum cortisol and osteocalcin levels at 08.00 hours with little or no further change after a second week at double the dose.²² This may indicate the occurrence of desensitisation or a "floor effect" in response. Measurement of lymphocyte glucocorticoid receptor mRNA expression also showed attenuation with both drugs which essentially reached a plateau level after the first week. After a third week of washout, glucocorticoid receptor mRNA remained significantly blunted in the group receiving fluticasone but not budesonide (36% fall versus 7% fall), in keeping with more prolonged retention of fluticasone in the systemic compartment. In the same subjects, topical effects assessed on nasal mucosal biopsy samples showed a similar pattern in terms of reduced expression of glucocorticoid mRNA during treatment, although levels remained suppressed after washout with both drugs for up to six weeks.²³ These data also showed inter-individual and tissue specific variation in glucocorticoid receptor regulation.

Similar studies with these molecular probes are required in asthmatic subjects to look at the effects of inhaled corticosteroids. Whether the mRNA changes are faithfully translated into altered receptor density is also unclear in the crucial regions of the HPA axis responsible for feedback and other regions of potential glucocorticoid toxicity. In a longer term study inhaled fluticasone propionate 2 mg/day and beclomethasone dipropionate 1.6 mg/day were administered for 12 weeks to patients with moderate to severe asthma.²⁴ The degree of suppression of morning serum cortisol (08.00–10.00 hours) was found to be 132 nmol/l from baseline after four weeks on treatment and was unchanged at 12 weeks (133 nmol/l). Unfortunately, measurements were not made prior to four weeks and so it is unclear whether subsensitivity may have occurred in the initial phase of treatment. Additional complexities which may underpin inter-individual variation in the glucocorticoid response include known receptor polymorphisms, prereceptor metabolism, and interactions at the level of control of transcription of the target gene, all of which show documented variation (fig 1).

Bone metabolism

Biochemical markers of bone formation (osteoblast activity) and bone resorption (osteoclast activity) have been employed to evaluate systemic bioactivity, although markers of bone resorption tend to be less sensitive. In a study comparing various markers of bone metabolism in asthmatic children receiving 800 µg/day beclomethasone dipropionate or budesonide for two weeks it was shown that markers of collagen formation – namely, aminoterminal propeptide of type III procollagen (PIIINP) and carboxyterminal propeptide of type I procollagen (PICP) – were the most sensitive indices showing a 36% and 20% fall, respectively.²⁵ Similar data in asthmatic children receiving budesonide 800 µg/m² per day

for one month followed by 400 µg/m² for four months revealed a 28% fall in PICP and a 6% fall in osteocalcin.²⁶

In asthmatic adults treated for six weeks with beclomethasone dipropionate 1500 µg/day there was a small but significant decrease in osteocalcin (18%) and PICP (22%), whereas half the dose of fluticasone had no significant effect.²⁷ In contrast, in a two week crossover study with healthy volunteers given either budesonide 1600 µg/day or fluticasone 1500 µg/day there was a paradoxical decrease in bone resorption in terms of a reduction in carboxyterminal telopeptide of type I procollagen (ICTP) and a fall in 24 hour urinary calcium.²⁸ A similar paradoxical short term rise in PICP has been observed after treatment for four weeks with 800 µg/day budesonide although this was no longer evident after 2.5 years.²⁹

Hanania *et al* showed that a dose response effect on bone mineral density was seen in patients receiving inhaled budesonide and beclomethasone dipropionate in doses above 800 µg/day for a median duration of two years.³⁰ Toogood *et al*³¹ also demonstrated a dose response effect of inhaled beclomethasone and budesonide taken over 10 years, with a 2 mg daily dose resulting in a reduction in bone density of one standard deviation which implies a 1.5–3-fold increased life time risk of fracture resulting from osteoporosis. Their data also suggested that, in patients who were previously dependent on prednisone, the subsequent use of long term inhaled corticosteroids may result in a reduced risk of vertebral fracture in keeping with an improved benefit to risk ratio for inhaled versus oral corticosteroid therapy. Furthermore, bone density was increased in association with supplemental oestrogen therapy in postmenopausal women, suggesting a protective effect of hormone replacement therapy in this group of patients. In two separate studies of asthmatic children receiving up to 400 µg/day of beclomethasone dipropionate for six months there has been no detectable adverse effect on vertebral bone mineral density.^{32,33}

Comparison with measures of HPA axis activity suggests that bone markers are in general less sensitive at picking up systemic effects of inhaled corticosteroids. In a study with 1000 µg twice daily fluticasone propionate and budesonide in adult asthmatics there was a 45% and 17% fall, respectively, in 08.00 hours serum cortisol levels compared with a 28% and 7% fall in osteocalcin and a 9% and 3% fall in PICP.³⁴ However, in a study reported by Knuttson *et al* treatment for one week with intranasal fluticasone propionate 200 µg/day produced a 37% fall in serum cortisol levels at 08.00 hours and a 43% fall in serum osteocalcin levels at 08.00 hours, with corresponding figures for 400 µg/day aqueous budesonide of 26% and 53%.²² At first glance the latter results might be surprising, given the relatively small mucosal surface area for intranasal absorption, although this may be offset by a larger proportion of the nominal dose being deposited in the nose than in the lung (fig 2). Pharmacokinetic studies with direct instillation of

radiolabelled intranasal budesonide have shown that it exhibits approximately 100% systemic bioavailability.³⁵ However, in real life the total systemic bioavailability of the nominal dose is more likely to be 30–40% because of rapid nasociliary clearance into the throat. The data of Knutsson *et al*²² show that systemic absorption must have occurred directly from the nose where there is no first pass metabolism for either budesonide or fluticasone. This is supported by another study in patients with rhinitis where 200 µg/day of intranasal aqueous fluticasone produced a 13% fall in urinary 24 hour free cortisol and a 37% fall in the blood eosinophil count.³⁶

Growth in children

The systemic effects of inhaled corticosteroid on short term growth velocity can be assessed accurately and reproducibly using the technique of knemometry which electronically measures lower leg growth to within 0.2 mm. It is possible to show a dose response effect with inhaled budesonide (200–800 µg) on knemometry at doses which have no detectable suppression of 24 hour urinary cortisol.³⁷ In another study greater effects on knemometry were found with beclomethasone 400 µg/day and 800 µg/day than with fluticasone 200 µg/day.³⁸ These findings suggest that knemometry is a particularly sensitive marker of systemic bioactivity in children receiving inhaled corticosteroid therapy even at conventional dosage. However, it would appear that short term effects on knemometry do not predict effects on long term statural height as measured with a stadiometer.³⁹ Indeed, in a prospective 3–5 year cohort follow up of asthmatic children no evidence of growth suppression was found with inhaled budesonide at doses of 400 µg/day.⁴⁰ Doses of inhaled fluticasone and budesonide (200–400 µg/day) in children are not associated with any alteration in biochemical bone markers, suggesting that these may also be relatively insensitive measures of systemic bioactivity in children as well as adults.⁴¹ Recent case reports in children⁴² of adrenal and growth suppression in association with high doses of fluticasone propionate (>1000 µg/day) should be interpreted with caution until results of properly controlled long term studies with more conventional doses are available.

There is now increasing evidence to suggest that suppressing asthmatic disease activity in children will usually outweigh any potential systemic adverse effects of inhaled corticosteroid in terms of determining long term growth.^{43,44} It is likely that with high doses of inhaled corticosteroid in children that there may be a delay in the pubertal growth spurt, but after a subsequent “catch-up” phase in growth velocity there will be little difference in the final height.^{45,46} Furthermore, in asthmatic children with stunted growth there appears to be no evidence of any effect of disease or treatment on the growth hormone axis.⁴⁷ It is not clear, however, whether long term effects of high doses of inhaled corticosteroids in children will adversely affect bone mineralisation and

density and, in particular, studies are needed to assess what happens to these children once they enter adulthood. However, it should be emphasised that, for most children with asthma, the use of conventional doses of inhaled corticosteroid (400 µg/day or less) is an effective and safe treatment option which is very unlikely to have adverse effects on bone metabolism or growth in the long term. Even at high doses of inhaled corticosteroids the benefit to risk ratio is much better than that of oral prednisolone in doses required to achieve comparable anti-asthmatic control. High dose inhaled corticosteroids therefore remain the current preferred treatment option for the small proportion of severe cases who require them.

Conclusions

The dose related systemic adverse effects of inhaled corticosteroids can be reproducibly evaluated using measures of HPA axis activity. Although there is considerable inter-individual variability in adrenal suppression at a given dose of inhaled corticosteroid, in general the dose response curve is relatively flat below 800 µg/day in adults and 400 µg/day in children. Measurements of HPA axis activity are more sensitive than biochemical indices of bone metabolism for detecting systemic bioactivity of inhaled corticosteroids. Further work is required to evaluate whether polymorphism of the glucocorticoid receptor is responsible for the variation in response, as this may enable us to identify at risk individuals with a greater propensity for long term systemic effects. However, it should be appreciated that the measurement of adrenocortical activity represents a marker for evaluating potential systemic toxicity rather than being indicative of clinically relevant impaired adrenal function.

In everyday clinical practice there is good rationale for measuring systemic activity in patients who require maintenance therapy with higher doses of inhaled corticosteroid such as >400 µg/day in children and >800 µg/day in adults. One of the more reproducible and practical screening measurements of HPA axis activity for use in clinical practice is the overnight urinary-free cortisol collection which may be further refined by correcting for creatinine and can be used in both adults and children. Normal reference ranges should be set up for an individual laboratory for a given type of assay. Patients with an abnormally low urinary cortisol value should have this repeated on a second occasion and, if it remains lower than the normal reference range, it should be followed by some form of stimulation test to evaluate the degree of adrenocortical reserve. The use of the low dose (0.5 µg) tetracosactrin test is likely to be a more appropriate physiological stimulus and is more sensitive than the higher 250 µg dose. The CRH stimulation test is a possible alternative, but more data are required for its evaluation as a measure of impaired reserve in patients receiving long term inhaled corticosteroids.

In clinical practice a single measurement of bone density may be of value in at risk patients

– for example, postmenopausal women and those with a family history of osteoporosis – in terms of defining an initial reference point for any further decline as a possible consequence of long term inhaled corticosteroid therapy. In this respect detailed guidelines have recently been published by the American College of Rheumatology task force on the prevention and treatment of steroid induced osteoporosis.⁴⁸ However, the relevance of this to inhaled corticosteroids still remains unclear.

In addition, in asthmatic children serial measurements of height should be performed as part of the routine clinical work-up, as is the norm for any chronic paediatric illness. Indeed, there is evidence in asthmatic children that the systemic clearance of inhaled budesonide is increased, and hence even at a high dose the benefit to risk ratio is probably much better than with oral prednisolone in patients with severe asthma.

The revised British Thoracic Society management guidelines for asthma which advocate initiating treatment with a higher dose of inhaled corticosteroid to gain more rapid control followed by stepping down should, in theory, serve to emphasise the importance of always trying to achieve the lowest possible maintenance dose of inhaled corticosteroid in each individual.⁴⁹ Striving to achieve this therapeutic aim for a given patient will minimise the potential systemic toxicity burden over the long term. However, it is also conceivable that the new guidelines might instead result in patients being inadvertently left on higher doses of inhaled corticosteroid after initial control has been achieved. For those patients who require higher maintenance doses of inhaled corticosteroid it is always important to reappraise the individual anti-asthmatic dose response effect, particularly since other agents such as long acting β_2 agonists may be used as an alternative therapeutic option to increasing the steroid dose. Finally, it should be appreciated that topical corticosteroids such as budesonide and fluticasone propionate are well absorbed from the nose, as in the lung, where there is no first pass inactivation. Hence, the relative moieties of bioavailability from the lung and the nose will contribute in an additive fashion to the long term overall systemic burden.

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