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Pharmacokinetics of Prednisolone in Normal and Asthmatic Subjects in Relation to Dose

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Summary. The pharmacokinetics of prednisolone have been studied in asthmatic patients following intravenous injection at three different doses and in normal volunteers at five oral doses. Plasma prednisolone concentrations were measured by radioimmunoassay. With increasing dose there is an increase in the apparent volume of distribution, plasma clearance and half life. The relationship between area under the plasma concentration time curve, maximum concentration and dose is linear but the regression lines do not pass through the origin. These findings following oral and intravenous administration confirm that prednisolone shows non-linear kinetics.

Key words: prednisolone, asthma; oral dosing, intravenous dosing, plasma clearance, half life, pharmacokinetics

The clinical use of prednisolone in terms of dosage regimens and frequency and duration of treatment is largely empirical despite 25 years of use in a wide variety of diseases. It is an essential drug in a number of life threatening conditions and of undoubted benefit in several chronic diseases. It is therefore to be hoped that pharmacokinetic studies will help in developing more rational therapeutic attitudes. These studies should be directed to some of the basic problems which have arisen but surprisingly few have been performed and prescription of prednisolone has been based on the assumption that it obeys linear pharmacokinetic behaviour. Recent work (Pickup et al. 1977; Loo et al. 1978; Rose et al. 1978; Tanner et al. 1979) suggests that in fact prednisolone shows dose-dependent, non-linear kinetics. However these studies are deficient in various respects in that either they studied only two doses; or give several doses to different individuals and compare results; or only mention one or two parameters. Furthermore, prednisolone pharmacokinetics have not been investigated throughout the full oral dosage range used in clinical practice. This was the object of this study. The pharmacokinetics of the drug in three asthmatic patients following intravenous administration have also been assessed.

Methods

The five male volunteers in the oral study were on no medication, had no history of illness and none took alcohol excessively. The age range was 24–32 years and weight range 64–82 kg. The doses of 5, 10, 20, 40 and 80 mg Prednisolone B. P. (Precortisyl, Roussel) were given in random order after an overnight fast at 0800 with an interval of at least a week between individual doses. No food was taken until 11.00 h and at 12.00 and 16.00 h thereafter. No tobacco or alcohol were allowed for 24 h before and after drug ingestion. Blood samples were taken at 0,

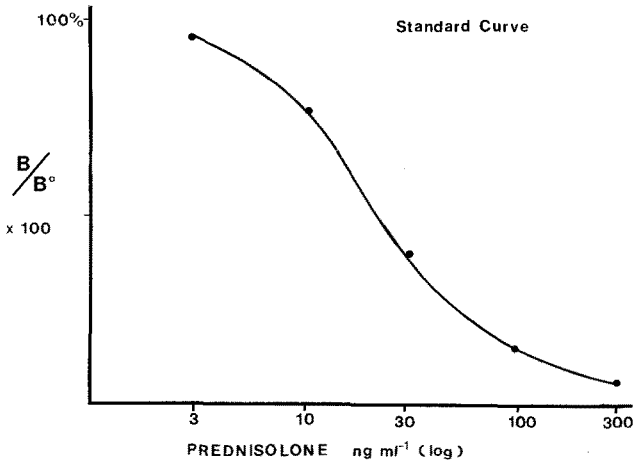

Fig. 1. A representative standard curve plotted semilogarithmically

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Table 1. Data following intravenous administration of prednisolone phosphate to three female asthmatic patients

Subject	Dose [mg]	A. U. C. [ng h ml^{-1}]	Cl [l·h^{-1}]	Vd [l]	$t_{1/2}$ [h]
1	20	2512	7.96	28.3	2.5
	40	3187	12.6	32.5	1.8
	80	5347	14.9	90.2	4.2
2	20	1586	12.6	32.0	1.8
	40	2438	15.4	41.8	1.8
	80	4544	17.6	54.0	2.1
3	20	1672	11.9	46.7	2.7
	40	2600	15.4	76.8	3.4
	80	4497	17.8	86.3	3.4

Table 2. Data following oral administration of prednisolone B. P. to five normal volunteers

Subject	Dose [mg]	A. U. C. [ng h ml^{-1}]	Cl [l h^{-1}]	Vd [l]	$t_{1/2}$ [h]
1	5	791	6.3	23.2	2.6
	10	1721	5.8	16.1	1.9
	20	1709	11.7	48.0	2.9
	40	2773	14.4	55.3	2.7
	80	6307	12.6	58.0	3.2
2	5	972	5.1	20.1	2.7
	10	1499	6.6	30.7	3.2
	20	1958	10.2	39.4	2.7
	40	3547	11.2	67.6	4.2
	80	5775	13.8	83.0	4.2
3	5	837	5.9	25.3	3.0
	10	1967	5.0	16.0	2.2
	20	2296	8.7	30.1	2.4
	40	3805	10.5	59.0	3.9
	80	7217	11.0	53.6	3.4
4	5	824	6.0	26.2	3.0
	10	1466	6.8	33.0	3.2
	20	2373	8.4	39.0	3.2
	40	3864	10.3	41.0	2.8
	80	6571	12.1	92.9	5.3
5	5	802	6.2	26.0	2.9
	10	1448	6.0	31.7	3.2
	20	1798	11.1	50.9	3.2
	40	3847	11.4	63.4	3.8
	80	6595	12.8	88.0	5.0

0.5, 1, 2, 3, 4, 5, 8, 10, 12 and 24 h, and the plasma immediately separated by centrifugation, frozen and stored at −20 °C until assayed for prednisolone.

Intravenous doses of 20, 40 and 80 mg of prednisolone as prednisolone phosphate (Codelsol®: Merck, Sharp, Dohme) were given in random order to three female chronic stable asthmatics (ages 28, 37 and 48 years; weights 68, 54 and 58 kg respectively). The doses were injected slowly over five minutes in order to avoid the paraesthesiae of the so called 'phosphate reaction' following fast i. v. administrations. Similar conditions prevailed as those in the oral study except that patients were not fasting. Concurrent therapy consisted of salbutamol aerosols and tablets, and slow release aminophylline and remained unchanged throughout the study. Blood samples were taken at 0, 1, 3, 5, 10, 15, 30, 60, 120, 180, 240 and 420 min following the end of the injection and the plasma was processed as in the oral study.

All subjects were non-smokers apart from two normals in the oral study. All volunteers gave verbal, informed consent and patients gave written, informed consent to the protocol which was approved by the Brompton Hospital ethical committee.

Plasma prednisolone levels were measured using a radioimmunoassay as described by Chakraborty et al. (1976) and Henderson et al. (1979) with the exception that we added 78 pg ^{3}H prednisolone (New England Nuclear; Amersham Radiochemicals) to each tube. The standard curve was plotted semi-logarithmically and was essentially linear over the range 10–100 ng. A representative standard curve is demonstrated (Fig. 1). The sensitivity of the standard curve: the smallest amount of steroid that is significantly different from 0 at the 95% confidence limits, was 6 ng. The prednisolone antiserum was that described by Henderson et al. (1979). Cross reactivity with cortisol was 3.2%. The affinity constant calculated be means of a Scatchard plot (Feldman and Robard 1971) was 2.76×10^8 litres mole^{-1}. The dilution of the antiserum required to bind 50% of the labelled tracer was 1/1500 and this was the dilution used in the assay. Small amounts of radioactive tracer were added to each plasma sample prior to extraction. An aliquot was taken of the plasma before extraction and an aliquot of the residue after reconstitution with buffer and compared to calculate recovery which averaged 90%.

Internal standards were included in the assays and there was a coefficient of variation of 7.42% (n = 25 mean = 44.5 ng/ml) between assays.

The prednisolone levels were used to estimate various pharmacokinetic parameters using conventional methods (Gibaldi and Perrier 1975). The area under the plasma concentration time curve (A. U. C.) was calculated using the linear trapezoidal rule, with addition of an appropriate correction for the infinite portion of the curve in the case of the patient study. The average percentage of the A. U. C. contributed by extrapolation was 8%, 16%, 20% respectively for the 20, 40, and 80 mg dose. The apparent first order elimination rate constant (Ke) was determined by linear regression of ln (plasma concentration) against time. The plasma half life ($t_{1/2}$) was estimated from $t_{1/2} = 0.693/Ke$.

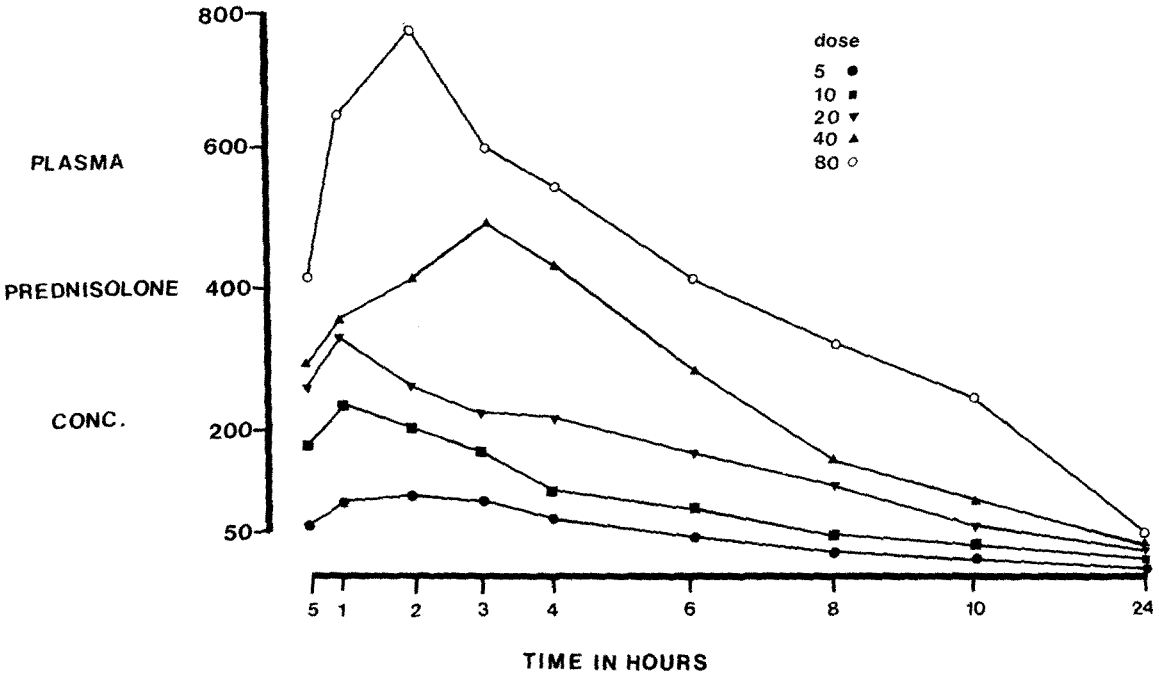

Fig. 2. Plasma concentration time curves for one individual in oral study at five different doses

Two recent studies (Tanner et al. 1979; Uribe et al. 1978) have shown that intravenous and oral prednisolone have approximately equivalent bioavailability, therefore allowing calculation of apparent volume of distribution (Vd) and systemic clearance (Cl) from oral administration with the assumption that $F = 1$. These approximate estimates of Cl and Vd were determined from: $\frac{F(\text{Dose})}{\text{A.U.C.}}$ and $\frac{F(\text{Dose})}{\beta(\text{A.U.C.})}$ respectively where $\beta = \frac{0.693}{t_{1/2}}$ and F is the bioavailability fraction. The maximum plasma concentration and the time of this concentration taken directly from the subject data were also considered in the analysis of the results.

All parameters including half-life were compared using two way analysis of variance to assess differences between values through the dosage range. These results were further assessed by the studentized range procedure using Tukey's studentized range test (Kendell and Stuart 1966).

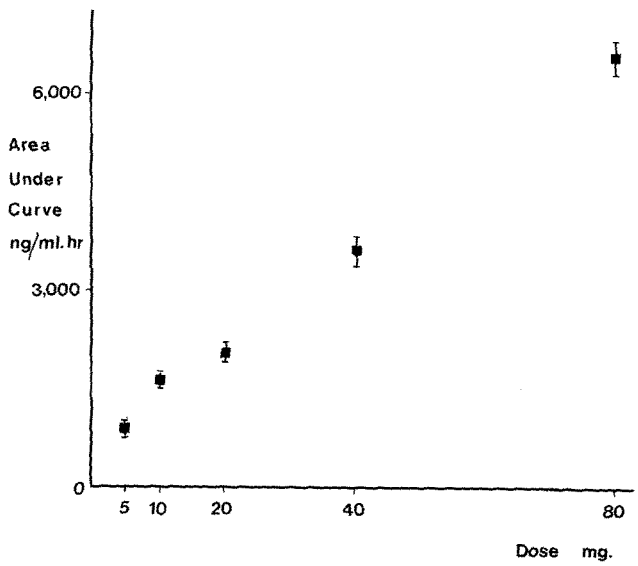

Fig. 3. Area under the plasma concentration time curve (±SD) of five subjects at five different oral doses

Results

The mean values for the various pharmacokinetic parameters for all the subjects at each dose and for each route of administration were calculated and plotted against dose (Tables 1 and 2). Figure 2 demonstrates the plasma concentration of prednisolone against time for one individual in the oral study at 5 different doses. There was a fair amount of interindividual variation in prednisolone levels measured and in kinetic parameters. A. U. C., Cl and Vd all increase with dose in both the intravenous and oral studies (Figs. 3, 4, 5). A. U. C. in both studies and Cmax in the oral study bear an apparently linear relationship to dose ($r = 0.98$, $p = 0.001$) but the

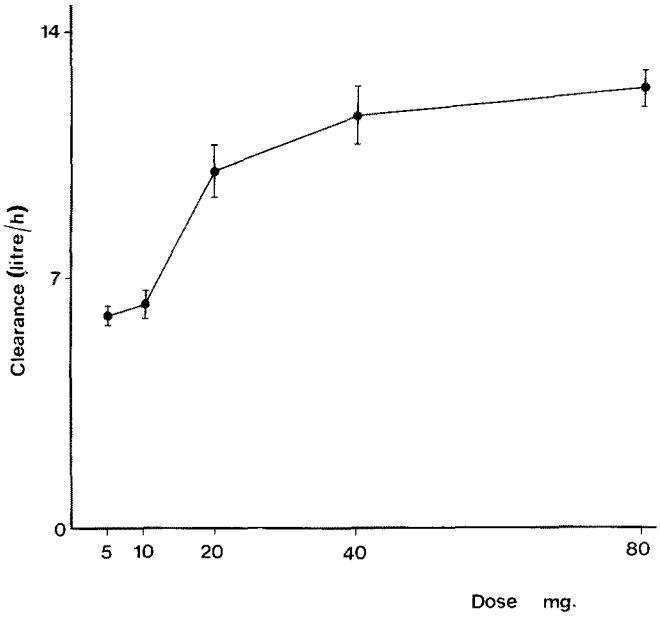

Fig. 4. Plasma clearance (±SD) values of five subjects at five different oral doses

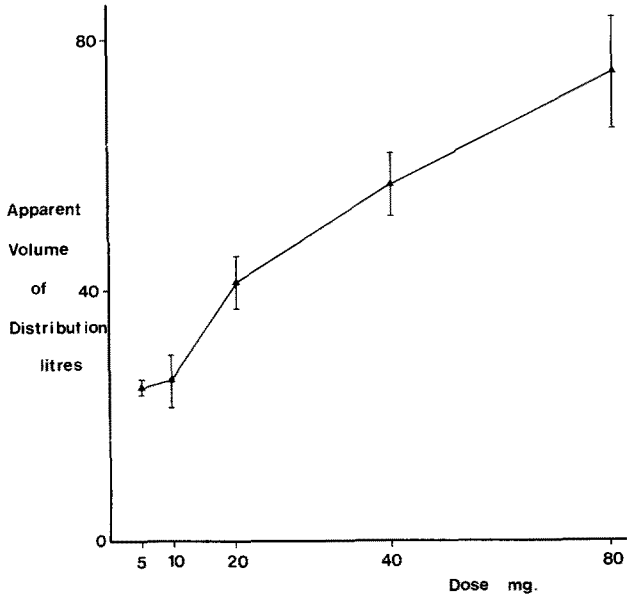

Fig. 5. Values for apparent volume of distribution (±SD) of five subjects at five different oral doses

intercept does not pass through the origin in either instance. Linear regression of all the oral A. U. C. data is described by the relationship A. U. C. = 73.10 dose + 618.87. The intercept is 618.87± 150.80 with 95% confidence limits. Two way analysis of variance as described showed that the increases noted above reach statistical significance with Cl in both studies ($p = 0.001$) and Vd in the oral study only ($p = 0.001$). Although Vd increases in the i. v. study this is not significant. The half life ranged from 1.92–5.93 h, mean 3.22±0.61 h (±SD) in the oral study. The values for the intravenous study were: range 1.76–4.19 h, mean 2.62±0.87 h (± SD). Two way analysis of variance showed a statistically significant ($p = 0.01$) increase in half life considering the oral group as a whole throughout the range. However, this increase only occurred above 20 mg and the half life at the first three doses did not change. Two of those given oral medication and the three patients in the intravenous group showed no increase in $t_{1/2}$ throughout their respective dosage ranges.

The concentration time plots were not identical when normalised for dose thus violating the superimposition principle, which is a critical test of linearity. For an orally administered drug each plasma concentration is divided by the dose and the ratio plotted against time. If the curves for each dose are not superimposable then non-linearity exists (Wagner 1974).

The relationships described above therefore show non-linear dose dependent pharmacokinetics for prednisolone in both oral and intravenous studies.

Discussion

Reports on the pharmacokinetics of prednisolone have appeared over the past three years but there has been incomplete agreement between the various studies. We can find no other report which has studied the full oral therapeutic dosage range in the same subjects and considered results for several parameters.

Pickup et al. (1977) studied a mixed group of patients and normals. Subjects received intravenously, on separate occasions, a tracer dose of ^{3}H-prednisolone alone and 0.15 mg/kg and 0.3 mg/kg dose of prednisolone 21 phosphate together with the tracer dose of tritiated prednisolone. Six subjects were given two doses of unlabelled prednisolone alone and only four received all three doses. Apparent volume of distribution and plasma clearance increased significantly with dose. This is in agreement with our findings and those of Loo et al. (1978), Rose et al. (1978) and Tanner et al. (1979) although, as discussed below, the oral doses were not given to the same subjects in the latter study. There was a significant difference in half life only between the tracer dose and the other two doses in Pickup's paper. This highlights a problem of this study which is whether it is valid to extrapolate from tracer dose kinetics to therapeutic dose kinetics. Half life did not increase if

only two therapeutic doses are considered. In our intravenous study we showed no significant increase in half life however we did so above 20 mg in the oral study. Green et al. (1978) and Tanner et al. (1979) found no increase in half life in children and adults however the different doses in the oral study were not given to the same individuals. It is impossible to draw conclusions about increasing dose and its' relationship to pharmacokinetic parameters when the doses are not taken by the same subjects because the intersubject variability of age, weight, height and other confounding factors make interpretation of such data difficult. Therefore of the studies where two or more doses are given to the same individuals Pickup et al. (1977) (2 doses i. v.) and ourselves (3 doses i. v.) have shown no increase in $t_{1/2}$. However, in our oral study (5 doses p. o.) we found an increase in half life above 20 mg. It is not clear what happens, therefore, to half life with increasing dose.

There is little disagreement that Vd and Cl increase with dose however values are quoted only by Pickup et al. (1977), Tanner et al. (1979) and Loo et al. (1978). The difficulties in interpreting the results of Tanner et al. (1979) have been mentioned. Loo quoted no values for Cl. We found similar results in this study but the increase in Vd in the i. v. study does not reach significance.

Rose et al. (1979) and Green et al. (1978) demonstrate that in their studies with oral prednisolone when peak plasma concentrations are expressed as a function of dose the regression line has a positive intercept. This was also demonstrated by Tanner et al. (1979) for A. U. C. This concurs with our findings for both Cmax and A. U. C. where, although the relationships are linear ($r = 0.98$), the regression lines do not pass through the origin. These are indications of non-linear, disproportionate changes with dose.

It seems probable that the most likely cause of the dose dependent kinetics of prednisolone demonstrated here and elsewhere is its non-linear protein binding due to the saturation of the binding sites on transcortin. The binding globulin has high affinity and low binding capacity and as the serum concentration of prednisolone increases the capacity is exceeded and the percentage unbound increases (Rocci et al. 1980).

There is some measure of agreement that prednisolone obeys non-linear dose dependent pharmacokinetics. In a study through the full oral therapeutic dosage range in normals and in asthmatics in an intravenous study we have confirmed this. Prednisolone is one of the most frequently and diversely used drugs and some of the findings above are of clinical relevance to a broad spectrum of clinicians. Care must be taken when increasing dose as half life increases at higher doses. Doubling the dose does not result in a doubling of the drug available to the tissues as evidenced by the findings for Cmax and A. U. C.

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