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PHARMACOKINETICS OF INTRAVENOUS AND ORAL PREDNISOLONE

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1 Doses of 16, 32, 48 and 64 mg prednisolone were administered intravenously to normal volunteers who also received 10 mg prednisolone orally. Plasma prednisolone concentrations were estimated by quantitative thin layer chromatography.

2 The bioavailability fraction was 1.063 ± 0.154 (s.d.) indicating complete availability of prednisolone following oral administration.

3 The mean $T_{½}$ over all doses were 4.11 ± 0.97 (s.d.) h and there was no evidence of a dose-related change in its value.

4 The mean systemic clearance over all doses was 0.104 ± 0.034 (s.d) 1 h^{-1} kg^{-1}. There was no evidence of a dose-related change in clearance or in the apparent volume of distribution (overall mean 0.588 ± 0.152 1 kg^{-1}).

5 The area under the plasma concentration–time curve was linearly related to dose.

6 Plasma concentration–time curves normalised for dose were superimposable.

7 It was concluded that over the dose range investigated, non-linear pharmacokinetic behaviour had not been demonstrated in this group of normal volunteers.

Introduction

A number of recent studies have suggested that non-linear kinetics may be required to describe some aspects of the pharmacokinetic behaviour of prednisolone (Pickup, Lowe, Latham, Rhind, Wright & Downie, 1977; Loo, McGilveray, Jordan, Moffat & Brien, 1978; Rose, Yurchak & Jusko, 1978; Tanner, Bochner, Caffin, Halliday & Powell, 1979). There is, however, some disagreement over the effect of this non-linear behaviour on pharmacokinetic parameters, the dose range over which it is operative and its relationship to the plasma protein binding of prednisolone and its urinary clearance. A study has therefore been carried out in which a series of intravenous doses of prednisolone ranging from 16 to 64 mg has been administered to normal volunteers and a pharmacokinetic analysis carried out to detect deviations from linear kinetic behaviour.

Methods

Human volunteer study

Subjects studied were normal healthy volunteers and comprised five male subjects (age range 23–35 years; weight range 65–89 kg) and two female subjects (aged 23 and 27 years, both weighing 48 kg). All subjects were medical personnel and gave informed consent to undertake the protocol which was approved by the Hospital Ethical Committee. No subject was taking any regular medication. Each subject was fasted from midnight and, after a baseline blood sample had been taken, they received (at between 08.00–09.00 h) either 16, 32, 48, 64 mg prednisolone (as prednisolone sodium phosphate: Codelsol[R], Merck, Sharp & Dohme Ltd, Hoddesdon, Herts) given over 1 min intravenously or 10 mg prednisolone orally (as Precortisyl[R], Roussel, Wembley Park, Middx). These treatments were administered in random order. Subjects 1–5 received all treatments, subject 7 only the 10 mg and 16 mg dose and subject 6 only the 16 mg dose. The tablets were swallowed whole with 100 ml water and no food or beverages were permitted for 3 h after dosing. After this time food and beverages were allowed as required. A washout period of at least 1 week separated each treatment. Following intravenous prednisolone 5 ml venous blood samples were taken at 0.083, 0.16, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12 h, following oral prednisolone blood samples were taken at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10 h. In some cases

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additional samples were also collected to better define the plasma concentration–time curve.

Prednisolone assay

This was by the quantitative thin layer chromatographic technique developed by Morrison, Bradbrook & Rogers (1977) with minor modifications. Following extraction with ethyl acetate, the samples were applied as a spot, rather than as a band, to the high performance thin layer plates (Kieselgel 60—without fluorescent indicator). The plates were developed in a solvent mixture of chloroform : ethanol : water (90 : 10 : 2). After visualisation with a spray of concentrated sulphuric acid : ethanol (6.5 : 3.5) and heating at 60°C for 45 min, the fluorescent intensity of the spots was determined by scanning the plates at a wavelength of 598 nm using a Vitatron flying spot densitometer. In the presence of high levels of cortisol and low prednisolone concentrations the scanning wavelength was altered to 638 nm where the fluorescence of cortisol was negligible and interference between the peaks (cortisol R_F 0.3, prednisolone R_F 0.25) is eliminated. Prednisone, a minor metabolite of prednisolone, has an R_F of 0.43 and is well resolved from prednisolone.

The within assay coefficient of variation is 5.4% at 25 ng ml^{-1} (n = 5); 3.8% at 100 ng ml^{-1} (n = 9); 5.8% at 200 ng ml^{-1} (n = 9) and 7.9% at 1000 ng ml^{-1} (n = 8).

Pharmacokinetics

A two compartment, open pharmacokinetic model was fitted by digital computer to the plasma concentration (C), time (t) data following intravenous prednisolone administration using the simplex algorithm of Nelder & Mead (1965) utilising the equation

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where A and B are coefficients with units of concentration and α and β are the hybrid first order rate constants of distribution and disposition respectively. Plasma concentration–time data following oral drug administration were found to be fitted most satisfactorily by a one compartment open model with a first order input as expressed by

$$C = \frac{F D k_a}{V_d(k_a - k)} (e^{-k(t - t')} - e^{-k_a(t - t')})$$

where D is the dose, V_d is the apparent volume of distribution, t′ the lag time before prednisolone is detected in the plasma, F is the bioavailability fraction and k_a and k are the apparent first order absorption and elimination rate constants. The data were fitted in their original scale of measurement and goodness of fit was assessed by minimisation of the sum of squared deviations. The areas under the plasma concentration–time curves (AUC) were estimated by the linear trapezoidal rule with the addition of (C (at last measured time point)/elimination rate constant) to approximate the tail region of the curve. The systemic clearance (Cl) was found from D/AUC and $V_d\beta$, the apparent volume of distribution in the β-phase from Cl/β. The bioavailability was assessed from $F = \frac{16\,(AUC)^{10\,mg}_{p.o.}}{10\,(AUC)^{16\,mg}_{i.v.}}$ which assumes that bioavailability is not dose-dependent. No formal study has been made of this assumption but Tanner, Bochner *et al.* (1979) gave two healthy volunteers oral and intravenous doses of 20 and 100 mg prednisolone and found no obvious dose-related difference in the estimated bioavailability. The determination of F allowed an approximate estimate of the apparent volume of distribution following oral prednisolone from the computer generated estimate of FD/V_d.

Results

Table 1 shows the computed pharmacokinetic parameters following intravenous administration of the indicated doses of prednisolone. No obvious trend is observed in any of these parameters with dose apart from an increase in the AUC with dose. This was clearly a linear relationship (figure 1). The plasma concentration–time curves were normalised by dividing the individual observations by the dose administered. Figure 2 shows the family of curves obtained for subject 1. The superimposability of these curves will be noted.

Table 2 shows the pharmacokinetic parameters determined following oral prednisolone administration.

All subjects receiving intravenous prednisolone noted, to varying degrees, perineal pruritus and paraesthesiae lasting for up to 5 min following the injection. This is akin to similar symptoms described with intravenous hydrocortisone sodium phosphate which is attributed to the presence of the phosphate ester (Novak, Gilbertson, Seckman, Stewart, Di Santo & Stubbs, 1976).

Discussion

The mean half-life of prednisolone found in these subjects, although longer than observed in a previous study (Morrison *et al.*, 1977) was comparable with data reported by other workers (Pickup *et al.*, 1977; Tanner, Bochner *et al.*, 1979; Tanner, Caffin, Halliday & Powell, 1979). We have found no change

Table 1 Pharmacokinetic parameters estimated following intravenous administration of 16–64 mg prednisolone

Dose				*16 mg*						*32 mg*		
Subject	α (h^{-1})	β (h^{-1})	$T_{½}\beta$ (*h*)	*AUC* (*ng ml*$^{-1}$ *h*)	*Cl* (*l h*$^{-1}$ *kg*$^{-1}$)	$V_d\beta$ (*l kg*$^{-1}$)	α (h^{-1})	β (h^{-1})	$T_{½}\beta$ (*h*)	*AUC* (*ng ml*$^{-1}$ *h*)	*Cl* (*l h*$^{-1}$ *kg*$^{-1}$)	$V_d\beta$ (*l kg*$^{-1}$)
1	21.93	0.169	4.10	2820	0.086	0.511	10.27	0.153	4.53	5823	0.085	0.551
2	39.19	0.157	4.41	2808	0.118	0.759	10.62	0.157	6.37	5331	0.125	0.798
3	6.57	0.121	5.73	2460	0.073	0.605	6.15	0.142	4.88	5878	0.061	0.432
4	1.08	0.171	4.05	2370	0.087	0.506	4.92	0.175	3.96	3852	0.107	0.609
5	28.82	0.212	3.26	2330	0.132	0.622	2.8	0.241	2.87	3520	0.175	0.724
6	5.15	0.105	6.60	2790	0.079	0.748	—	—	—	—	—	—
7	8.97	0.194	3.57	3080	0.108	0.558	—	—	—	—	—	—
Mean	15.96	0.161	4.53	2665	0.098	0.616	6.95	0.174	4.52	4881	0.111	0.623
s.d.	14.24	0.038	1.20	281	0.022	0.104	3.41	0.039	1.28	1117	0.043	0.144
Dose				*48 mg*						*64 mg*		
Subject	α (h^{-1})	β (h^{-1})	$T_{½}\beta$ (*h*)	*AUC* (*ng ml*$^{-1}$ *h*)	*Cl* (*l h*$^{-1}$ *kg*$^{-1}$)	$V_d\beta$ (*l kg*$^{-1}$)	α (h^{-1})	β (h^{-1})	$T_{½}\beta$ (*h*)	*AUC* (*ng ml*$^{-1}$ *h*)	*Cl* (*l h*$^{-1}$ *kg*$^{-1}$)	$V_d\beta$ (*l kg*$^{-1}$)
1	6.24	0.185	3.75	9229	0.080	0.432	5.78	0.193	3.59	11587	0.085	0.441
2	1.61	0.168	4.13	7836	0.128	0.758	35.07	0.202	3.43	13785	0.097	0.479
3	16.48	0.182	3.81	7944	0.068	0.373	5.73	0.163	4.25	13045	0.055	0.338
4	7.86	0.20	3.47	5426	0.114	0.568	2.36	0.160	4.33	7546	0.109	0.679
5	1.63	0.215	3.22	4850	0.190	0.886	0.32	0.272	2.55	6485	0.190	0.697
6	—	—	—	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—	—	—	—
Mean	6.76	0.190	3.68	7057	0.116	0.603	9.85	0.198	3.63	10490	0.107	0.527
s.d.	6.09	0.018	0.35	1847	0.048	0.217	14.28	0.045	0.72	3289	0.050	0.156

in the elimination rate of prednisolone over the dosage range investigated and in this we agree with the results of Tanner, Bochner *et al.* (1979), who investigated 43 subjects usually only at one dose level over a range of 5–200 mg prednisolone orally and three subjects with doses of 20 and 100 mg intravenously. Pickup *et al.* (1977) on the other hand, using a tritiated prednisolone marker, investigated doses of 0.15 mg/kg and 0.3 mg/kg in the same subjects and found significant prolongation of the half-life at these doses when compared to the half-life of a small tracer dose. A direct comparison of half-lives at 0.15 and 0.3 mg/kg, however, revealed no significance. The extrapolation of this comparison of the disposition of a minute tracer dose with that of a much larger therapeutic dose to the clinical situation is open to question. The details of the work of Rose *et al.* (1978), as yet only available in abstract, may elucidate the problem. They studied five subjects and state that the half-life increased from 3 to 5 h as the dose of prednisolone increased from 5 to 50 mg although it is not clear how many doses were studied in each subject, by what route drug was administered and the variability of their data. Certainly over the range of doses studied in the present work the observed half-lives varied between 2.5 and 6.6 h but without consistent pattern. The source of this variable behaviour, particularly when the drug has been given intravenously thereby excluding absorption variables, is obscure.

The values for systemic clearance of prednisolone may be compared with the values quoted by Pickup *et al.* (1977) which were 0.06 l kg^{-1} h^{-1} (tracer dose), 0.09 l kg^{-1} h^{-1} (0.15 mg/kg) and 0.12 l kg^{-1} h^{-1} (0.3 mg/kg). Loo *et al.* (1978) gives 0.10 l kg^{-1} h^{-1}

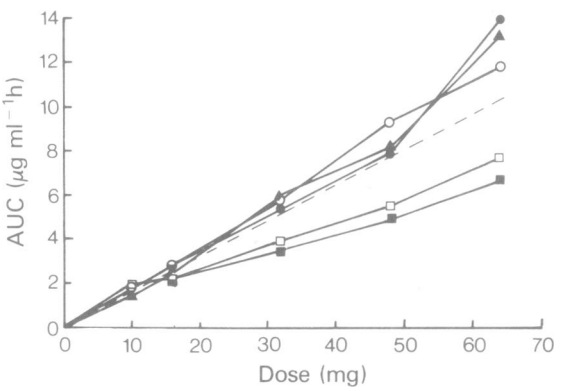

Figure 1 Relationship between area under plasma prednisolone concentration–time curve and dose. (○ subject 1; ● subject 2; ▲ subject 3; □ subject 4; ■ subject 5). Broken line is the regression line for the mean at each dose level.

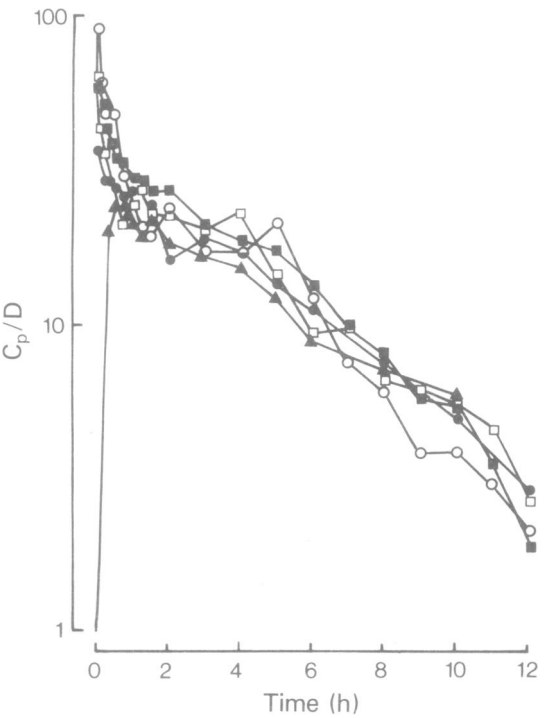

Figure 2 Dose-normalised plasma concentration, time profile for subject 1. (▲ 10 mg p.o.; ● 16 mg i.v.; □ 32 mg i.v.; ■ 48 mg i.v.; ○ 64 mg i.v.).

Table 2 Pharmacokinetic parameters estimated following oral administration of 10 mg prednisolone

Subject	k (h^{-1})	$T_{1/2}$ (h)	AUC ($ng\,ml^{-1}h$)	$\frac{FD}{V_d}$ ($ng\,ml^{-1}$)	Cl ($ml\,h^{-1}\,kg^{-1}$)	V_d ($l\,kg^{-1}$)	F
1	0.152	4.56	1669	249.0	0.092	0.619	0.947
2	0.159	4.36	1836	301.0	0.114	0.692	1.046
3	0.273	2.54	1450	376.3	0.078	0.299	0.943
4	0.115	4.47	1898	302.4	0.068	0.424	1.281
5	0.199	3.48	1785	356.1	0.108	0.540	1.224
7	0.137	5.06	1800	269.4	0.116	0.773	0.935
Mean	0.179	4.08	1740	309.0	0.096	0.558	1.063
s.d.	0.050	0.91	161	49.0	0.020	0.175	0.154

(0.134 mg/kg) and 0.13 l kg^{-1} h^{-1} (0.268 mg/kg). In this latter study, prednisone was administered orally and clearance calculated assuming prednisone is completely converted to prednisolone. Tanner, Caffin, *et al.* (1979) have shown that this assumption is partially invalid since complete conversion does not occur. These workers found that the ratio of prednisone to prednisolone varies from 7–19% when prednisone is given orally although following oral prednisolone this ratio is a little higher and less variable at 26 ± 2% over the dosage range 5–120 mg (Tanner, Bochner, *et al.*, 1979). A similar conclusion was reached by Tse & Welling (1979) who found that prednisone consistently yields only 75% of the AUC of an equivalent dose of prednisolone.

Tanner, Bochner, *et al.* (1979) have also reported an increased systemic prednisolone clearance from 11.3 ± 0.01 h^{-1} to 17.4 ± 0.6 l h^{-1} with doses of 20 and 100 mg prednisolone respectively in three subjects. The present study with five subjects over a dose range of 16 to 64 mg has not revealed this trend. Similarly, unlike Pickup *et al.* (1977) and Tanner, Bochner, *et al.* (1979), we have not found an increased apparent volume of distribution for prednisolone although our values are within the range reported by these workers. The reason for the discrepancy is not immediately obvious but since the estimation of both clearance and apparent volume of distribution are dependent upon the determination of the area under the plasma concentration–time curve it may be instructive to compare this data. Our data show linear dependence of AUC with dose. As can be seen by an examination of the figure of Tanner, Bochner, *et al.* (1979) there is much scatter in their AUC–dose plot. This is understandable since in most cases each subject contributed only once to the plot and few subjects received a series of doses. Although linear regression of all their data showed the best correlation, they suggested that proportionality of AUC to dose was only operative over the range 5–20 mg and that above this dose a lesser increase in AUC than might be expected was produced by dosage increments. Pickup *et al.* (1977) used an extrapolation method to estimate the apparent volume of distribution (from which they then calculated clearance). This assumes that prednisolone confers the properties of a single compartment model on the body following intravenous administration although their results (and ours) show this to be invalid. The error produced by making this assumption for our data would have been of the order of 10% (Dvorchik & Vesell, 1978). There is no evidence of changes in the degree of compartmentalisation with dose and therefore it is unlikely that this factor will alone explain the discrepancy between our results and those of Pickup *et al.* (1977).

One suggested cause of non-linear pharmacokinetics for prednisolone is saturation of plasma protein binding (Pickup *et al.*, 1977). Agaheyoglu, Bergstrom, Gillespie, Wagner & Kay (1979) have demonstrated that *in vitro* the plasma protein binding of prednisolone changes as a non-linear function of the total plasma prednisolone concentration over a plasma concentration range of 30–300 ng ml^{-1}. On the other hand, Tanner, Bochner, *et al.* (1979) found that protein binding remains very constant over a very wide dosage (5–200 mg) and concentration (400–2000 ng ml^{-1}) range. For comparison, the maximum plasma concentration observed in any of our subjects after 64 mg prednisolone given intravenously was 5850 ng ml^{-1} but in other subjects the early plasma concentration prior to distribution was approximately 3000 ng ml^{-1}. By 1 h the concentration had fallen in all cases to below 2000 ng ml^{-1}. The mean peak plasma prednisolone concentration following 10 mg prednisolone given orally was 307 ng ml^{-1}. It may be noted that Rose *et al.* (1978) have reported that the apparent renal clearance of prednisolone is a non-linear function of the plasma concentration but further details of their work and its confirmation are not yet available.

Surprisingly, there have been few previous estimates of prednisolone bioavailability. Tanner, Bochner, *et al.* (1979) found a mean bioavailability of 98.5 ± 4% which is consistent with our own observations.

Classical tests for linear pharmacokinetics (Wagner, 1975) include demonstration of (i) a linear relationship between the area under the plasma concentration–time curve (AUC) and dose (Figure 1); (ii) superimposable dose-normalised plasma concentration, time curves (Figure 2); (iii) derived rate parameters which are independent of dose (Tables 1 and 2). It is seen that all these tests are satisfied by our data. However, it should be recognised that these tests are not infallible and may be too insensitive to detect violation of superimposition over the dose range studied. Wagner (1972) has demonstrated that some types of non-linear pharmacokinetic models which incorporate tissue binding will also satisfy these criteria and can given apparent biexponential plasma concentration, time curves.

We were therefore unable to confirm the suggested non-linear pharmacokinetic behaviour of prednisolone over the dose range studied in our group of volunteers.

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