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DISCORDANCE BETWEEN THE CORTISOL DOSE FOR REPLACEMENT AND THAT REQUIRED FOR SUPPRESSION OF ANDROSTENEDIONE (A4) AND 17 HYDROXYPROGESTERONE (17OHP) IN CONGENITAL ADRENAL HYPERPLASIA

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to a deficiency in the enzyme 21-hydroxylase (P450c21) is the commonest form of CAH. The conventional treatment of the condition uses hydrocortisone as a replacement glucocorticoid along with 9 alpha-Fludrocortisone as the mineralocorticoid replacement. Hydrocortisone is usually given in a three times per day regimen although in infancy and in puberty a four times per day regimen is more common.

Androstenedione and 17OHP are often used as measures of cortisol replacement in congenital adrenal hyperplasia (CAH) rather than cortisol itself. Very little is known of the dose response relationships between cortisol and A4 and 17OHP.

METHODS

We have studied the relationship between 24 hour serum cortisol, 17OHP and A4 in 33 (18M) children with biochemical and genetic proven CAH due to P450c21 deficiency aged between 6.1 and 17.0 years. 24 hour serum cortisol and 17OHP profiles were constructed using 20 minute sampling intervals. Serum A4 concentration was measured in a single sample drawn at 08.00h. The normal range for 24 hour mean serum cortisol concentration was derived from 80 normal adults aged 50-60 years of age and 30 short normal children aged 7-10 years. There was no difference between the ages so the data were pooled.

Serum total cortisol was measured using the Coat-A-Count radioimmunoassay (Coat-A-Count, DPC, Los Angeles, California, USA). The assay sensitivity was 6 nmol/l. The within-assay coefficients of variation were 5.7% and 2.6% at serum concentrations of 28 nmol/l and 552 nmol/l respectively. The between-assay coefficients of variation were 6.3% and 4.5% at 138 nmol/l and 276 nmol/l respectively.

The 24 hour serum 17OHP and cortisol concentrations were expressed as mean values. Dose response relationships were explored using a number of models including linear and log transformed data

RESULTS

Figure 1
There was a significant relationship between mean 24h serum 17OHP and A4 concentrations ($r=0.62$; $P<0.001$). For every 1 nmol/l rise in 17OHP, A4 rose by 0.2 nmol/l.

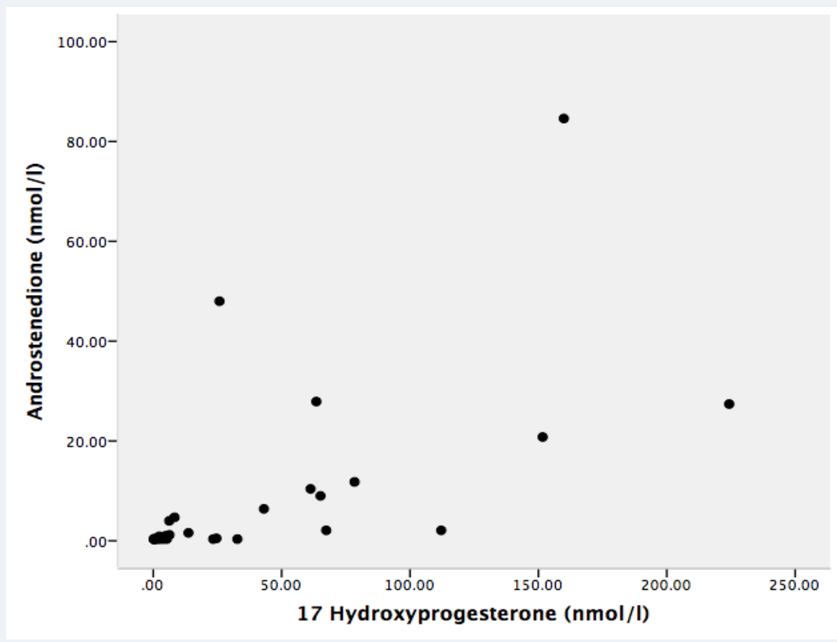
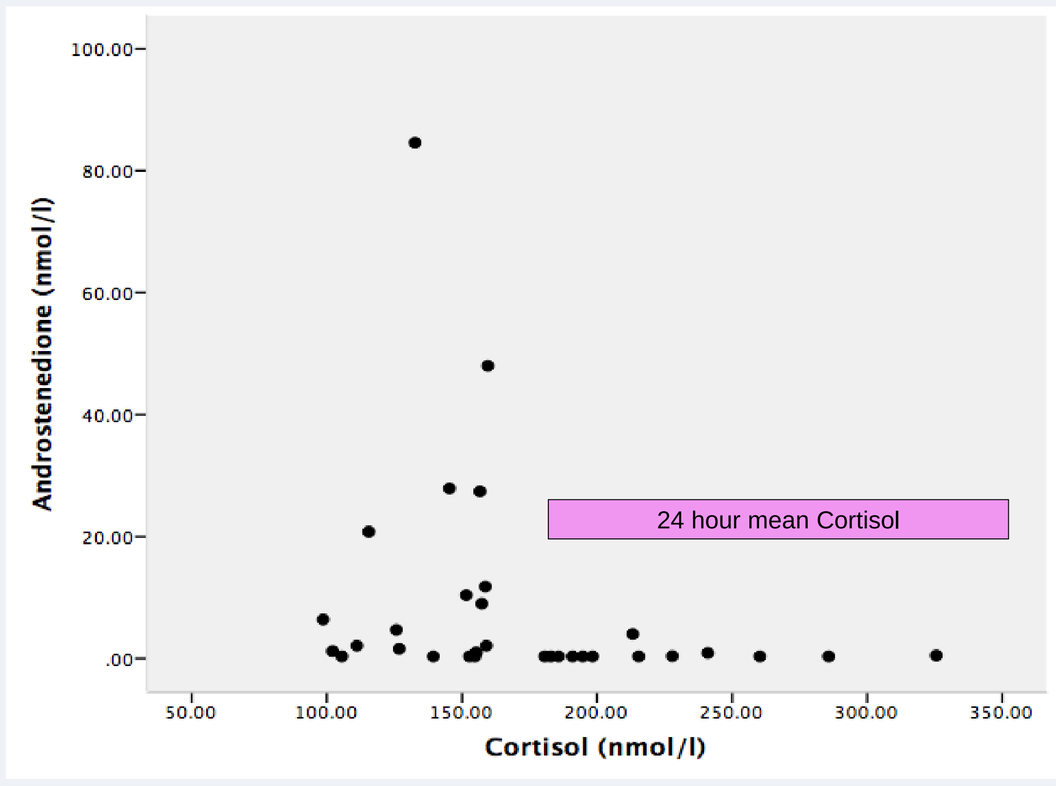


Figure 2
Both mean 24h 17OHP and A4 concentrations showed suppression when the 24h mean cortisol concentration exceeded 150 nmol/l, although 50% showed suppression with a cortisol less than 150nmol/l. This threshold was a step threshold and 4 standard deviations below the mean 24 hour cortisol production of normal individuals.



DISCUSSION

These data demonstrate that there are not equimolar changes in A4 and 17OHP, and that suppression of A4 and 17OHP occurs at cortisol concentrations that are below those associated with normal cortisol secretion. If only A4 and/or 17OHP are used to assess cortisol replacement it will leave many individuals under replaced with cortisol and at risk of Addisonian crisis.
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