Pharmaceutical Research, Vol. 5, No. 8, 1988

Report

Comparative Pharmacokinetics of Methylprednisolone Phosphate and Hemisuccinate in High Doses

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Received December 1, 1987; accepted February 17, 1988

The pharmacokinetics of methylprednisolone and two methylprednisolone esters, the phosphate and the hemisuccinate, were investigated after intravenous administration of the esters to 12 healthy male subjects in two different doses (250 and 1000 mg). Methylprednisolone was formed more rapidly from phosphate than from hemisuccinate. During the first 30 min methylprednisolone levels were three to four times higher after phosphate administration than after hemisuccinate. The mean residence time of the hemisuccinate was significantly longer and the total-body clearance lower than those of the phosphate. Whereas very little of the phosphate (mean, 1.7%) was eliminated unchanged into the urine, there were significant amounts of hemisuccinate (mean, 14.7%) excreted renally and therefore not bioavailable. Methylprednisolone saliva levels paralleled plasma levels; the average saliva/plasma ratio was 0.22. Neither phosphate nor hemisuccinate could be detected in saliva. An average of 7.2% of the administered dose was eliminated in the form of methylprednisolone in urine. Renal clearance was 24 ml/min and not dose or prodrug dependent. For both doses endogenous hydrocortisone levels were lowered after 24 hr. For the 1000-mg dose the depression was still significant after 48 hr. The results indicate that methylprednisolone phosphate results in a faster and more efficient conversion to its active form, methylprednisolone, than methylprednisolone hemisuccinate.

KEY WORDS: methylprednisolone phosphate; methylprednisolone hemisuccinate; pharmacokinetics; saliva analysis; endogenous hydrocortisone.

INTRODUCTION

High doses of glucocorticoids are indicated for emergency treatment of shock symptoms. To be immediately active these drugs are administered intravenously. However, since these drugs are poorly soluble in water, they cannot be injected directly and are given in the form of water-soluble prodrugs such as phosphate esters or hemisuccinate esters. These glucocorticoids esters are not pharmacologically active. Therefore, an important objective for the design of these prodrugs is that they release the active free glucocorticoid as rapidly as possible after the administration. The pharmacokinetics of methylprednisolone phosphate (1) and hemisuccinate (2,3) have been studied in high doses up to 1000 mg. A comparison of these studies suggested that the *in vivo* release of methylprednisolone will be faster when given as a phosphate than as a hemisuccinate. However, this conclusion was drawn from two independent studies in two different groups of patients. In the hemisuccinate study (2) the pharmacokinetics of methylprednisolone were nonlinear, whereas in the phosphate study (1) linear pharmacokinetics were observed. The present paper compares the two prodrugs in a double-blind crossover study. Both methylprednisolone and methylprednisolone prodrugs were measured in plasma, saliva, and urine. Also, endogenous hydrocortisone levels were measured as a pharmacodynamic correlate.

METHODS

Methylprednisolone phosphate and hemisuccinate were administered intravenously to 12 male subjects at a dose of 250 mg and to 12 other male subjects at a dose of 1000 mg. The subjects were 18–40 years old. Their body weight was 53–83 kg. Before the study they underwent a physical examination. All laboratory values were in the usual range; ECG and chest X ray were normal. All subjects were informed of the nature, purpose, and risks of the study and signed an informed consent form.

All subjects were asked to abstain from strenuous physical activity, beverages containing caffeine or other xanthine derivatives, nicotine, and alcohol from 36 hr before until 36 hr after drug administration. Drugs other than the study medication were not allowed from 1 week before the beginning of the trial. On the previous day subjects were asked to drink a volume of fluids of at least 1 liter between 6 and 10 PM in order to obtain a standardized basal situation. On the

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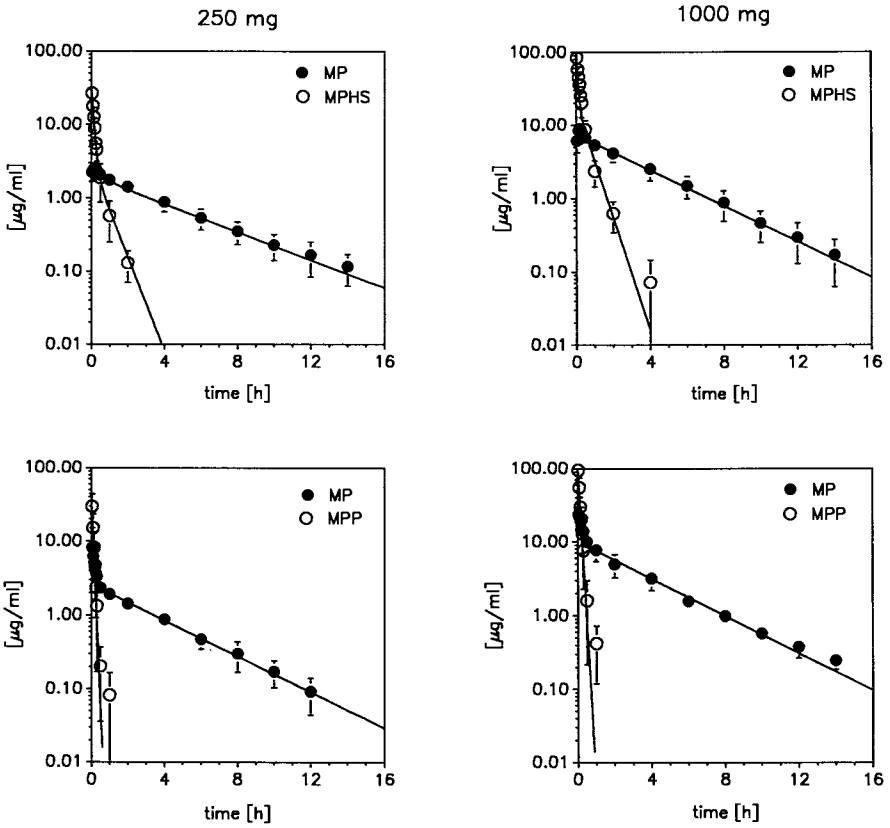

Fig. 1. Plasma levels of methylprednisolone (●; MP) after intravenous administration of methylprednisolone hemisuccinate (○; MPHS) or methylprednisolone phosphate (○;MPP). The curves represent the mean of the pharmacokinetic parameters of the individual data (N = 12); the points represent the plasma levels (means ± SD).

dosing day a standard breakfast was served 1.5 hr after drug administration. Blood sampling was performed on the contralateral arm with respect to drug administration. Blood samples were drawn immediately before dosing and at 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 24, and 48 hr after dosing. Blood was centrifuged and plasma was separated. The samples were frozen immediately and stored at −20°C until assayed. Urine was collected in fractions (0–2, 2–4, 6–8, 8–10, 10–12, and 12–24 hr) and aliquots were frozen until analyzed. Saliva was collected without stimulation but with chewing and was frozen until analyzed. All samples were assayed for methylprednisolone, methylprednisolone ester, and endogenous hydrocortisone by a modified high-performance liquid chromatographic (HPLC) method (4).

Pharmacokinetic Analysis

Pharmacokinetic parameters from plasma and saliva were determined by nonlinear regression and noncompartmental analysis. β is the hybrid constant that describes the terminal elimination phase of the plasma concentration–time curve. It was determined by nonlinear regression. $t_{1/2}$ is the terminal elimination half-life. It was calculated as 0.693/β. AUC is the area under the plasma concentration–time curve. It was calculated by the trapezoidal rule. The terminal part of the area beyond the last measured concentration C_{p_x} was estimated as C_{p_x}/β. AUMC is the area under the first moment curve. It was calculated as the area under the curve of a plot of the product of plasma concentration and time versus time using the trapezoidal rule. The terminal part of the area beyond the last measured concentration C_{p_x} at time t_x was estimated as $C_{p_x}t_x/\beta + C_{p_x}/\beta^2$. MRT is the mean residence time. It was calculated as AUMC/AUC. Cl_{tot} is the total-body clearance and was calculated as D/AUC, where D is the dose. $V_{d_{ss}}$ is the volume of distribution at steady state. It was calculated as $Cl_{tot} \cdot$ MRT. $V_{d_{area}}$ is the volume of distribution at pseudo-steady state during the elimination phase. It was calculated as Cl_{tot}/β. S/P is the saliva/plasma ratio. It was calculated as $AUC_{saliva}/AUC_{plasma}$.

Pharmacokinetic parameters were also obtained from urine. U_{MP} is the total amount of methylprednisolone eliminated into the urine, expressed as a percentage of the dose administered. U_{MPP} is the total amount of methylprednisolone phosphate eliminated into the urine, expressed as a percentage of the dose administered. U_{MPHS} is the total amount of methylprednisolone hemisuccinate eliminated into the urine, expressed as a percentage of the dose administered. $Cl_{ren(MP)}$ is the renal clearance of methylprednisolone. It was calculated as $(U_{MP}/D) \cdot Cl_{tot}$. $Cl_{ren(MPP)}$ is the renal clearance of methylprednisolone phosphate. It was calculated as $(U_{MPP}/D) \cdot Cl_{tot}$. $Cl_{ren(MPHS)}$ is the renal clearance of methylprednisolone hemisuccinate. It was calculated as $(U_{MPHS}/D) \cdot Cl_{tot}$.

Table I. Pharmacokinetic Parameters (Means and SD) from Plasma

	Phosphate		Hemisuccinate	
	250 mg	1000 mg	250 mg	1000 mg
Methylprednisolone				
β (hr^{-1})	0.28 (0.04)[a]	0.29 (0.05)	0.22 (0.02)	0.28 (0.04)
$t_{1/2}$ (hr)	2.53 (0.38)	2.54 (0.49)	3.16 (0.35)	2.50 (0.38)
AUC (μg · hr/ml)	10.5 (2.1)	38.9 (7.2)	10.3 (2.5)	27.8 (7.4)
AUMC (μg · h^2/ml)	36.8 (12.6)	133.2 (23.5)	47.8 (15.8)	101.3 (40.7)
MRT (hr)	3.45 (0.48)	3.46 (0.53)	4.60 (0.53)	3.53 (0.40)
Cl_{tot}/f (liters/hr)	18.6 (3.0)	19.9 (3.3)	18.4 (4.2)	27.3 (6.4)
$V_{d_{ss}}/f$ (liters)	62.5 (6.6)	69.0 (17.6)	82.8 (17.6)	91.7 (13.1)
$V_{d_{area}}/f$ (liters)	66.6 (8.5)	71.9 (18.8)	83.9 (15.9)	96.0 (17.3)
Methylprednisolone ester				
β (hr^{-1})	13.6 (3.2)	10.3 (1.7)	1.48 (0.38)	1.78 (1.08)
$t_{1/2}$ (min)	3.0 (0.6)	4.2 (0.6)	30.0 (0.6)	36.0 (12.1)
AUC (μg · hr/ml)	4.6 (2.3)	15.8 (5.2)	6.1 (1.8)	23.5 (6.3)
AUMC (μg · hr^2/ml)	0.38 (0.22)	1.83 (0.79)	1.69 (0.66)	8.18 (3.85)
MRT (min)	4.65 (0.93)	7.00 (2.64)	16.7 (3.9)	18.8 (3.9)
Cl_{tot} (liters/hr)	73.8 (43.8)	69.6 (20.4)	40.1 (13.4)	42.3 (11.4)
$V_{d_{ss}}$ (liters)	5.31 (2.67)	8.18 (4.77)	11.5 (6.4)	13.2 (4.0)

[a] SD in parentheses.

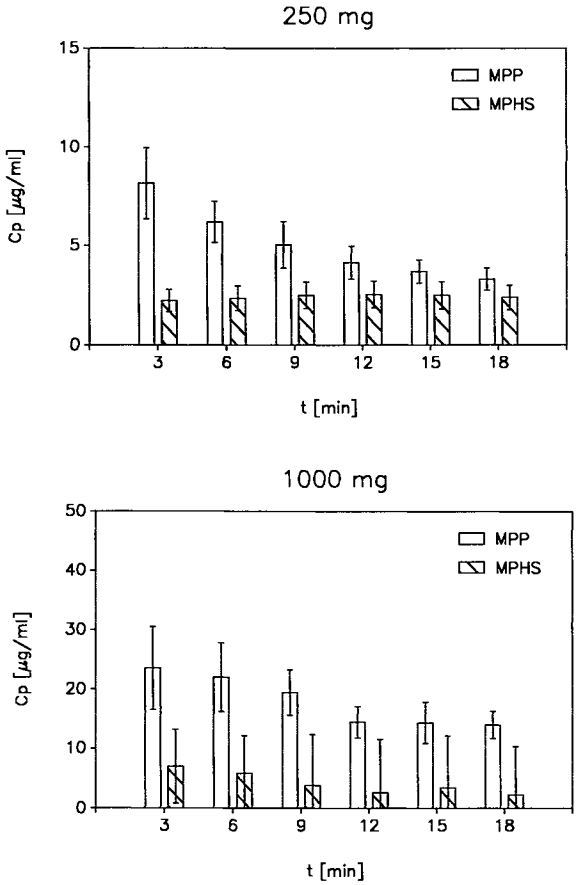

Fig. 2. Initial plasma levels of methylprednisolone after administration of methylprednisolone phosphate (MPP) and methylprednisolone hemisuccinate (MPHS) in two different doses.

RESULTS

Pharmacokinetics of Methylprednisolone

The pharmacokinetics of methylprednisolone could best be described by a two-compartment body model with first-order formation. Figure 1 shows the average plasma concentrations for the two doses of the two prodrugs. The mean pharmacokinetic parameters are listed in Table I. For both doses no significant difference in methylprednisolone concentrations can be obtained in the postdistribution phase after 1 hr. However, marked and highly significant differences can be seen during the first 20 min. Figure 2 shows a comparison of the initial methylprednisolone levels after the administration of the two doses. After phosphate administration the levels exceed those after hemisuccinate administration up to three- to fourfold.

In the case of methylprednisolone the calculation of Cl_{tot}, $V_{d_{ss}}$, and $V_{d_{area}}$ assumes complete conversion of the prodrug to methylprednisolone. However, this assumption is not valid, as unchanged prodrug could be detected in the urine. Therefore, Table I lists the ratios Cl_{tot}/f, $V_{d_{ss}}/f$, and $V_{d_{area}}/f$. The average total-body clearance of methylprednisolone is 21 liters/hr. The mean residence time is 3.8 hr, and the terminal half-life 2.7 hr. All of these numbers agree with previously published results (1,2) in the high dose range. No dose or prodrug dependency could be observed. However, $V_{d_{ss}}/f$ was found to be significantly larger after hemisuccinate than phosphate administration. This may be due to the higher bioavailability after phosphate administration as indicated by the recovery of unchanged phosphate in the urine.

Pharmacokinetics of Methylprednisolone Esters

The pharmacokinetics of the two methylprednisolone esters investigated were found to be linear and not dose dependent. For both esters there were no significant differences in clearance, volume of distribution, half-life, or mean

Table II. Pharmacokinetic Parameters (Means and SD) from Saliva and Urine

	Phosphate		Hemisuccinate	
	250 mg	1000 mg	250 mg	1000 mg
Saliva				
β (hr^{-1})	0.30 (0.11)[a]	0.33 (0.06)	0.41 (0.08)	0.37 (0.10)
$t_{1/2}$ (hr)	2.98 (2.06)	2.11 (0.28)	1.73 (0.31)	1.96 (0.44)
AUC ($\mu g \cdot hr/ml$)	2.23 (0.52)	10.88 (1.98)	1.81 (0.59)	7.00 (1.80)
S/P	0.22 (0.04)	0.28 (0.05)	0.18 (0.04)	0.23 (0.08)
Urine				
U_{MP} (%)	7.5 (2.4)	7.8 (2.2)	6.9 (2.5)	6.6 (3.7)
$Cl_{ren(MP)}$ (liters/hr)	1.33 (0.28)	1.52 (0.47)	1.19 (0.26)	1.71 (0.93)
U_{MPP} or U_{MPHS} (%)	2.4 (0.8)	1.1 (0.4)	16.0 (3.8)	13.4 (5.3)
$Cl_{ren(MPP)}$ or $Cl_{ren(MPHS)}$ (liters/hr)	1.87 (1.64)	0.71 (0.30)	6.24 (1.88)	5.27 (1.45)

[a] SD in parentheses.

residence time between the two doses administered (Table I). However, there were marked differences between the two esters. The average terminal half-life for methylprednisolone phosphate is 0.06 hr; that for the hemisuccinate, 0.55 hr. There was a significant difference in mean residence time (MRT). The average MRT for methylprednisolone phosphate is 5.8 min; that of the hemisuccinate, 17.7 min. The total-body clearance for the phosphate was 71 liters/hr; for the hemisuccinate, 41 liters/hr. The volume of distribution at steady state is 6.8 liters for the phosphate and 12.4 liters for the hemisuccinate.

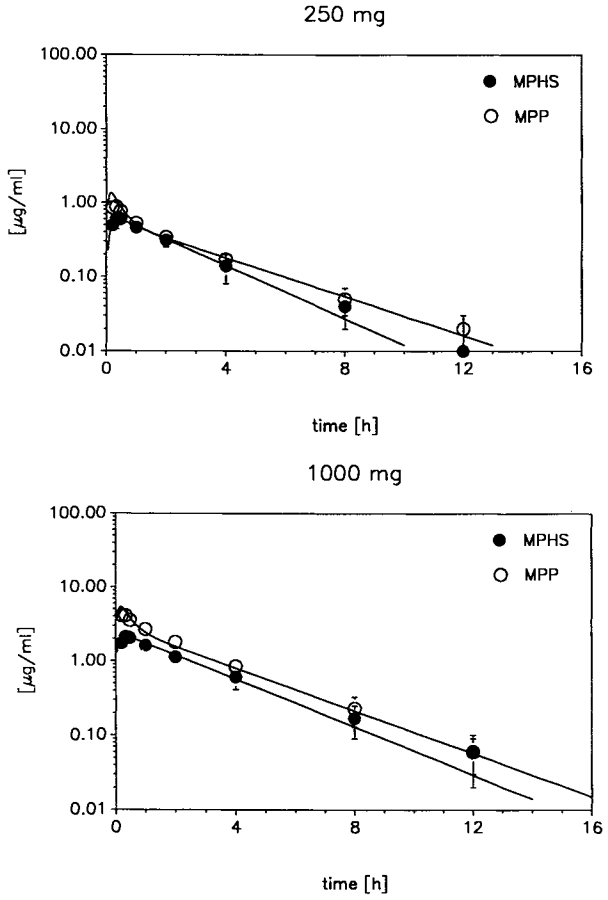

Fig. 3. Saliva levels of methylprednisolone after intravenous administration of two different doses of methylprednisolone hemisuccinate (●) and phosphate (○).

Saliva Analysis

Methylprednisolone was monitored in saliva. No methylprednisolone phosphate or hemisuccinate could be detected in saliva. The pharmacokinetics of methylprednisolone generated from methylprednisolone phosphate could best be described using a two-compartment body model with first-order formation, whereas after hemisuccinate administration a one-compartment body model was appropriate. The mean pharmacokinetic parameters derived from saliva are listed in Table II. Figure 3 compares the methylprednisolone levels in saliva for the two different prodrugs. Saliva levels are higher during the first hour after administration of the phosphate. Whereas there is no significant difference in the area under the saliva-level curve for the 250-mg doses of phosphate and hemisuccinate, the AUC for the 1000-mg hemisuccinate dose is significantly lower than that for the phosphate. This is in agreement with the results seen in plasma. There is no difference in the terminal half-life, with a mean of 2.2 hr. A comparison of the saliva/plasma ratios did not indicate a significant difference among the four treatments. The average saliva/plasma ratio was 0.22. This result agrees well with the previous observation (1) that sa-

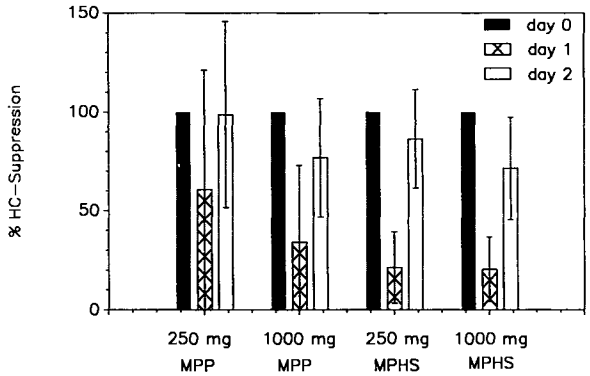

Fig. 4. Endogenous hydrocortisone suppression (means ± SD) as a percentage of the predose levels 24 (day 1) and 48 (day 2) hr after intravenous administration of methylprednisolone phosphate or hemisuccinate.

liva levels of methylprednisolone are equivalent to the free, non-protein-bound fraction of methylprednisolone in plasma. The plasma protein binding of methylprednisolone is known to be 77% (5).

Urinary Excretion

For each subject the total amounts of methylprednisolone and its respective prodrug were determined as a percentage of the administered dose (Table II). An average of 7.2% of the dose was excreted in the form of methylprednisolone. The renal clearance of methylprednisolone was not dose or prodrug dependent. There was a marked difference in the amount of prodrug excreted. Whereas only a small fraction of the phosphate (mean, 1.7%) was eliminated renally, methylprednisolone hemisuccinate was excreted to a much greater extent (mean, 14.7%). There was a significant difference in the renal clearance of the two methylprednisolone esters. The average renal clearance was 1.3 liters/hr for the phosphate and 5.8 liters/hr for the hemisuccinate.

Hydrocortisone Suppression

The endogenous hydrocortisone concentrations after the administration of two different doses of the two esters are shown in Fig. 4. To compensate for differences in hydrocortisone concentrations before drug treatment, the data were transformed using the predrug hydrocortisone level as a reference (100%) to calculate the percentage of prodrug level after drug administration. After 24 and 48 hr both esters result in the same degree of suppression (Fig. 4). The subjects administered 1000 mg showed greater hydrocortisone suppression than the subjects who were administered 250 mg. Statistically significant hydrocortisone suppression could be observed after 24 hr for both doses, whereas after 48 hr only the 1000-mg dose showed a significant effect.

DISCUSSION

The results of the present study clearly show the faster bioactivation of methylprednisolone phosphate in comparison to the hemisuccinate. This is of major clinical significance, as high doses of these glucocorticoids are used in emergency situations where immediate availability of the active steroid is desired. The reasons for this difference are the faster hydrolysis rate of phosphates in plasma (6) and their smaller volume of distribution due to less tissue distribution. Besides the advantage of having a higher *in vivo* lability, the phosphates also show a higher *in vitro* stability (6,7), which allows them to be stored in ready-to-inject syringes, so the dissolution step that is necessary with the hemisuccinates can be avoided. Finally, the phosphates provide a higher bioavailability of methylprednisolone, as less unhydrolyzed ester is eliminated into the urine. For these reasons the pharmacokinetic data suggest the preferability of the phosphate ester over the hemisuccinates.

ACKNOWLEDGMENT

The skillful technical assistance of Alwine Schulze-Elfringhoff is gratefully acknowledged.

REFERENCES

1. H. Möllmann, P. Rohdewald, J. Barth, M. Verho, and H. Derendorf. *Biopharm. Drug Dispos.* (in press).
2. H. Derendorf, H. Möllmann, P. Rohdewald, J. Rehder, and E. W. Schmidt. *Clin. Pharm. Ther.* 37:502–507 (1985).
3. P. K. Narang, R. Wilder, D. C. Chatterji, R. L. Yeager, and J. R. Gallelli. *Biopharm. Drug Dispos.* 4:233–248 (1983).
4. P. Rohdewald, J. Rehder, G. Drehsen, G. Hochhaus, H. Derendorf, and H. Möllmann. *J. Pharm. Biomed. Anal.* 3:565–573 (1985).
5. S. J. Szefler, W. F. Ebling, J. W. Georgitis, and W. J. Jusko. *Eur. J. Clin. Pharmacol.* 30:323–329 (1986).
6. H. Derendorf, P. Rohdewald, G. Hochhaus, and H. Möllmann. *J. Pharm. Biomed. Anal.* 4:197–206 (1986).
7. E. Novak, A. R. DiSanto, C. E. Seckman, G. Elliott, J. G. Lee, and S. S. Stubbs. *J. Clin. Pharmacol.* 17:324–333 (1977).