PREDNISOLONE PHARMACOKINETICS COMPARED BETWEEN NIGHT AND DAY IN ASTHMATIC AND NORMAL SUBJECTS

Prednisolone has proved to be an essential and even life saving drug in a number of medical conditions over the past twenty-five years. However its use remains largely empirical despite this long experience. One problem facing clinicians is whether to prescribe prednisolone once a day in the morning or evening, in divided doses or even on alternate days. There are good theoretical reasons for giving the drug once a day in the morning as this results in less pituitary adrenocortical suppression (Nichols, Nugent & Tyler, 1965; Siegre & Klaiber, 1966).

Another factor affecting this choice would be the presence of a circadian rhythmicity in the disposition of prednisolone. There are reasons for suspecting that this might be the case as antipyrine and aminopyrine have been shown to exhibit a significant diurnal variation in half-life (Vesell, Shively & Passananti, 1977; Poley, Shively, Elliot & Vesell, 1978). Prednisolone has also been shown to exhibit a diurnal variation in binding to its carrier protein transcortin, the binding capacity is highest during the night (Angeli, Frajria, DePaoli, Fonzo & Ceresa, 1977). In this study we attempted to assess whether there is a significant diurnal variation in prednisolone pharmacokinetics. If this were so it might allow us to recommend its prescription at a particular time of day. Even though the effect on adrenal suppression would suggest an advantage in taking the drug in the morning, it could be that the circadian difference in pharmacokinetics might outweigh this if significant enough.

Study design

Six physically normal male volunteers (24–35 years; 65–70 kg) were studied. Three were smokers but none were excessive alcohol takers and none had ever previously received prednisolone. Five chronic stable asthmatics (35–46 years; 63–76 kg) who had been on daily prednisolone for at least 6 months were also studied. All subjects were given 20 mg prednisolone B.P. orally (Precortisyl; Roussel) at 08.00 and 20.00 h on two separate days at least 1 week apart. Plasma samples were taken during the ensuing 12 h for measurement of prednisolone levels. Conditions including food and medication remained constant between night and day except that all subjects slept at night. No subject lay down for at least 3 h after taking the drug. The prednisolone was ingested following a 10 h fast and no food was taken for 2 h thereafter. Day and night studies were performed in random order. All those studied gave informed consent, following Brompton Hospital Ethical Committee approval.

Analytical procedure

Plasma prednisolone levels were estimated using a radioimmunoassay as described by Chakraborty, English, Marks, Dumasia & Chapman (1976) and Henderson, Wheatley, English, Chakraborty & Marks (1979). Cross reactivity with cortisol was 3.2%. Internal standards were included in all assays and there was a coefficient of variation of 6.9% (n = 20 mean 44.5 ng/ml) between assays. Plasma prednisolone concentrations were used to calculate the following pharmacokinetic parameters by conventional methods (Gibaldi & Perrier, 1975): area under plasma concentration time curve (AUC), half life ($T_{½}$), systemic clearance (Cl), apparent volume of distribution (V_d). AUC was calculated by the trapezoidal method and an appropriate correction was used to approximate the infinite portion of the curve using

$$\frac{\text{last plasma concentration measured}}{\text{Ke}}$$

where Ke is the first order rate constant for elimination which was calculated from the half-life. The observed maximum plasma concentration (C_{max}) and the time of this maximum concentration (T_{max}) were also considered in the analysis of the results. Two studies (Tanner, Bochner, Coffin, Halliday & Powell, 1979; Uribe, Schalm, Summerskill & Go, 1978) have shown that intravenous and oral prednisolone have approximately equivalent bioavailability allowing calculation of apparent V_d and Cl from oral administration. All these parameters were compared between night and day using two way analysis of variance. Variations between subjects in each group and between patients and normals were also studied. The results from the variance analysis were further assessed by the studentized range procedure using Tukey's studentized range test (Kendall & Stuart, 1966). Table 1 shows the mean values for night and day of both patients and normals. No significant difference was found between night and day for any of the pharmacokinetic data in either patients or normals, nor were there differences between the two groups of subjects.

The possibility that prednisolone pharmacokinetics might show a diurnal rhythmicity was not confirmed in this study. This implies that from the pharmacokinetic standpoint there is no reason why prednisolone should be given at any particular time of day or night. However. Angeli *et al.* (1977) showed a diurnal fluctuation in the binding of prednisolone to

Table 1 Pharmacokinetic data for night and day in normals and asthmatics (mean values ± s.d.)

	AUC (*ng h ml*$^{-1}$)	*Cl* (*l h*$^{-1}$)	V_d (*l*)	C_{max} (*ng*)	T_{max} (*min*)	$T_{1/2}$ (*h*)
Normals						
Day	1170 ± 139	11.36 ± .89	49.3 ± 6.2	374 ± 44	44 ± 29	3.19 ± .64
Night	1692 ± 330	12.21 ± 2.28	54.4 ± 5.3	333 ± 76	72 ± 34	3.05 ± .42
Patients						
Day	1921 ± 295	10.59 ± 1.47	40.9 ± 6.4	386 ± 91	52 ± 11	3.38 ± 1.3
Night	1772 ± 67	11.30 ± .43	48.2 ± 9.3	374 ± 22	52 ± 24	2.95 ± .50

transcortin. It may be therefore that if the pharmacokinetics of the unbound drug were studied a difference would be found between night and day. This is only one aspect of the problem and it does not answer the question as to whether prednisolone is as effective when prescribed once or twice a day or on alternate days. It has been shown that in normal subjects given dexamethasone at 08.00 h, adrenal suppression lasts for 10 h while if given at midnight suppression lasts 24 h (Nichols *et al.*, 1965). Seigre *et al.* (1966) have shown that there is a much larger decrease in urinary 17-hydroxycorticosteroids when corticosteroids are taken in the evening rather than in the morning. As our study does not suggest that differences in drug disposition exist between night and day, in view of the adrenal suppression data above, it is recommended that prednisolone be prescribed in the morning so that when the pituitary is ready for the next diurnal surge of ACTH secretion the administered corticosteroid will no longer be circulating in concentrations sufficient to block its response. In addition the finding of Angeli *et al.* (1977) that there is a greater proportion of free, active prednisolone during the day than at night would support the desirability of morning dosing.

Clearly further studies are required to assess whether there are differences in therapeutic efficacy when prednisolone is prescribed at different times or on alternate days.

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