

## Systemic effects of inhaled corticosteroids

The effectiveness of, and increasing indications for, the use of inhaled corticosteroids in asthma of varying severity prompts important questions to be raised relating to safety and the possibility of adverse systemic steroid effects. This concern is not new and has already resulted in guidelines on the use of spacer devices for high dose inhaled steroids in order to decrease systemic absorption. Important questions remain, however, and this issue of the journal contains two papers addressing various aspects of this problem.

The paper by Brown *et al*<sup>1</sup> in this issue of *Thorax* (pp 967-973) assesses the relative effects of equivalent high doses of beclomethasone dipropionate and budesonide in normal volunteers. Their data show clearly that, with the exception of the use of beclomethasone dipropionate without a spacer, the effects on hypothalamic-pituitary-adrenal (HPA) function are limited to short term minor suppression of serum cortisol levels which is not of sufficient magnitude to reduce 24 hour urinary free cortisol levels. Approaches to the assessment of the HPA axis in previous studies in patients receiving treatment with inhaled steroids have included measurements of morning serum cortisol levels,<sup>2,3</sup> integrated serum cortisol levels,<sup>4,5</sup> urinary free cortisol levels,<sup>5,6</sup> and serum cortisol response to tetracosactrin;<sup>5</sup> the interpretation of these studies and their possible relevance to the prediction of adverse systemic steroid effects is discussed further below. Brown *et al* also document the absence of an effect of inhaled steroids on bone metabolism as indicated by serum levels of osteocalcin, a marker of osteoblastic activity. This aspect of their study is more contentious because, although treatment with inhaled steroids has been shown to reduce serum levels of osteocalcin,<sup>7</sup> the relation of this to increased bone loss is speculative.

Kiviranta and Turpeinen<sup>8</sup> on pp 974-978 of this issue of *Thorax* provide interesting data indicating a paradoxically beneficial effect of treatment with inhaled steroids on various indices of carbohydrate metabolism, including insulin sensitivity and glucose tolerance, which they attribute to improved control of the condition with consequent reduction in endogenous stress responses. These findings are particularly important because they suggest that any adverse effects of absorbed steroids may be insignificant in comparison with the perturbations of normal physiology occurring with poorly controlled asthma. This may not, however, remain the case once asthma has been brought under control, and it is therefore appropriate to consider the accumulated evidence for potential adverse effects of inhaled steroids on the HPA axis, bone, and carbohydrate metabolism, and also on linear growth in children.

### HPA suppression

The effects of inhaled steroids on the HPA axis may be important for two reasons. Firstly, it is clearly important to ensure that adrenal reserve and particularly stress-induced steroid responsiveness are not compromised; fortunately this does not appear to be the case.<sup>9</sup> The second consideration relates to the possible relation between various indices of HPA suppression and adverse tissue effects of inhaled steroids. In this context it is useful to remind ourselves of the well documented

differential effects of oral steroids on tissues and on the HPA axis which are used to therapeutic advantage; single morning or alternate day regimens are designed to achieve a pharmacological steroid effect while minimising overnight suppression of ACTH secretion whereas reversed circadian steroid regimens, used in various androgen excess syndromes, have the opposite effect. While any degree of suppression of endogenous steroid secretion is indicative of systemic absorption of inhaled steroid, this will only become pathologically important if the quantity absorbed is substantially in excess of the quantity suppressed. In fact it is possible to hypothesise an alternative situation in which the effect of inhaled steroid may be greater if, by virtue of dose timing, suppression of endogenous secretion does not occur and therefore absorbed steroid is additive.

The use of different methods of assessing the HPA axis does not help to get round this problem since they differ only in the precision with which they document subtle suppression of the axis but can neither confirm nor refute excessive tissue exposure to steroids. Morning cortisol measurements, if more than 350 nM, usually indicate intact pituitary adrenal reserve<sup>10</sup> but must be interpreted with caution in the poorly controlled asthmatic patient who may show a stress-induced increment masking some degree of HPA suppression by treatment. Short tetracosactrin tests provide a fairly crude assessment of readily releasable cortisol, and by inference of prevailing ACTH secretion, and are most useful in indicating the probability of an intact steroid response to stress.<sup>11</sup> Conclusions concerning adverse effects of inhaled steroids on tissues must therefore be based on direct observations of specific areas including bone, carbohydrate metabolism, and growth.

### Effects on bone and carbohydrate metabolism

The interpretation of previous reports of reduced bone density in asthmatic patients receiving high dose inhaled steroids<sup>12</sup> is rendered difficult by the confounding effect of systemic steroid treatment. Thus although treatment with inhaled steroids has been associated with modest reductions in bone calcium content,<sup>13</sup> measurements of vertebral bone density by single energy computed tomography of the lumbar spine in well categorised groups of patients who had received either intermittent or continuous systemic steroids in addition to inhaler therapy have shown similar reductions compared with a control group of asthmatic patients. Furthermore, the calculated fracture risk in these patients appeared to be very low. The same study did not show any differences in markers of bone formation, including osteocalcin, or in urinary pyridinoline and deoxypyridinoline levels, sensitive indices of bone collagen breakdown,<sup>14</sup> between the three groups of patients. These results indicate, firstly, that any compensatory increase in bone formation does not appear to persist after steroid-induced bone loss, and secondly that, if bone resorption is continuing at an increased rate, this is sufficiently slow to be beyond the resolution of our most sensitive indices of bone loss.

Whether there is a secondary effect of steroids on osteoblast function is as yet unclear. Studies documenting acute and reversible reduction of serum osteocalcin

concentrations in patients on inhaled steroids<sup>7,15</sup> suggest that this is so, but extrapolation of these findings to the effect of steroids on bone loss is not justified on present evidence. On balance there is no definite evidence that treatment with inhaled steroids may be solely responsible for increased bone loss, although it is probable that subtle changes do occur. Future studies in this area will necessitate longitudinal follow up of patients receiving high dose inhaler treatment, carefully categorised in relation to previous treatment with systemic steroids, with assessment of bone density by dual energy x ray absorptiometry in addition to biochemical measurements.

Changes in indices of carbohydrate metabolism and particularly insulin concentrations in subjects receiving inhaled steroids tend towards decreased insulin sensitivity.<sup>16</sup> It is improbable, however, that this is ever clinically relevant except perhaps in patients with subclinical diabetes mellitus. Furthermore, as Kiviranta and Turpeinen<sup>8</sup> have indicated, these effects may be substantially outweighed by the adverse stress-induced changes in insulin sensitivity associated with uncontrolled asthma which may be theoretically exacerbated by treatment with  $\beta$  agonists.

### Effects on growth

The possible effects of inhaled steroids on linear growth in asthmatic children have been extensively studied; although no definite consensus has emerged there is general agreement that poor control of the condition is the major determinant of poor growth.<sup>17,18</sup> Some studies have shown an acute reduction in lower leg growth velocity in patients receiving inhaled steroids,<sup>19</sup> whereas longer term studies have in general confirmed the safety of treatment in this respect.<sup>18,20</sup> In fact optimising asthma control may be associated with an increment in growth rate<sup>21</sup> although the immediate prepubertal growth velocity may be more vulnerable to high doses of inhaled steroids.<sup>20</sup> The clear message would seem to be that adequate control of the asthma is paramount, that inhaled steroids do not substantially retard growth, but that the lowest effective dose should be used particularly in the peripubertal period.

### Conclusions

There is ample evidence that treatment with inhaled steroids is associated with some degree of systemic absorption. However, to date there is no convincing evidence that this gives rise to any of the well known clinical sequelae of corticosteroid excess and it is improbable that subtle effects will be documented with certainty, bearing in mind that patients receiving high doses of inhaled steroids will have had variable exposure to systemic steroid treatment. While patients and clinicians will be reassured by those studies which show that the deleterious effects of poorly controlled asthma exceed the theoretical risks of treatment with inhaled steroids, it is nonetheless important that the lowest effective doses should be used and measures taken to limit systemic absorption where possible.

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