Inhaled corticosteroid therapy reduces the early morning peak in cortisol and aldosterone

Andrew M. WILSON, Erika J. SIMS, Allan D. STRUTHERS and Brian J. LIPWORTH
Department of Clinical Pharmacology and Respiratory Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, Scotland, U.K.

ABSTRACT

1. As mineralocorticoid and adrenocorticoid activity are both under the diurnal control of adrenocorticotropic hormone secretion, we aimed to evaluate whether the normal circadian rhythm of cortisol and aldosterone secretion was suppressed by inhaled corticosteroid therapy.

2. Ten normotensive patients with mild–moderate asthma, mean age 24.0 (S.D. 9.8) years and mean arterial pressure 90.7 (9.8) mmHg, were studied in a double-blind, randomized crossover design comparing placebo with fluticasone propionate, 1000 µg administered twice daily at 08:00 h and 20:00 h. After 5 days of repeated dosing at steady state, measurements were made of plasma cortisol and aldosterone at midnight and 08:00 h.

3. With placebo there was a significant (P < 0.05) difference between cortisol values at 08:00 h (588.6 ± 83.8 nmol/l) and midnight (109.6 ± 35.0 nmol/l), whereas after treatment with fluticasone propionate there was no significant difference between levels at 08:00 h (143.3 ± 57.4 nmol/l) and midnight (64.3 ± 22.3 nmol/l). For cortisol at 08:00 h there was also a significant (P < 0.05) difference between placebo and fluticasone propionate. The same pattern was observed for aldosterone. Plasma aldosterone levels at 08:00 h after treatment with placebo (129.6 ± 30.9 nmol/l) were significantly different (P < 0.05) to those seen at midnight (40.4 ± 6.2 nmol/l). After treatment with fluticasone propionate, there was no significant difference between levels at midnight (55.4 ± 11.7 nmol/l) and 08:00 h (64.8 ± 12.7 nmol/l).

4. These results show that inhaled corticosteroid therapy abolishes the circadian rhythm of aldosterone and cortisol secretion. This may have possible implications for patients taking inhaled corticosteroids in terms of the beneficial cardiac effects of suppressing early morning aldosterone.

INTRODUCTION

Inhaled corticosteroids are regarded as first-line anti-inflammatory therapy for asthma and are frequently used in the treatment of chronic obstructive pulmonary disease (COPD) [1,2]. Although inhaled corticosteroids have a more favourable therapeutic index than oral corticosteroids, they have been shown to cause systemic adverse effects even at clinically recommended doses [3]. Of the many adverse effects of corticosteroids, the changes in adrenocortical function have been the most widely investigated and documented [4].

Both cortisol and aldosterone are known to exhibit a normal diurnal circadian rhythm, with peak levels occurring in the morning as a result of increased adrenocorticotropic hormone (ACTH) secretion [5]. Although the predominant factor controlling aldosterone secretion during the day is angiotensin II, it is thought that the...
early morning rise in aldosterone is mainly due to ACTH secretion, especially as the rise occurs before patients get up in the morning. Furthermore, the morning rise in aldosterone levels may well be contributing to the high frequency of myocardial ischaemia and sudden cardiac death which has been well described at this time of day [6]. This is because aldosterone has now been clearly shown to have adverse autonomic effects in the early morning [7]. So marked are these autonomic effects that spironolactone even reduces the normal early morning increase in heart rate [7], which in turn should reduce early morning ischaemia. This effect on heart rate is thought to be because aldosterone augments sympathetic activity and blunts parasympathetic activity [7,8], and this pattern of autonomic effects is particularly malignant since the parasympathetic system normally acts to suppress the arrhythmogenic effects of sympathetic stimulation [9].

Fluticasone propionate (FP) is a new potent topical corticosteroid which is used for the treatment of asthma and allergic rhinitis. Previous studies have shown that at clinically recommended dose levels, significant adrenal suppression occurs whether given by the inhaled [10,11] or intranasal [12] route. However, the suppressive effects of inhaled corticosteroids on aldosterone secretion have not previously been investigated even though the early morning rise in aldosterone is thought to be induced by ACTH and to mediate harmful effects. It was therefore hypothesized that if inhaled corticosteroids cause suppression of the hypothalamic–pituitary–adrenal axis sufficient to cause suppression of cortisol, then similar effects may be seen on aldosterone. The purpose of this study was to prove or disprove the concept that inhaled steroids might suppress early morning levels of aldosterone.

**METHODS**

**Patients**

Ten patients (five male, five female) with stable mild to moderate asthma, with a mean age of 25.9 (9.8) years and a mean forced expiratory volume in 1.0 s of 84.0 (12.6) % of predicted value, were recruited into the study. All patients had asthma according to the criteria of the American Thoracic Society and were receiving inhaled corticosteroid at doses of up to 1200 µg/day. The patients were all normotensive with a mean arterial blood pressure of 92.4 (9.8) mmHg. No patient had received oral steroids or antihypertensive medication within the previous 6 months. All subjects had a normal full blood count and biochemical profile (including creatinine, urea and electrolytes, liver function and bone group tests) and normal urinalysis. Approval for the study was obtained from the Tayside Medical Ethics Committee and all patients gave written informed consent.

**Study design**

A randomized, double-blind, placebo-controlled, crossover design was used. Patients were randomized to receive either inhaled fluticasone propionate or matching placebo first in balanced blocks. Fluticasone propionate (Fluticotide™, 125 µg per puff, Glaxo–Wellcome U.K., Uxbridge, U.K.) was given at a dose of 8 puffs twice daily (i.e. 2 mg/day) for 5 days. For the duration of the 5-day placebo arm patients were given a matching placebo meter-dose inhaler, 8 puffs twice daily, in order to make the study double blind. Between each of the treatment or placebo periods there was a 12-day period of crossover where patients received their usual medication. Fluticasone propionate was given as the highest licensed dose and prescribed according to manufacturer’s labelling. In addition, instructions were given to discharge inhalers twice before use on each occasion and all inhalations were followed by mouth rinsing.

Before the study and at each visit, subjects were given detailed tuition by a third party in how to use their metered dose inhalers, according to the manufacturer’s package insert instructions. Co-ordination between inspiration and actuation was also checked at every attendance with the use of a Vitalograph aerosol inhalation monitor device (Vitalograph, Bucks, U.K.). Subjects received a detailed written instruction sheet to follow while taking their inhaler at home and a simple tick chart was used as an aid to compliance.

**Measurements**

The subjects were admitted to the investigation ward from 22:00 h on the fourth day of each treatment period until 08:30 h on the fifth day. Subjects continued to take their study medication as usual on the fourth and fifth treatment days. A cannula was inserted into the antecubital fossa vein on arrival at the ward, to permit blood sampling, and was flushed with heparinized saline with dead space removal before each sampling. Blood samples were taken for measurement of serum cortisol and aldosterone at midnight and 08.00 h. Subjects rested, lying supine, for at least 30 min before samples were taken. All blood samples were taken within a 5-min window for both time points.

**Assays**

All assays were performed in duplicate and in a blind fashion by a separate technician. Serum cortisol excretion was measured using a commercial RIA kit with no cross-reactivity for fluticasone propionate (Immudagnostic Systems Ltd, Boldon, Tyne and Wear, U.K.). The coefficient of variation for analytical imprecision for serum cortisol was 7.1 % for within assay and 7.2 % for between assay. The serum aldosterone was measured using a commercial RIA kit (Sorin Biomedical Diagnostics, Vercelli, Italy). The coefficient of variation was 4.0 % for within assay and 4.8 % for between assay.
Statistical analysis
The study was designed with a sample size of 10 with 80% power ($\beta$ error = 0.2) to detect a 20% difference in serum cortisol (the primary end-point) between placebo and FP with the $\alpha$ error set at 0.05 (two-tailed). All data were analysed using a Statgraphics software package (STSC Software Group, Rockville, MD, U.S.A.). Comparisons between placebo and FP for both midnight and 08:00 h time-points were made by an overall multifactorial analysis of variance, with subject, treatment and period as factors. Duncan’s multiple-range testing was then applied to assess where there were significant differences between treatments. The Duncan’s multiple-range test was set with 95% confidence intervals and hence any significant differences between treatments are reported only at the $P < 0.05$ level.

RESULTS

Serum aldosterone
The mean and individual values of aldosterone are presented in Figures 1 and 2 respectively. For aldosterone at midnight, there was no significant difference between placebo (PL) (40.4 $\pm$ 6.2 nmol/l) and FP (55.4 $\pm$ 11.8 nmol/l). However, for aldosterone at 08:00 h, there was a significant ($P < 0.05$) difference between PL (129.6 $\pm$ 30.9 nmol/l) and FP (64.8 $\pm$ 12.7 nmol/l). With PL there was a significant difference between aldosterone values at 08:00 h and midnight (95% CI 30.7 to 147.6), but with FP there was no significant difference between values at 08:00 h and midnight (95% CI for difference $-23.0$ to 41.8).

Serum cortisol
The mean values of cortisol are presented in Figure 1. Compared with PL (109.6 $\pm$ 35.0 nmol/l) there was suppression with FP (64.3 $\pm$ 22.3 nmol/l) for cortisol at midnight, although this was not significant. However, for cortisol at 08:00 h, there was a significant ($P < 0.05$) difference between PL (588.6 $\pm$ 83.8 nmol/l) and FP (143.3 $\pm$ 57.4 nmol/l). With PL there was a significant difference between cortisol values at 08:00 h and midnight (95% CI for difference 306.5 to 651.4), but with FP there was no significant difference between values at 08:00 h and midnight (95% CI for difference $-93.4$ to 251.48).

DISCUSSION
Our study has confirmed that inhaled FP causes significant suppression of 08:00 h cortisol compared with PL. The level of 08:00 h cortisol with FP was similar to midnight levels with PL. In other words, FP eliminated the normal 08:00 h peak in cortisol concentration which occurs with the normal diurnal circadian rhythm of cortisol secretion. Although there was suppression of midnight cortisol levels with FP compared with PL, this was not significant. It would need a much larger study to determine differences in midnight cortisol as the level is normally very low. This highlights the rationale for measuring peak cortisol levels at 08:00 h when attempting to determine cortisol suppression with exogenous corticosteroid therapy.

The new finding in this study is that the effects of FP on cortisol were mirrored by those on aldosterone. Indeed the main aim of this study was as a ‘proof of concept’ study to see if inhaled steroid really does suppress the early morning increase in aldosterone. In this respect, FP also caused a dramatic suppression of 08:00 h aldosterone secretion when compared with PL. There was no significant difference between 08:00 h aldosterone levels with FP and the midnight levels with PL, indicating that FP also abolished the normal diurnal rhythm of aldosterone secretion.

Having proved the concept that therapeutic doses of inhaled corticosteroids suppress the morning rise in
aldosterone level, we need to address the clinical relevance of this phenomenon. In which group of patients will this be clinically relevant? The obvious candidates are those suffering from COPD as inhaled corticosteroids form the cornerstone of their treatment. This phenomenon is particularly important to patients with COPD for two reasons. Firstly, they often have covert ischaemic heart disease as smoking is an important aetiological factor to both diseases. Secondly, patients with cor pulmonale due to hypoxaemic COPD have increased aldosterone levels [13] due to diuretic therapy. These patients are at risk of myocardial ischaemia and have increased aldosterone levels.

This phenomenon could also be relevant to patients with congestive heart failure, especially since they often have superimposed lung disease as a result of cigarette smoking. It is also worth noting that this phenomenon could still occur in congestive heart failure despite the use of angiotensin-converting enzyme inhibitor because early morning aldosterone is due to ACTH rather than angiotensin II. In addition, reductions in daytime aldosterone induced by angiotensin-converting enzyme inhibitor reach 20% at the most and are variable and unsustainable from one patient to the next [14].

As well as adverse autonomic effects which might predispose to ischaemia and cardiac death, aldosterone is also known to promote myocardial fibrosis [15]. Although it is interesting to look for a benefit in those patients who are treated appropriately with inhaled glucocorticoids for their obstructive pulmonary disease, it would be unlikely that this therapy would form a major role in chronic heart disease or in the prevention of myocardial fibrosis in the face of more acceptable methods of treatment such as oral spironolactone.

Further dose-ranging studies need to be performed in patients with COPD to see if the effects of inhaled FP are reproduced at lower doses which are more frequently used in clinical practice.

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