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 fluid of at least 1 liter between 6 and 10 PM in order to obtain a standardized basal situation. On the
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. $\beta$ 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 $0.693/\beta$. 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 $C_p$ was estimated as $C_v/\beta$. 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 $C_p$, at time $t$, was estimated as $C_p t/\beta + C_v/\beta^2$. MRT is the mean residence time. It was calculated as AUMC/AUC. $C_{\text{tot}}$ is the total-body clearance and was calculated as $D/AUC$, where $D$ is the dose. $V_{\text{app}}$ is the volume of distribution at steady state. It was calculated as $C_{\text{tot}} \cdot MRT$. $V_{\text{app}}$ is the volume of distribution at pseudo-steady state during the elimination phase. It was calculated as $C_{\text{tot}} / \beta$. $S/P$ is the saliva/plasma ratio. It was calculated as $\text{AUC}_{\text{saliva}} / \text{AUC}_{\text{plasma}}$.

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

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).