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Assessment of systemic corticosteroid activity

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Many studies have reported suppression of the hypothalamic-pituitary-adrenal (HPA) axis following use of corticosteroids. Thus, HPA axis suppression has been used to assess the systemic bioavailability of inhaled corticosteroids, permitting *in vivo* microgram per microgram comparisons between various compounds (1–4). A number of factors, however, influence HPA-axis suppression with inhaled corticosteroids (Table 1). The potency of the compound, dosage and duration of treatment all play a role in action on the HPA axis, while a confounding factor in many studies is also prior long-term, oral steroid use (5). In addition, the study population is important, since healthy volunteers absorb more of an inhaled dose into the lung compared with asthma patients, possibly because of different airway patency. Thus, at comparable inhaled doses, greater systemic bioavailability from the lung has been shown in studies in healthy volunteers, compared to asthmatics. It is also known that there is significant inter-individual variability of side-effects in different populations taking a given dose of a glucocorticoid. However, it is not clear whether this variability reflects pharmacokinetic, pharmacodynamic and/or genetic differences.

Tests of Adrenal Function

Adrenal function tests (6) can either assess basal secretory function (morning serum cortisol, 24-hr serum cortisol profile, or 24-hr urinary free cortisol) or involve stimulation testing (e.g. short [60-min] or long [6–8 hr] exogenous adrenocorticotrophic hormone [ACTH], metyrapone or insulin-induced hypoglycaemia). Holt *et al.* (7) examined the effects of beclomethasone dipropionate (BDP), 2000 μg/day for 14 days, in 12 healthy volunteers using 4 different tests of HPA axis function. It was found that urinary free cortisol and single-dose metyrapone tests were the most sensitive to assess the acute effects of inhaled corticosteroids on HPA axis function. The ACTH test was the least sensitive, but this might be expected as 14 days is probably not long enough to cause adrenocortical atrophy.

When analysing the results of HPA axis suppression with inhaled corticosteroids, it is important to define the study end-points as well as the clinical implications of the findings. For example, even though there may be statistically significant HPA axis suppression, the functional status of the HPA axis in most instances is normal. Low-medium dosing with inhaled corticosteroids results in physiological perturbation and partial suppression of HPA axis function; clinically relevant changes would only be expected, however, when there is complete HPA suppression (adrenocortical atrophy) following high dose, long-term treatment.

The clinical relevance of HPA axis suppression is illustrated in a study following single-dose inhalation of fluticasone propionate (either 250, 500 or 1000 μg) or budesonide (800 μg) at 22.00 h in healthy volunteers (8). Plasma cortisol profiling was performed every 2 hours, morning cortisol levels were measured and areas under the curve (AUC) were calculated. The study design exaggerated HPA suppression with fluticasone propionate, as high doses were used and inhalation was administered at the end of the day. However, the results illustrate several important points. First, there was a dose-related reduction in mean morning cortisol levels and AUC following evening administration of fluticasone propionate. Second, consistent with *in vitro* studies, fluticasone propionate was found to be about twice as potent as budesonide on a microgram per microgram basis. Finally, and possibly of considerable clinical relevance, cortisol suppression was only partial at the low and medium doses of fluticasone propionate. Hence, from a physiological standpoint, the inhaled

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TABLE 1. Factors influencing the incidence of adrenal suppression with inhaled corticosteroids

- Characteristic of specific compounds
- Dose frequency and timing of administration
- Duration of treatment
- Prior oral steroid
- Population studies:
  Healthy vs. patients with asthma
  Children vs. adults
- Significant inter-individual variability

drug supplies a small proportion of the daily glucocorticoid requirement, while endogenous cortisol production is largely preserved.

High-dose Inhaled Corticosteroids and HPA Axis Suppression

Brown *et al.* (9) evaluated morning cortisol, urinary free cortisol and short ACTH stimulation testing in 78 asthma patients who had been treated with a median dose of 1600 μg of either BDP or budesonide for a duration of 13 months. Approximately 30% of these patients had received prior systemic steroids, but had not received such treatment within 6 months of HPA axis evaluation. The results of this study showed that 80% of patients did not exhibit HPA axis suppression. In the remaining 20% of patients, HPA axis suppression was correlated with the duration of high dose inhaled corticosteroids treatment, as well as prior systemic steroid use. It is possible that in this study, patients with long-term steroid exposure could have had suppressed HPA axis function, which was sustained by the high-dose inhaled corticosteroid treatment.

Summary

The potency of the inhaled corticosteroid, dose, duration of treatment, and the study subject receiving treatment all play a role in the effects observed on the HPA axis. At low/medium doses of inhaled corticosteroids, where there is minimal/modest HPA axis suppression, there should be no risk of adrenal crisis even under stressful conditions (6). Thus, the risk of acute adrenal insufficiency, culminating in adrenal crisis, in patients taking inhaled steroids is extremely unlikely.

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