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Variation in Absorption and Half-life of Hydrocortisone: A need to consider Plasma Terminal Half-Life in Dosing Schedules

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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.

The concentration of cortisol resulting from the administration of hydrocortisone is dependent on the absorption of hydrocortisone from the gastrointestinal tract, balanced against the clearance of cortisol from the circulation. Although there are other components operative, such as the enterohepatic circulation, cortisol concentrations in the circulation can be conceived as a balance between the two parameters absorption and clearance. Clearance of cortisol from the circulation can be measured by an intravenous bolus administration of hydrocortisone, whereas absorption can be determined from a series of pharmacological parameters, such as the maximum concentration attained (C_{max}) and the time to peak concentration (t_{max}). The conventional replacement dosing when using hydrocortisone is calculated on a body size basis. Other than this very little attention has been paid to individualise the dosing schedule using measures of absorption and clearance.

Methods

48 patients (21 males and 27 females) with biochemical and genetic proven CAH aged between 6.1 and 20.3 years were reported in the pharmacokinetics paper (5) and were used in the analysis

Patients were admitted to the Endocrine Unit one day before the investigations were undertaken and two indwelling intravenous catheters, one for the intravenous administration of hydrocortisone and the other for blood sampling were inserted. On the day of the study, an intravenous bolus of hydrocortisone sodium succinate (15 mg/m^2 body surface area). Blood samples for cortisol concentrations were collected through the second cannula at 10 minute intervals for a total of 6 hours following the injection of hydrocortisone. On the second day of the study patients were given their usual oral hydrocortisone dose at 09:00h and blood samples for serum cortisol were collected at 20 minute intervals for a 24 hour period. For the purpose of the analysis in this study the first oral dose taken in the morning was used and samples included for a 4 hour period thereafter.

From the oral ingestion of hydrocortisone maximum plasma concentration (C_{max}), time of the maximum plasma concentration (t_{max}) and time to when plasma cortisol concentration of less than 100 nmol/l was recorded were noted. Half-life and clearance were derived from the intravenous studies. For both the oral and intravenous pharmacokinetic parameters values were described as either short half-life or fast absorption if values were below the mean for the data set and as long half-life and slow absorption for values above the mean.

Results

Table of Pharmacokinetic Data

Age (years)	**6.1 – 20.3**
Gender	**21M : 27F**
Hydrocortisone (mg/m^2/day)	**11.5 – 22.6**
Fludrocortisone (µg/m^2/day)	**44 - 160**
Oral Measures	
(C_{max}) (nmol/l)	**780.7 (61.6)**
(t_{max}) (min)	**66.7 (5.9)**
Time to 100 nmol/l (min)	**289.2 (15.4)**
Intravenous Measures	
Half-life (min)	**76.5 (5.2)**
Clearance (ml/min)	**578.5 (100.6)**

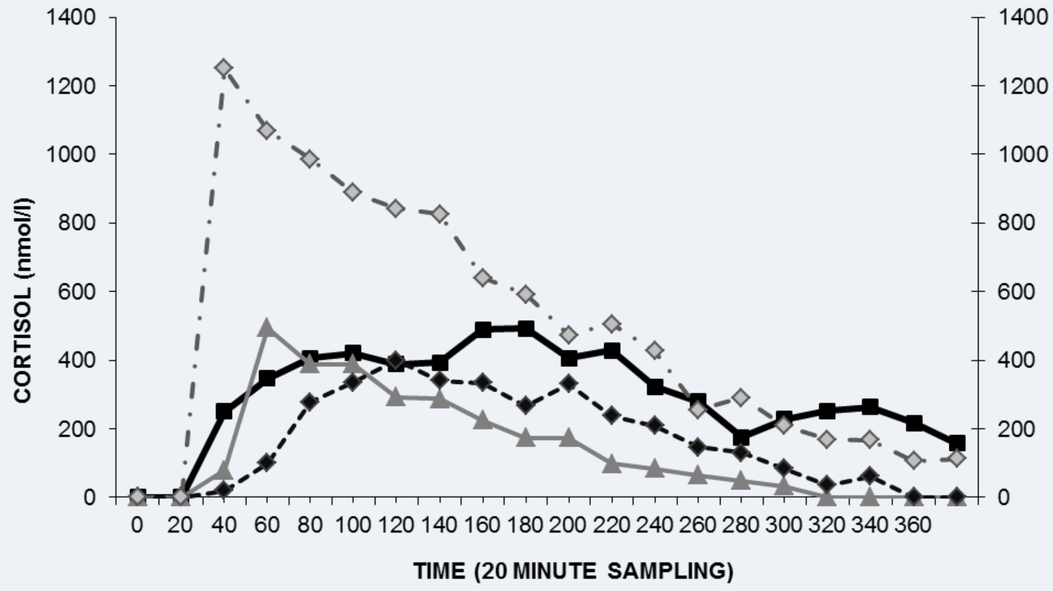

Figure shows differences in absorption and clearance
Black solid line and squares slow absorption long half-life
Grey line and triangles fast absorption and short half-life
Black dash line and diamonds slow absorption and short half-life
Grey dash dot line with diamonds fast absorption and long half-life

Those with a fast half-life and slow (t_{max}) took the longest time to reach a plasma cortisol concentration of less than 100 nmol/l (380 ± 34.6 min). Those with a slow half-life and fast absorption had the next slowest time (298 ± 34.8 min) and patients with a fast half-life and fast absorption had the fastest time to achieve a concentration below 100 nmol/l (249.5 ± 14.4 min).

Discussion

Both rate of absorption and half-life of cortisol in the circulation play important roles in determining overall exposure to oral glucocorticoid. Dose regimens need to incorporate estimates of these parameters into determining the optimum dosing schedule for individuals.