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METABOLISM OF EXOGENOUS CORTISOL IN HUMANS—I

DIURNAL VARIATION IN PLASMA DISAPPEARANCE RATE

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Abstract—A variation in the rate of disappearance from plasma, at different times of the day, has been observed for exogenous cortisol in humans after i.v. administration. This appears to correlate with the endogenous cortisol plasma levels.

The possibility of a circadian fluctuation of drug metabolizing enzyme activities in man is discussed.

A DIURNAL rhythm for hepatic drug-metabolizing enzyme activity in rats and mice has been described by Radzialowsky and Bousquet.[12] Recently Szeberenyi *et al.*[17] and Marc *et al.*[10] observed that the plasma disappearance rate for metyrapone and cortisol in the rat follows a diurnal rhythm. The pituitary adrenal axis seems to be involved in short term regulation of hepatic drug metabolizing activity since high metabolic rates are concomitant with low corticosterone levels and vice versa.[10, 12, 17] In addition adrenalectomized animals lose their diurnal rhythm of liver microsomal enzymatic activity.[12]

These data are in good agreement with the observations that a diurnal variability of drug effect is present in experimental animals.[2, 6, 9, 11]

Since diurnal changes of drug-metabolism in humans have not been previously investigated, the purpose of this study was to establish the possible occurrence of daily variations in the plasma disappearance rate of exogenous cortisol and moreover if the phenomenon could be correlated with the endogenous cortisol circadian rhythm.

A knowledge of different plasma disappearance rate during different hours of the day may in fact have an important role for establishing optimal dosage-schedules in therapy.

MATERIALS AND METHODS

Plasma disappearance of intravenously administered cortisol† was studied in four female, chronic psychiatric patients, free of acute psychotic symptoms.

The four subjects were kept on constant diet and living schedule‡ and on a maintenance therapy with Haloperidol. Drug therapy was discontinued 7 days before cor-

* Merck Sharp & Dohme's Fellow for clinical pharmacology.
† Flebocortid Richter.
‡ 6.00 a.m. getting up; 6.30 a.m. breakfast; 8.00 a.m. occupational therapy; 12.00 a.m. lunch; 1.00 p.m. napping; 2.30 p.m. occupational therapy; 6.00 p.m. supper; 9.30 p.m. bed time.

tisol administration. Circadian rhythm of endogenous cortisol was determined two and three days before the experimental sessions. In the first session two subjects (S.C. and R.M.T.) received cortisol intravenously at 8 a.m. and two (M.G. and R.M.) at 4 p.m. Blood samples were collected at 0, 15, 30, 60 and 120 min after the drug administration, and plasma cortisol levels determined according to Guillemin[5] and Stockham[16] with minor modifications. Blood levels of endogenous cortisol at 0 time did not differ significantly from those observed during the circadian rhythm determinations. Plasma proteins were also determined on 0 time samples. The four subjects were then put back to their maintenance therapy, which was again discontinued after 21 days. One week later subjects S.C. and R.M.T. received the same amount of cortisol at 4 p.m., while M.G. and R.M. were injected at 8 a.m. Blood samples were collected as before. Clinical and laboratory tests for circulatory, liver and kidney functions were within normal ranges.

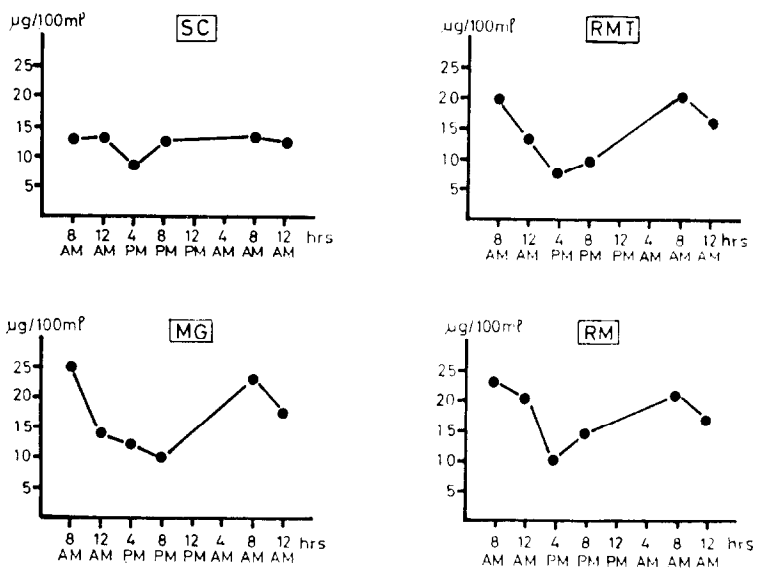

FIG. 1. Endogenous cortisol circadian rhythm in the four subjects studied. In ordinates: cortisol plasma concentration.

Menstrual cycles were also considered: all the four subjects had a regular cycle of 28 days. Cortisol administration was always performed on the 15th day of the cycle.

Apparent volume of distribution (v.d.) was calculated by dividing the intravenous dose by the apparent initial exogenous cortisol concentration in the plasma. The latter value was determined by extrapolating at zero time the linear portion of logarithmic cortisol concentration versus time.

Plasma half life was determined graphically on the semilogarithmic plot. Curves were calculated according to the correlation coefficient test and statistical evaluation of the disappearance curves was performed according to *t*-test.

TABLE 1. PHARMACOKINETIC CONSTANTS FOR EXOGENOUS CORTISOL PLASMA DISAPPEARANCE. DIURNAL VARIATIONS

Subject	Age	Sex	Body weight (kg)	Dose (mg/kg, i.v.)	Morning (8.00 a.m.) $T_{\frac{1}{2}}$ = min	Morning (8.00 a.m.) Vd = l/kg	Afternoon (4.00 p.m.) $T_{\frac{1}{2}}$ = min	Afternoon (4.00 p.m.) Vd = l/kg
S.C.	31	F	65	1·54	77	1·311	62*	0·964
R.M.T.	31	F	65	1·54	120	1·435	63†	1·321
M.G.	30	F	53	1·88	127	1·613	98*	1·319
R.M.	30	F	53	1·88	106	1·317	72‡	1·027
				means	107·50 ±11·06	1·419 ±0·070	73·75* ±8·39	1·157* ±0·094

Pharmacokinetics constants for exogenous cortisol plasma disappearance rate in four female human subjects. Diurnal variations in the two experimental sessions.
$T_{\frac{1}{2}}$ = apparent plasma half life.
Vd = apparent volume of distribution.
* P 0·05; †P 0·01; ‡P 0·02.

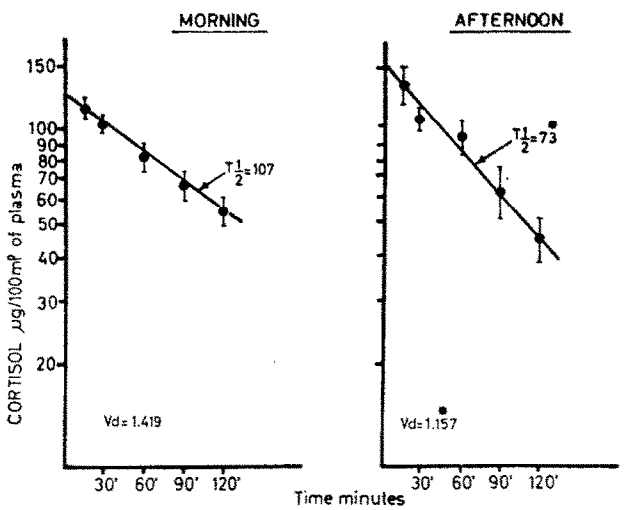

FIG. 2. Exogenous cortisol plasma disappearance rate. Average of the four cases in the two experimental sessions: morning (8 a.m.) and afternoon (4 p.m.).
$T_{\frac{1}{2}}$ = apparent plasma half life.
Vd = apparent volume of distribution.
* $P < 0.05$.

RESULTS

The circadian rhythm of endogenous cortisol well reproducible within the single subject, showed, as expected, individual variability. As illustrated in Fig. 1 not only the rhythm profiles of the four subjects were quite different, but a 2-fold variation in endogenous levels was also present. The differences were more marked at 8 a.m. than at 4 p.m. The pharmacokinetic constants for exogenous cortisol disappearance from plasma are reported in Table 1 and Fig. 2.

In this regard it is interesting that subject S.C. who had the lowest endogenous

cortisol level showed an apparent plasma half life ($T_{\frac{1}{2}}$) for exogenous cortisol of only 77 min, while subject M.G., with a high endogenous cortisol level had an apparent plasma $T_{\frac{1}{2}}$ for exogenous cortisol 127 min. In the afternoon session all the apparent plasma half-life values for exogenous cortisol appeared significantly reduced ($P < 0.05$ and $P < 0.01$) in respect to the morning values. Differences in the apparent volume of distribution were also present: the volume values of the afternoon session were lower than the morning session ones.

A linear correlation between the apparent plasma $T_{\frac{1}{2}}$ and the apparent volume distribution was present ($r = 0.77$ and $P < 0.05$). Similarly there was a linear correlation between the apparent plasma $T_{\frac{1}{2}}$ of exogenous cortisol and the endogenous cortisol plasma concentration at 0 time ($r = 0.88$ and $P < 0.01$) (see Fig. 3).

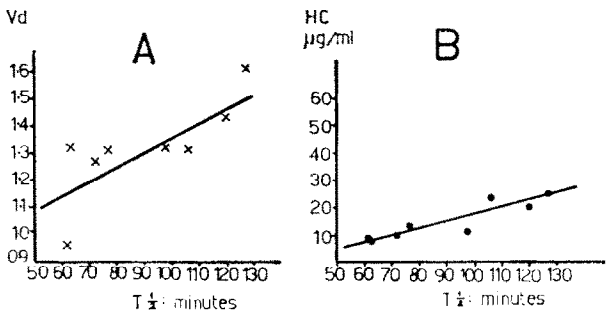

FIG. 3. (A) correlation between apparent volume of distribution (Vd) and exogenous cortisol apparent plasma half life ($T_{\frac{1}{2}}$) ($r = 0.7719$ and $P < 0.05$). (B) correlation between endogenous cortisol plasma levels at 0 time (H.C. µg/ml) and exogenous cortisol apparent plasma half life ($T_{\frac{1}{2}}$) ($r = 0.8851$ and $P < 0.01$).

DISCUSSION

A different plasma disappearance rate for exogenous cortisol, in different hours of the day is evident from the data reported. The apparent plasma half life for exogenous cortisol was in fact higher in the morning (8 a.m.) when the endogenous cortisol plasma levels were at the peak of the daily rhythm and lower in the afternoon (4 p.m.) in correspondence with the fall of endogenous plasma cortisol level.

Factors determining such variations may be of multiple origins. Endogenous cortisol plasma levels and apparent volume of distribution of the drug seem to be somehow correlated with the described phenomenon.

Modifications in physiological conditions such as bed resting or ambulatory status are known to modify the apparent volume distribution for concomitant changes in hydrostatic pressure, extracellular fluids and proteins concentration.[3, 8, 15]

Muscular exercise is also known to increase total metabolic activity.[15] Meals do not seem to be very important since in the experimental animal the circadian variation of drug-metabolizing activity are present at the same degree both in fed and fasted animals.[10, 12] Protein electrophoretic patterns too did not show any significant difference in the two sessions although the limited number of cases does not allow any conclusion in this respect. In fact a circadian rhythm in plasma proteins is known in the rat[14] and daily variations of plasma aminoacids have been demonstrated also in humans.[4, 13, 18]

The linear relationship observed between the endogenous cortisol values at 0 time and the apparent plasma half life for exogenous cortisol is very suggestive if we take into consideration the hypothesis of an influence of endogenous cortisol on drug-metabolizing activities of the liver.[12] On the basis of the reported data it is difficult to draw any conclusion, nevertheless, the difference observed in exogenous cortisol plasma disappearance rates could also be present with other drugs and further studies in this regard are needed.

A different metabolic rate in various hours of the day could be in fact very important for establishing correct dosage-schedule and for determining the final therapeutic results.

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