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Editorial

Inhaled corticosteroids and the hypothalamic–pituitary–adrenal (HPA) axis: do we understand their interaction?

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Introduction

Inhaled corticosteroids (ICS) have a very favourable ratio of topical *vs.* systemic activity. To assess the systemic availability and/or potency of different types of ICS, measurements are used that reflect the function of the hypothalamic–pituitary–adrenal (HPA) axis (1). The most sensitive measurements of the function of the HPA axis include measurement of cortisol levels in multiple blood samples with frequent sampling, particularly overnight or for 12–24 h, measurement of cortisol production through steroid measurements in urine collected overnight or for 24 h, and stimulation tests with adrenocorticotropic hormone (ACTH) (2,3).

Using these tests, it has been shown that ICS may, in a dose-dependent manner, reduce cortisol secretion into serum [reflected in a reduced area under the concentration-time curve {AUC} and overnight or 24-h urinary-free cortisol (UFC) excretion] and total cortisol metabolite output. Stimulation tests using supraphysiological dosages of 250 or 500 μg 1·73 m^{-2} ACTH usually do not reveal changes in the function of the HPA axis. In contrast, the response to a low (physiological) dose of ACTH (0·5 μg 1·73 m^{-2}) was dampened in ~30% patients on treatment with beclomethasone dipropionate (BDP) or budesonide (BUD) (daily dose ~500 μg m^{-2}) (4). Thus, ICS appear to downregulate the production and secretion of cortisol, reflecting their systemic activity. This, however, has no clinical significance in the vast majority of adult patients treated with these drugs at recommended doses.

There are two routes by which ICS can enter the systemic circulation. The majority of the inhaled fraction which is delivered into the lung easily enters the pulmonary circulation and is systemically available before inactivation in the liver takes place. The fraction deposited in the oropharynx is swallowed and its systemic availability is determined by the gastrointestinal absorption and first-pass effect in the liver. Since the fraction retaining activity following oral absorption and first-pass metabolism is very low with currently used ICS [BDP ~20%, BUD ~11%, and fluticasone propionate (FP) ~1%], most of the ICS systemically available is derived from absorption via the airways. As a consequence, one would expect that the greater the pulmonary deposition of a particular ICS, the higher the serum levels of that ICS and metabolites, and thus the greater the suppression of cortisol secretion would be. Differences in these effects among ICS are likely to be explained by, for example, differences in lipophilicity, receptor binding kinetics, and/or plasma elimination time.

Recent data, however, suggest that this relationship between serum levels of ICS and changes in serum cortisol levels is not that straightforward. Chlorofluorocarbon (CFC) containing pressurized aerosolized medications have been reformulated, using hydrofluoroalkanes (HFA) as propellants (5). The reformulated BDP (HFA-134a-BDP) represents a change from the current CFC suspension formulations to that of a solution formulation. This change has resulted in an HFA-134a-BDP aerosol with a lower median mass aerodynamic diameter (MMAD) in comparison with CFC-BDP, being ~1·1 μm instead of ~3·5–4 μm in CFC-BDP (6). The respirable mass of HFA-134a-BDP is ~52% compared with ~35% for the CFC-BDP (7). In line with these *in vitro* characteristics, the lung deposition of HFA-134a-BDP is much higher (i.e. ~54% of delivered dose) compared with ~9% with CFC-BDP (8).

As a consequence, serum concentrations of total beclomethasone [i.e. unchanged BDP, beclomethasone-17-monopropionate (17-BMP), beclomethasone-21-monopropionate (21-BMP), and beclomethasone-free base (BOH), referred to as total-BOH (9)] following HFA-134a-BDP inhalation are increased compared with a similar dose of CFC-BDP. HFA-134a-BDP in a dose of 400 μg resulted in a maximal serum total BOH concentration (C_{max}) of 1191 pg ml^{-1} *vs.* 410 pg ml^{-1} for 400 μg CFC-BDP, and a serum AUC of total-BOH of 4962 pg h ml^{-1} *vs.* 2092 pg h ml^{-1} for CFC-BDP (10). There was also a significant difference in serum T_{max} of total-BOH; 0·8 h after HFA-134a-BDP *vs.* 2 h for CFC-BDP.

Thus, the enhanced lung deposition of HFA-134a-BDP results in more than doubling of serum total BOH concentration. There is no linear relationship between

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serum total BOH concentrations and 24-h UFC concentrations; doubling of the AUC from 2000 pg h ml^{-1} to 4000 pg h ml^{-1} results in only about a 10% reduction in the 24-h UFC (9). Even such a reduction of cortisol production, however, was not observed after HFA-134a-BDP. Two weeks of inhalation of HFA-134a-BDP 800 μg daily reduced UFC by (median) $\sim$38% *vs.* $\sim$48% after inhalation of CFC-BDP 800 μg daily (P = NS) (11). Morning serum cortisol levels and the response to a conventional (high) dose of ACTH were also not different among HFA-134a-BDP and CFC-BDP-treated patients.

Before discussing potential explanations, we briefly discuss the regulation of adequate systemic cortisol levels by the HPA axis.

Features of the HPA axis

In a 24-h period serum cortisol levels change most during the night with the highest levels between 06:00 and 10:00 hours and the lowest levels at midnight [Fig. 1(a)]. The timing and frequency of sampling influences the extent to which this is accurately portrayed. In contrast to the representation of the diurnal rhythm as often published, blood sampling at 10-min intervals shows that three or four peaks of increasing amplitude and 90-min frequency may be defined. The actual peak concentrations may be higher than recorded, conversely nadir concentrations may be lower. The actual pattern is a sawtooth curve and follows serum ACTH concentrations (12,13). Blood samples need to be taken even more frequently (2-min intervals) to define ACTH pulsatility because of the short half-life of this peptide hormone.

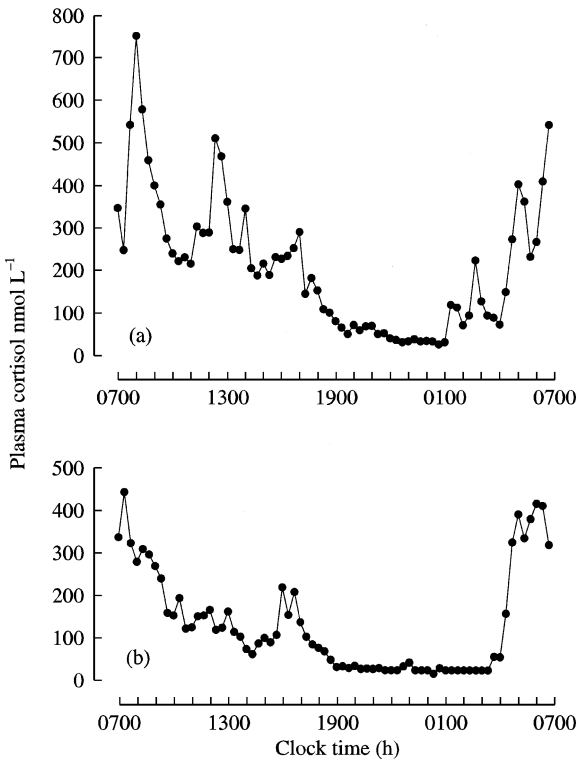

Fig. 1. Course of plasma cortisol levels during a 24-h period. Each dot represents a separate blood sample. (a) A healthy subject without any medication; (b) an asthmatic subject on ICS.

In many studies, frequent blood samples have been taken and the mean or integrated cortisol concentration was calculated. Typically mean serum cortisol levels are 140–400 nmol l^{-1} in normal subjects but 50–300 nmol l^{-1} in ICS-treated patients. Instead of a normal pattern of several peaks of cortisol during the night a patient taking ICS shows a delay in the time of onset of pulsatility and a reduction in the number of peaks up to mid-morning [Fig. 1(b)].

ACTH regulates cortisol secretion in three, partly interrelated ways (i) The *circadian rhythm* is controlled by a biological clock in the midbrain, and is mediated by variations in corticotrophin releasing factor (CRF) from the hypothalamus. This hormone regulates the synthesis and release of ACTH by the basophilic cells of the anterior pituitary. ACTH is released in around 30–50 secretory bursts per 24 h. The magnitude (amplitude) of the bursts, but not the frequency, varies during the day, with a 3·8-fold higher amplitude at 08:00 hours compared to midnight (12). This pattern is closely followed by serum cortisol levels. (ii) *A negative feedback* system regulates that CRF, ACTH and cortisol secretion are reduced when serum corticosteroid levels are too high, and, conversely, increased when serum corticosteroid levels are too low. (iii) *Stress* accounts for a rapid increase in CRF, ACTH and cortisol secretion, irrespective of the time of day or state of the feedback system.

The interaction between ACTH and steroidogenesis has a fast and a slow component. The acute effect, occurring within minutes, comprises the conversion of cholesterol to δ5-pregnenolone, the initial and rate-limiting step in cortisol biosynthesis. The chronic effects, requiring hours or days, involve increased synthesis of most of the enzymes required for the steroidogenesis. ACTH-mediated secretion accounts for $\sim$70% of total cortisol production. The remaining part is controlled by neurotransmitters, neuropeptides, inflammatory and other cytokines, growth factors and lipid mediators (3).

Cortisol in the circulation is largely bound to cortisol binding globulin (CBG), and to a lesser extent, to albumin. At cortisol concentrations around 400 nmol l^{-1}, only 3% of the cortisol is free in plasma. Most methods for the quantitative determination of cortisol in plasma measure the total concentrations. Free cortisol in plasma is filtered at the kidney glomerulus and is not reabsorbed by the tubules. Cortisol is normally excreted in the urine at a rate of less than 200 nmol day^{-1}. Normal concentrations of free cortisol in urine are often less than 100 nmol l^{-1}, especially in children. At these low levels (either due to normal variation or suppression by steroids) the immunoassays can be imprecise.

Hepatic metabolism of cortisol is largely by reduction, after which the steroid metabolites are conjugated before excretion in the urine. The sum of the excretion rates of individual cortisol metabolites in the urine for 24 h is an

index of production rate and the output comes close to the production rate of cortisol (14). The daily production rate of cortisol is 6–9 mg m^{-2} body surface area when measured using stable isotope dilution techniques. In blood, cortisol has a half-life of 25–35 min.

Basal adrenal activity in patients is often assessed by a single morning plasma concentration. Due to the circadian rhythm in cortisol secretion as described above, extended period measurements such as repeated plasma cortisol levels over 24 h or during the night, free cortisol excretion in the urine, and urine excretion rates of cortisol metabolites are more sensitive but rather impractical measures. One-time measurement of plasma cortisol concentration should only be used as a screening test in individual patients because of quite large inter-individual variations in circadian cortisol rhythms (15). When glucocorticoids are administered in the evening, the nocturnal pattern may be shifted into the day. Such variations may invalidate one-time measurements in clinical trials. The pattern of results from repeated sampling of blood or urine over time, however, is very reproducible in individual subjects and influences from inter-individual variations in diurnal rhythms are reduced. Blood samples need to be taken at a minimum of 15-min intervals to be able to define the pulses of cortisol. The use of integrated cortisol results is not a very sensitive test of adrenal function. More of the samples throughout the 24-h period have results below 300 nmol l^{-1} than above that concentration and these results dilute out the integrated level.

A plasma cortisol concentration higher than 200 nmol l^{-1} at 08:00 hours makes adrenal insufficiency unlikely, and further testing may not be needed. If plasma cortisol is below 200 nmol l^{-1} and fails to respond to a pharmacological dose of 250 μg ACTH, then a prolonged ACTH test should be performed (16). The potential risk of anaphylactic reactions to ACTH testing is very low.

Nocturnal and 24-h UFC excretion in the urine benefit from being non-invasive measures but are inconvenient for the patient to perform. The difference, if any, between the sensitivity of the two measures is small (2). Some reports have found correction for creatinine to be useful, but rigorous comparisons with measures of absolute UFC concentrations have not been reported (17,18). However, the sensitivity of measures of UFC excretion appears to depend on quite a small dose window. When cortisol secretion is suppressed, an initial reduction in UFC excretion occurs, but a state is reached in which cortisol binding proteins in the plasma are not saturated and the free cortisol and hence the free cortisol output in the urine will be low. At such concentrations there is also an increase in the imprecision of detection of cortisol in the urine. Together with a decrease in the analytical specificity of cortisol measurement this may explain why dose related effects may not be detected (19,20). These problems can be avoided by measuring the excretion of cortisol metabolites in 24-h urine. This measure combines non-invasiveness with a high sensitivity in the assessment of dose-related suppressive effects of topical glucocorticoids (21).

In clinical trials, adrenal stimulation is most frequently performed by ACTH. An increase in the plasma cortisol concentration after i.v. or i.m. administration of ACTH (ACTH-1-24, Synacthen) 250 μg to above 500 nmol l^{-1}, or an increment in the plasma cortisol from 0 to 30 min of 220 nmol l^{-1} are usually regarded as acceptable responses to adrenal stimulation. It is important to be aware that standard stimulation tests of the HPA axis do not reflect cortisol responses to minor stress. The adrenal gland is stimulated for probably a day after such a pharmacological dose of the peptide hormone. When lower doses of Synacthen are used (typically 500 ng) the test can be reproducible (22) although care must be taken in the dilution and delivery of the hormone to obtain repeatable data. Doses of ACTH 500 times lower than the conventional test dose of 250 μg are more sensitive in detection of suppressed responses in adults on ICS (see above) (4,22,23).

Although childhood cases of clinical glucocorticoid excess (24,25) and subnormal HPA stimulation results in patients on high doses of ICS (26) have been reported, there is no evidence that ICS in recommended doses have caused clinically significant HPA-axis insufficiency. Adrenal stimulation tests may therefore only be needed in patients on concomittant long term systemic glucocorticoids or on high doses of ICS. Whether there may be a place for adrenal testing in patients on concomittant insufflated and inhaled preparations remains to be evaluated.

Impact of ICS on the HPA axis

Now, the question is how the HPA axis reacts to ICS that enter the systemic circulation. It is well established that exogenous glucocorticoids suppress cortisol production by feedback mechanisms that act simultaneously on the hypothalamus and the pituitary in a similar way to endogenous glucocorticoids (3). There is also a possible direct effect on the adrenal cortex itself. After i.v. infusion of a dose of a steroid there is a triphasic feedback on ACTH secretion (27). The fast reaction occurs within minutes and continues for about 20–30 min. Increasing the administered dose only increases the suppressive effect on ACTH secretion but does not affect the duration of this reaction. The intermediate reaction occurs after 30–40 min and continues for 18–36 h. This reaction depends on the dose of the steroid administered. Slow feedback, occurring after days, involves reduction of the pituitary ACTH content by reducing the levels of mRNA encoding for the ACTH precursor molecules.

Coming back to the initial issue, being the cause of a difference in reaction of the HPA axis to HFA-134a-BDP and CFC-BDP, several potential mechanisms can be formulated, which either can be rejected based upon the current literature, or have to be explored.

ARE THERE DIFFERENCES IN THE ICS METABOLIC PRODUCTS ENTERING THE SYSTEMIC CIRCULATION?

BDP is metabolized in humans primarily to 17-BMP, 21-BMP and beclomethasone-free base (BOH). Studies with

human lung steroid receptors have shown that the highest binding affinity resides with 17-BMP. Pharmacokinetic studies of inhaled HFA-134a-BDP have confirmed that BDP is converted to 17-BMP within minutes. 17-BMP circulates in the serum, for up to 12 h at higher levels than unchanged BDP or other metabolites. Further metabolism to BOH occurs primarily in the liver. One might expect different metabolic profiles between HFA-134a-BDP and CFC-BDP, i.e. HFA-134a-BDP gives more 17-BMP in the systemic circulation (after absorption from the lungs), while CFC-BDP gives mainly BOH in the systemic circulation after oral absorption and first pass metabolism in the liver (28). The question then remains whether HPA axis reacts in a different way to these different metabolite profiles.

DO DIFFERENCES IN CONCENTRATION-TIME RELATIONSHIPS AFFECT THE HPA AXIS IN A DIFFERENT WAY?

The question arises whether the feedback loop works like a thermostat in that once glucocorticoid activity reaches a certain level secretion is stopped and not started again until the critical level is attained or is it more dependent on the direction and rate of change in activity. It may be hypothesized that a shorter 'rise time' (i.e. T_{max}) gives less input to the HPA axis to change its output of CRF and ACTH.

ARE THERE DIFFERENCES IN RECEPTOR AFFINITIES AMONG THE ICS METABOLITES

Perhaps because of the different lipophilicity associated with each metabolite, the receptors for the systemic effect of BDP have the opposite binding affinities to that observed for clinical efficacy, i.e. BOH > > 17-BMP. If this were the case, then HFA-134a-BDP, because it deposits more 17-BMP in the lungs and produces less BOH, would indeed be expected to have an improved therapeutic index over a product that deposits less 17-BMP in the lungs and produces more BOH.

It is clear that only incomplete answers can be given on the questions stated above. The data, however, show that our straightforward concept of increased systemic effect on the HPA axis as a result of increased pulmonary deposition and subsequent increased serum levels of metabolites of BDP needs to be reconsidered.

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