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Methylprednisolone pharmacokinetics after intravenous and oral administration

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1 The pharmacokinetics of methylprednisolone (MP) were studied in five normal subjects following intravenous doses of 20, 40 and 80 mg methylprednisolone sodium succinate (MPSS) and an oral dose of 20 mg methylprednisolone as 4 × 5 mg tablets. Plasma concentrations of MP and MPSS were measured by both high performance thin layer (h.p.t.l.c.) and high pressure liquid chromatography (h.p.l.c.).

2 The mean values (± s.d.) of half-life, mean residence time (MRT), systemic clearance (CL) and volume of distribution at steady state (V_{ss}) of MP following intravenous administration were 1.93 ± 0.35 h, 3.50 ± 1.01 h, 0.45 ± 0.12 l h^{-1} kg^{-1} and 1.5 ± 0.63 l kg^{-1}, respectively. There was no evidence of dose-related changes in these values. The plasma MP concentration–time curves were superimposable when normalized for dose.

3 The bioavailability of methylprednisolone from the 20 mg tablet was 0.82 ± 0.11 (s.d.).

4 *In vivo* hydrolysis of MPSS was rapid with a half-life of 4.14 ± 1.62 (s.d.) min, and was independent of dose. In contrast, *in vitro* hydrolysis in plasma, whole blood and red blood cells was slow; the process continuing for more than 7 days. Sodium fluoride did not prevent the hydrolysis of MPSS.

Keywords methylprednisolone prednisolone corticosteroids *in vitro* and *in vivo* hydrolysis analysis of corticosteroids

Introduction

A disagreement exists within the literature as to whether the kinetics of methylprednisolone are linear (Szefler *et al.*, 1986; Assael *et al.*, 1982; Shah *et al.*, 1987; Weber *et al.*, 1988; Derendorf *et al.*, 1988) or non-linear (Derendorf *et al.*, 1985, 1987). A similar conflict also exists for other steroids (Gustavson & Benet, 1985; Rose *et al.*, 1981; Al-Habet & Rogers, 1980; Lowe *et al.*, 1986; Pelsor *et al.*, 1987). The bioavailability of orally administered methylprednisolone is highly variable in normal subjects and patients (Antal *et al.*, 1983; Narang *et al.*, 1983; Baylis *et al.*, 1982; Brier *et al.*, 1985). The present study has therefore been carried out to investigate the pharmacokinetics of methylprednisolone in normal human subjects following intravenous (20, 40 and 80 mg) doses of methylprednisolone sodium succinate and an oral (20 mg) dose of methylprednisolone. *In vitro* and *in vivo* hydrolysis of the ester was also investigated

Part of this study was presented at the 68th World Annual Congress of FDI, Hamburg, Germany (1980), and at the joint annual meeting of American College of Clinical Pharmacology (ACCP) and American Association of Pharmaceutical Scientists (AAPS), Orlando, Florida (*J. clin. Pharmac.*, **28** (1988)).

Methods

Five healthy subjects volunteered for the study. They comprised four males (mean age 26.6 ± 1.8 (s.d.) years; and weight 70.4 ± 16.5 s.d. kg) and

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one female, age 28 years and weight 48 kg. The subjects gave informed consent to the study which had been approved by the local Ethics Committee. They were not taking any regular medication and were fasted from the previous midnight and 4 h after a baseline blood sample had been taken prior to the dose. In separate experiments each subject received intravenous doses of 20, 40 and 80 mg of methylprednisolone sodium succinate (Solu-Medrone, Upjohn Co) and oral doses of 20 mg (4 × 5 mg) tablets of methylprednisolone alcohol (Medrone, Upjohn Co). All treatments were given in random order. Administration was between 08.00–09.00 h. Intravenous doses were given over 1 min. The tablets were swallowed whole with about 100 ml water. A washout period of at least 2 weeks separated each treatment. Venous blood samples (5 ml) were taken over 0.016 to 24 h and 0.25 to 24 h following intravenous and oral administration, respectively.

The *in vitro* hydrolysis of methylprednisolone sodium succinate (MPSS) was studied following the incubation of 8 μg ml^{-1} (within the range of initial concentration observed after intravenous injections) of the injectable solution in plasma, whole blood, red blood cells (RBCs), phosphate buffer (pH 7.4) and methanol, all at 37°C. The biological fluids were incubated in the presence or absence of 7 mg ml^{-1} sodium fluoride in an attempt to prevent the hydrolysis (Garg *et al.*, 1978). Samples were taken into either plain plastic tubes or sodium oxalate coated tubes. Timed samples were taken over a period of 4 to 7 days from all fluids and immediately stored at −40°C pending analysis.

Methylprednisolone assay

Plasma concentrations of methylprednisolone (MP) were measured by a quantitative thin layer chromatographic (h.p.t.l.c.) method as described previously for prednisolone (Al-Habet *et al.*, 1981). The solvent system used was (chloroform : ethanol : water ; 45 : 5 : 7.5).

A high pressure liquid chromatographic (h.p.l.c.) assay was also used (Al-Habet, 1983) to validate the data obtained by h.p.t.l.c. Plasma samples containing 2 μg triamcinolone as internal standard were extracted with 3 ml ethyl acetate. The organic layer was removed and evaporated to dryness and the residue was taken up into 50 μl of the mobile phase (dichloromethane : methanol : acetic acid ; 95 : 1 : 3.75) of which 30 μl were injected onto the column (packed with Zorbax SIL-5 μm—Magnus Scientific Ltd, Sandbach, Cheshire, UK) via a Rheodyne injection port and a 200 μl solvent loop. The flow rate of the mobile phase was maintained at 2.5 ml min^{-1} by an Altex solvent Pump, model 110A (Altex Scientific Inc., California, USA). The Pye Unicam LC-UV detector (Pye Unicam Ltd., Cambridge, UK) was set at 254 nm. Authentic methylprednisolone used in this study was a gift from The Upjohn Company (Kalamazoo, Michigan, USA).

Pharmacokinetic analysis

The bioavailability (F) of the orally administered 20 mg dose of MP was estimated from the equation:

$$F = \frac{AUC^{(po)}\ 20\,mg}{AUC^{(i.v.)}\ 20\,mg}$$

where AUC is the area under the plasma methylprednisolone concentration–time curve. This was estimated by the linear trapezoidal rule which was also used to measure the first moment of the plasma methylprednisolone concentration–time curve (AUMC)—after multiplying each plasma concentration by its time. AUC and AUMC were both extrapolated to infinity. The mean residence time (MRT) was calculated from AUMC/AUC (Cutler, 1987; Kong & Jusko, 1988). The systemic clearance (CL) was calculated from D (dose)/AUC. The volume of distribution at steady state (V_{ss}) was calculated from CL.MRT (Kong & Jusko, 1988). The total plasma elimination half life was calculated from $0.693/k$ where k is the elimination rate constant calculated from the terminal points of the plasma drug concentraton–time profile.

Results

The h.p.t.l.c. and h.p.l.c. methods were simple, rapid, specific, reproducible (coefficient of variation < 10%) and sensitive (10 and 50 ng ml^{-1} of MP and MPSS, respectively, could be assayed by both methods). Following h.p.t.l.c. the R_F values and the band colours of a number of steroids were: MP 0.303 (pink), MPSS 0.09 (pink), cortisol 0.393 (faint green), prednisolone 0.292 (pink), prednisone 0.42 (faint blue) and progesterone 0.79 (blue). The retention times on h.p.l.c. were 4.8, 5.8, 7.2 and 8.2 min for MPSS, cortisol, MP and triamacinolone, respectively. The calibration curves of MP and MPSS for both methods were linear ($r \geq 0.995$) over a concentration range of 0.025 to 2 μg ml^{-1} for MP and 0.05 to 20 μg ml^{-1} for MPSS, and all passed through the origin.

Figure 1 shows the mean plasma concentration–time profiles of MP following intravenous and oral administration. MP data were best described by a single compartment pharmacokinetic open model at all doses. The ratio of AUC in RBCs to

that of plasma was 0.48. In all subjects, the overall mean plasma half-life of MPSS was 4.14 ± 1.62 (s.d.) min following all doses. In contrast, *in vitro* hydrolysis of MPSS was extremely slow and uninfluenced by the addition of sodium fluoride or oxalate (Figure 2).

Table 1 shows the mean pharmacokinetic parameters of methylprednisolone following oral and intravenous administration. The dose-normalized plasma concentration–time curves were superimposable (Figure 3) and there was a linear relationship ($r = 0.925$) between AUC and dose (Figure 4).

None of the subjects experienced perineal pruritus or paraesthesia following i.v. injection of MPSS. However, this was noted in all subjects who received i.v. injection of prednisolone sodium phosphate which confirms that this strange feeling was due to the presence of phosphate in the i.v. preparations (Al-Habet & Rogers, 1980) The mechanism of this is not clear.

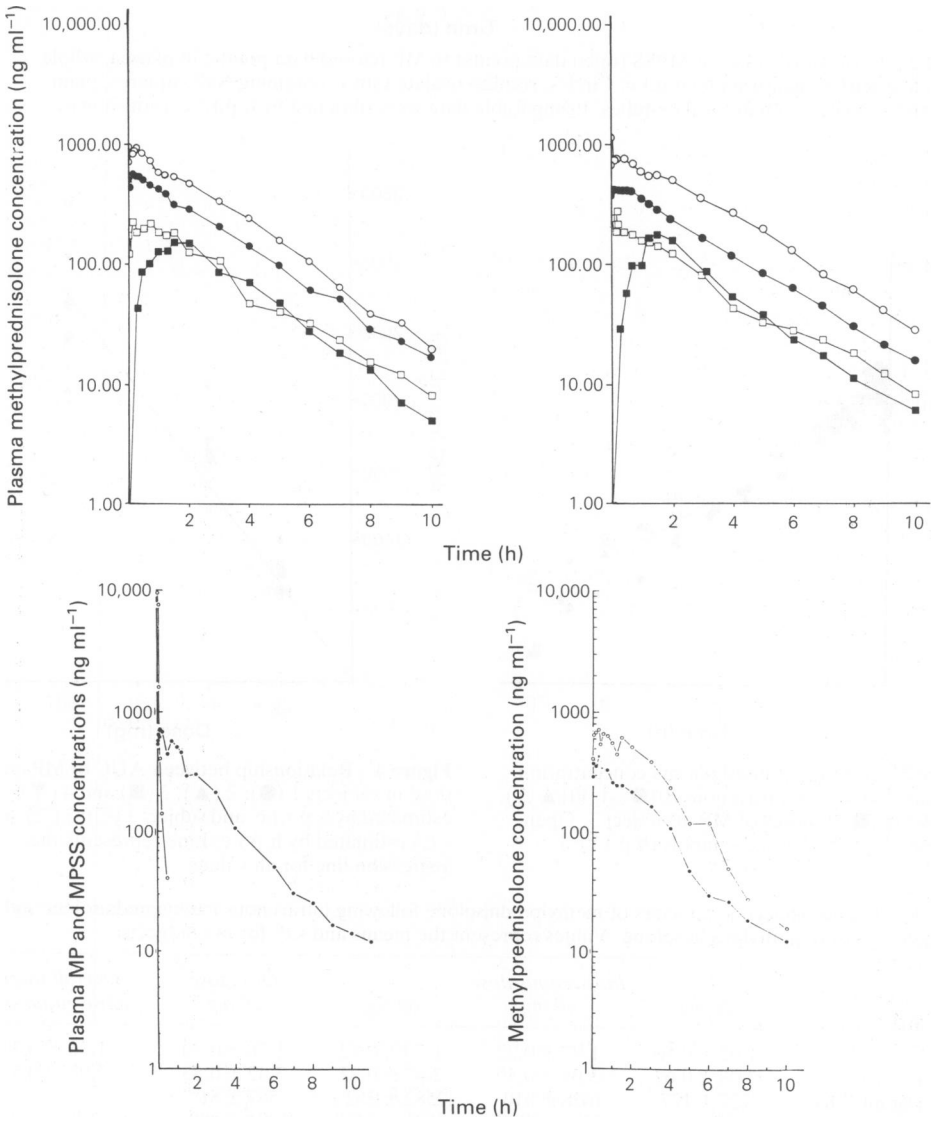

Figure 1 Mean plasma concentration–time profiles of MP following an oral 20 mg dose of MP (■) and intravenous doses of 20 (□); 40 (●) and 80 mg (○) MP sodium succinate [h.p.t.l.c. and h.p.l.c. data (top left) and for h.p.l.c. data (top right)]. Data shown in the lower left panel demonstrate the rapid hydrolysis of MPSS (○) and the generation of MP (●) following 80 mg intravenous Solu-Medrone in subject 2 (h.p.t.l.c. data). The lower right panel shows the concentrations of MP in plasma (○) and RBCs (●) in subject 1 following an 80 mg intravenous dose (h.p.t.l.c. data).

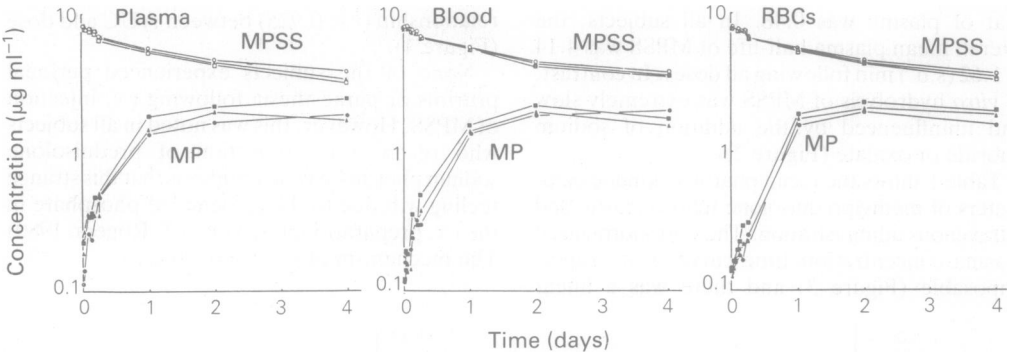

Figure 2 *In vitro* hydrolysis of MPSS (open data points) to MP (closed data points) in plasma, whole blood, and RBCs, measured by h.p.l.c. Circles, sodium oxalate tubes containing NaF, squares, plain tubes and triangles, sodium oxalate tubes. Comparable data were obtained by h.p.t.l.c. (not shown).

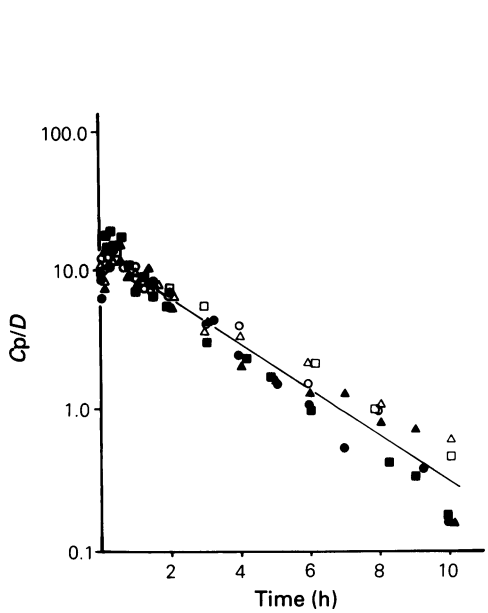

Figure 3 Dose-normalised plasma concentration–time curve following intravenous 20 (●○); 40 (▲ △); and 80 mg (■ □) doses of MP in subject 3. Open symbols (h.p.l.c.), closed symbols (h.p.t.l.c.).

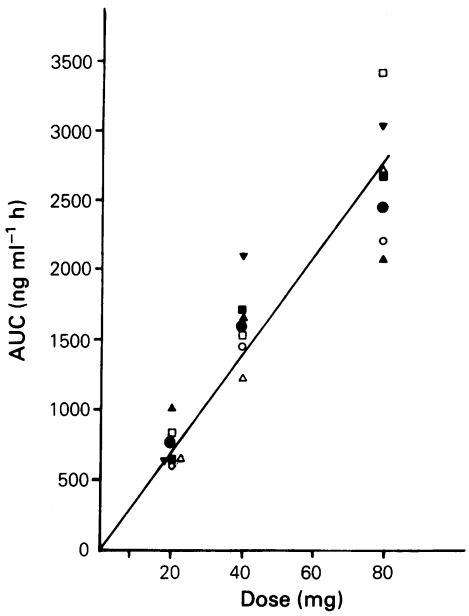

Figure 4 Relationship between AUC of MP and dose in subjects 1 (●); 2 (▲); 3 (■) and 4 (▼) estimated by h.p.t.l.c. and subject 1 (○); 3 (□) and 5 (△) estimated by h.p.l.c. Line represents the regression line for all values.

Table 1 Pharmacokinetic parameters of methylprednisolone following intravenous methylprednisolone sodium succinate and oral methylprednisolone. Values represent the means and s.d. for five subjects.

Parameter	*Intravenous dose* 20 mg	40 mg	80 mg	*Oral dose* 20 mg	*Overall means (Intravenous only)*
$t_{½}$(h)	1.92 ± 0.50	1.97 ± 0.32	1.70 ± 0.12	1.78 ± 0.30	1.86 ± 0.34
MRT (h)	3.08 ± 0.62	3.04 ± 0.59	2.67 ± 0.37	3.42 ± 0.83	2.93 ± 0.53
AUC (ng ml^{-1} h)	727 ± 177	1628 ± 310	2582 ± 362	587 ± 81	—
AUMC (ng ml^{-1} h)	2363 ± 693	5284 ± 1043	6831 ± 1498	1991 ± 488	—
CL (l h^{-1} kg^{-1})	0.413 ± 0.061	0.377 ± 0.105	0.477 ± 0.201	0.523 ± 0.894	0.422 ± 0.133
V_{ss} (l kg^{-1})	1.25 ± 0.24	1.13 ± 0.34	1.24 ± 0.43	1.78 ± 0.53	1.21 ± 0.32
C_{max} (ng ml^{-1})	—	—	—	207 ± 62	—
t_{max} (h)	—	—	—	1.45 ± 0.44	—
F	—	—	—	0.82 ± 0.11	—

Discussion

Several h.p.l.c. methods are available for the measurement of MP and its soluble prodrug esters (Shah & Weber, 1985; Ebling *et al.*, 1984; Anderson *et al.*, 1985; Garg *et al.*, 1977). However, some of these methods involve a relatively lengthy extraction procedure or suffer from a lack of adequate sensitivity. The h.p.t.l.c. and h.p.l.c. methods described in this report both compare favourably with the previous methods with respect to sensitivity, specificity and reproducibility.

Figure 1 clearly demonstrates the rapid *in vivo* hydrolysis of MPSS followed by the generation of MP. Rapid hydrolysis of other MP ester prodrugs was reported by others (Derendorf *et al.*, 1985; Antal *et al.*, 1983; Shah *et al.*, 1987). The *in vitro* hydrolysis of MPSS was extremely slow in all incubation fluids (Figure 2). Sodium fluoride did not prevent the hydrolysis of MPSS but at a comparable concentration it has been shown to inhibit the hydrolysis of MP acetate (Garg *et al.*, 1978). Myers *et al.* (1982) observed that purified plasma cholinesterase does not hydrolyze MPSS. Despite the presence of substantial concentrations of MP in RBCs (Figure 1) the data suggest that blood enzymes play little role in the *in vivo* hydrolysis of the ester and that this process occurs mainly in the liver and other body organs.

The bioavailability of MP found in the present study (Table 1) was comparable with that reported by others (Narang *et al.*, 1983; Antal *et al.*, 1983; Albert *et al.*, 1979; Garg *et al.*, 1979). The pharmacokinetic characteristics of MP in relation to dose are still a subject of debate since dose-independent pharmacokinetics were reported by some (Szefler *et al.*, 1986; Assael *et al.*, 1982; Shah *et al.*, 1987; Weber *et al.*, 1988; Derendorf *et al.*, 1988) but not by others (Derendorf *et al.*, 1985; 1987). The details of the work of Derendorf *et al.* (1987, 1988) and Weber *et al.* (1988) are not yet available.

The plasma elimination half-life and the MRT of MP remained constant with dose (Table 1) consistent with the findings of others for methylprednisolone (Szefler *et al.*, 1986; Shah *et al.*, 1987), prednisolone and other natural and synthetic steroids (Gustavson & Benet, 1985; Brady *et al.*, 1987; Rohdewald *et al.*, 1987; Al-Habet & Rogers, 1980, 1989). The observed linear pharmacokinetics of MP are consistent with the fact that its plasma protein binding is independent of concentration (Szefler *et al.*, 1986; Ebling *et al.*, 1985). The pharmacokinetics of MP are unlike those of prednisolone which are complicated by various factors such as non-linear plasma protein binding characteristics, although these may not explain fully its pharmacokinetic behaviour (Rose *et al.*, 1981; Tanner *et al.*, 1979; Ferry & Wagner, 1987; Al-Habet & Rogers, 1985). MP exhibits a lower AUC, a shorter half-life, a larger volume of distribution, a faster clearance and a lower bioavailability than prednisolone following approximately the same doses in normal subjects (Al-Habet & Rogers, 1980). The octanol/phosphate buffer (pH 7.4) partition coefficients of MP, prednisone and prednisolone are 238.18, 56.66 and 84.60 (Al-Habet *et al.* submitted for publication). This suggests that the higher lipophilicity of MP over that of prednisolone is probably one of the contributing factors to the increase in its volume of distribution. The renal clearance of MP and the percentage of the dose excreted unchanged in urine ($< 10\%$) have been reported to be independent of dose (Derendorf *et al.*, 1985; Assael *et al.*, 1982).

In conclusion, no evidence for non-linear pharmacokinetics of methylprednisolone was observed in this study and its bioavailability is incomplete following oral administration.

This paper is dedicated to Professor H. J. Rogers, the past Professor of Clinical Pharmacology, Guy's Hospital Medical School, University of London, who constructively supervised this research work. I am deeply saddened by the death of this young man who devoted so much of his life to the medical profession. I shall always remember him as a tireless researcher and compassionate human being.

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