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Pharmacokinetics, safety and bioavailability of HPMPC (cidofovir) in human immunodeficiency virus-infected subjects

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Abstract

We conducted a single-center, double-blind, placebo-controlled phase I study in HIV-positive subjects to ascertain the safety, tolerance, bioavailability, pharmacokinetics, and maximum tolerated dose of HPMPC (cidofovir). Five subjects were randomized to receive drug and two to receive placebo at each of three dosage tiers (1, 3, and 10 mg/kg) with a 2-week washout period between doses. Subjects at 1 and 3 mg/kg received single doses of HPMPC by subcutaneous (s.c.), intravenous (i.v.), and oral (p.o.) routes, while subjects at 10 mg/kg received only i.v. and p.o. doses. For subjects already taking zidovudine, zidovudine AUC values were determined before and then with HPMPC administration for each route. The AUC values of HPMPC were dose-proportional. Subcutaneous bioavailability was essentially equivalent to that of the intravenous route, but the development of transient local fibrosis and the volumes needed for subcutaneous dosing precluded higher subcutaneous dosing than 3 mg/kg. Oral bioavailability was poor, estimated to be less than 5%. Drug elimination was predominantly renal. Nephrotoxicity in one subject was the only serious adverse event observed. This subject had a significant lag period prior to oral absorption and also had the highest AUC values for both HPMPC and zidovudine. We found no consistent effect on zidovudine AUC by concomitant HPMPC.

Keywords: Cidofovir; Antiviral; Cytomegalovirus; Bioavailability; Clinical trial

1. Introduction

Several nucleoside analogs used as antiviral agents require phosphorylation by host or viral enzymes for activity (e.g. acyclovir, zidovudine). This requirement for phosphorylation restricts which viruses are susceptible to the agents and allows the development of resistance (Gentry, 1992). Therefore, analogs of nucleoside monophosphates have been developed. One such analog, HPMPC ((*S*)-1-[3-hydroxy-2-(phosphonylmethoxy)propyl] cytosine: (cidofovir) employs

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a phosphonomethylether (PME) bond to prevent hydrolysis by host enzymes.

HPMPC has shown promising activity against cytomegalovirus in preclinical testing (Neyts et al., 1991) and a small clinical trial (Polis et al., 1995). It has a prolonged intracellular half-life (Ho et al., 1992). In preclinical testing in rabbits and monkeys, the drug distributed with total body water and the majority was excreted unchanged in the urine within 24 h. The oral bioavailability was 3% in rats, 10% in mice, and 23% in monkeys. The dose-limiting toxicity in all animal models (mice, rabbits, guinea pigs, dogs, and monkeys) (K. Cundy, personal communication) and the only serious adverse event in clinical trials (Polis et al., 1995) was nephrotoxicity. A previous clinical study demonstrated that cidofovir distributed with total body water and was eliminated renally with a contribution of tubular secretion (Eddy et al., 1991).

We extend these previous observations on the pharmacokinetics and tolerance of cidofovir (Cundy et al., 1995) and report the bioavailability of three dosage levels of HPMPC in HIV-infected subjects. In addition, we assessed the influence of HPMPC on zidovudine pharmocokinetics.

2. Materials and methods

Subjects in this study had to be men, or women who were not pregnant or lactating, HIV+, and between the ages of 18 and 60. They were required to have an ambulatory performance of at least 70 on the Karnofsky scale (Grieco and Long, 1984) and to be in generally good health with life expectancy greater than 3 months. Screening tests were administered to assure preserved renal, hepatic and hematologic function (less than 1+ proteinuria and calculated creatinine clearance at least 70 ml/min, total bilirubin $\leq$ 1.5 mg/dl and hepatic transaminases less than three times the upper limit of normal, absolute neutrophil count $>$ 1000/mm^3, platelets $>$ 75 000/mm^3, hemoglobin $\geq$ 9.0 g/dl for females and $\geq$ 10.0 g/dl for males, prothrombin time $<$ 14 s and activated partial thromboplastin time $<$ 40 s). Subjects were excluded for serious ongoing medical disease, infections requiring antibiotic therapy within 2 weeks prior to enrollment, inability to tolerate oral medications, conditions that might influence absorption of oral medications, or evidence of active substance abuse. All subjects provided written informed consent, and the study was approved by the institutional review board of the Johns Hopkins Medical Institutions.

2.1. Design

This was a single-center, double-blind, placebo-controlled phase I study in HIV-positive subjects designed to ascertain the safety, tolerance, bioavailability, pharmacokinetics and the maximum tolerated dose of HPMPC given by subcutaneous (s.c.), intravenous (i.v.), and oral (p.o.) routes. Five subjects were randomized to receive drug and two to receive placebo at each of three dosage tiers (1, 3, and 10 mg/kg). Subjects at 1 and 3 mg/kg were given single doses of HPMPC by all three routes with a 2-week washout period between doses. The order of the route of administration was randomized. Only the oral and intravenous routes were assessed in the 10 mg/kg tier because of the excessive volume that would have been required for subcutaneous administration.

HPMPC was formulated as a sterile isotonic solution for administration by each route, to contain either 25 mg/ml or 75 mg/ml HPMPC. Subjects fasted from midnight the night prior to dosing until 4 h after the dose. For intravenous studies, drug was infused peripherally in 100 ml of normal saline over an hour. For subcutaneous studies, drug was injected using one or two sites, depending on the volume to be given. For oral studies, drug in liquid form was diluted up to 30 ml with tap water, swallowed under observation, and followed by an additional 100 ml of tap water. Serum for drug levels was obtained at 0 (predose), 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h after dosing to determine pharmacokinetic profiles for each route in each subject. Urine samples were collected prior to dosing, and collected and stored on ice over the intervals 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h post-dose, with subjects voiding immediately before dosing at the 0-h time point. Concomitant therapy with zidovudine (100 mg five

times a day) was permitted in subjects on a stable regimen for at least 6 weeks prior to entry. In subjects taking zidovudine, zidovudine pharmacokinetic profiles were determined after a 100 mg oral zidovudine dose before and then with each dose of either HPMPC or placebo. Subjects were observed daily during dosing and pharmacokinetic collection for toxicity, and at 2 and 4 weeks after the last dose of HPMPC. Provisions were made for further monitoring until toxicities resolved or were otherwise explained.

2.2. Materials

HPMPC reference standard and the internal standard, 9-(2-phosphonyl-methoxyethyl) guanine (PMEG), were synthesized by Gilead Sciences, Inc. (Foster City, CA). Potassium phosphate dibasic (anhydrous), sodium dihydrogen phosphate, and sodium hydroxide were obtained from Mallinckrodt (Paris, KY). *o*-Phosphoric acid, 85% was from Fisher Scientific (Fair Lawn, NJ). Tetrabutylammonium dihydrogen phosphate (TBAHP) was obtained from Fluka Chemical Corp. (Ronkonkoma, NY). Ion Pair Reagent, 0.5 M octyltriethylammonium phosphate (Q8), acetonitrile, methanol, and deionized water were obtained from Baxter (McGaw Park, IL). Pooled normal human serum was obtained from volunteers (Whitaker Bioproducts).

2.3. Determination of HPMPC concentrations

Concentrations of HPMPC in clinical serum samples were determined by a validated reverse-phase ion pairing HPLC method with UV detection as described elsewhere (Cundy et al., 1995). Briefly, serum samples (0.5 ml) were added to 250 μl of internal standard (2.5 μg/ml PMEG) in a polypropylene centrifuge tube and vortexed to mix. Tubes were incubated at 65°C for 25 min to inactivate HIV and allowed to cool prior to being run on an analytical column consisting of a Zorbax C-8 Column (5 μm, 250 × 4.6 mm) equipped with a Zorbax C-8 Guard Column (6.0 × 20 mm) (Mac Nod Analytical Inc., Chadds Ford, PA) followed by HPLC analysis with a Bond Elut SAX ion-exchange solid phase extraction column (Jones Chromatography, Lakewood, CO). The HPLC system consisted of a Model 600 E system controller and Model 715 Ultra Wisp sample processor (Waters Chromatography Div., Milford, MA), a Model LC 95 UV/Visible spectrophotometer detector, and a Model 1020 personal integrator (Perkin-Elmer, Norwalk, CT). Data were acquired using Millennium 2010 Chromatography Manager Version II (Waters). The method was linear over the range 220–2190 ng/ml, and the limit of quantitation was 220 ng/ml. The between-run precision and accuracy were $< 11\%$ and $< 3\%$, respectively, at the limit of quantitation.

Urine concentrations were analyzed as described elsewhere (Cundy et al., 1995). Briefly, urine samples (0.5 ml) were added to 100 μl of internal standard (250 μg/ml PMEG in 10 mM phosphate buffer, pH 7.0) in a polypropylene centrifuge tube and vortexed. HIV was neutralized as previously mentioned. Analytichem Baker Bond C-18 solid phase extraction columns (J.T. Baker, Phillipsburg, NJ) were conditioned with one column volume (1 ml) each of methanol and 0.1 N hydrochloric acid. Samples were applied and effluent (400 μl) was transferred to Ultrafree-ML 5000 NMWL molecular weight cut-off filter units (Millipore Corp., Bedford, MA). The filter units were centrifuged for 12 min at 13 000 × *g*. The filtrate (150 μl) was transferred to autoinjector vials for HPLC analysis. The HPLC and data acquisition system was as previously described with the substitution of a Model 486 UV/Visible detector (Waters). The HPLC column was a Beckman Ultrasphere ODS-IP (150 × 4.6 mm) (Alltech, San Jose, CA), equipped with a Brownlee RP-18 Newguard Column, (15 × 3.2 mm) (Alltech, Deerfield, NY). The method was linear over the range 1.0–99 μg/ml, and the limit of quantitation was 1.0 μg/ml. The between-run precision and accuracy were $< 6\%$ and $< 5\%$, respectively, at the limit of quantitation.

2.4. Determination of zidovudine concentrations

Serum zidovudine concentrations were determined using a commercially available radioimmunoassay (INCSTAR ZDV RIA kit, Incstar, Inc. Stillwater, MN). Results were compared with

an internal standard of a spiked serum calibration curve, with a multiple correlation coefficient of each calibration curve of at least 0.98.

2.5. Pharmacokinetic analyses

Terminal half-life and AUC estimates were identified by computer algorithms (Kowalski, 1994). Briefly, AUC values were calculated as the sum of the AUC to the last quantifiable serum level calculated using linear trapezoidal areas and the AUC calculated by log-linear extrapolation. C_{max} was the highest serum concentration observed. T_{max} was the time after dosing at which C_{max} was observed. Non-compartmental analyses were used to calculate Vd_{ss}, AUMC and MRT from the AUC by model independent methods (Rowland and Tozer, 1989).

The urine data used the urinary excretion during collection periods to estimate the rate of drug excretion (dD_u/dt) (Shargel and Yu, 1985). The plot of dD_u/dt over time allowed the extrapolation of dose at time zero. The slope of this plot allows estimation of the renal drug excretion coefficient (K_e).

3. Results

Twenty-two subjects were recruited to enter this study. One subject in the first tier was removed from the study due to elevation of liver transaminases following administration of HPMPC by the oral and subcutaneous routes. This subject was subsequently found to have antibody to hepatitis C virus. Five of the 21 subjects (24%) included in the final analysis were female. Weights ranged from 50 to 124 kg (mean 79 kg) and ages from 28 to 42 years (mean 35 years) at the start of the trial.

No consistent toxicity was observed with intravenous or oral HPMPC following single doses up to 3 mg/kg. Subcutaneous dosing at 3 mg/kg was limited by local pain upon injection (3 of 5 subjects receiving drug, vs. 1 of 2 receiving placebo), the development of modest transient subcutaneous nodules at the injection site (presumably fibrosis) (2 of 5 subjects receiving drug, vs. 0 of 2 receiving placebo) and the volume needed for drug administration.

At the 10 mg/kg dose, nephrotoxicity was seen in 1 of 5 subjects that received drug. This was manifested as proteinuria, up to a maximum of 4+, and elevation of serum creatinine, from 0.8 mg/dl up to 2.6 mg/dl. This subject had the highest AUC for both oral and intravenous dosing in our study, and the subject received them in that order. In this subject, proteinuria was accompanied by glucosuria (maximum of 250 mg/dl), reduced serum uric acid (minimum of 2.1 mg/dl), and alkaline urine (maximum pH of 8.5) (Fanconi syndrome). The nephrotoxicity was only partially reversible over 10 months, with serum creatinine declining to 1.3 mg/dl (Fig. 1). No concomitant nephrotoxic medications were being used by this subject throughout the study period. No other subject receiving HPMPC had 2+ proteinuria nor an increase of serum creatinine of 0.2 mg/dl.

As shown in Fig. 2, HPMPC had a non-linear decay of logs of concentration following intravenous dosing. Using non-compartmental analysis for the data on intravenous dosing, the volume of distribution was 341 ± 61 ml/kg at 1 mg/kg, 609 ± 189 ml/kg at 3 mg/kg, and 482 ± 81 ml/kg at 10 mg/kg. The estimated terminal half-life following intravenous dosing was 1.7 ± 0.4, 2.5 ± 0.9 and 2.9 ± 0.7 h for 1, 3, 10 mg/kg, respectively. Clearance was 164 ± 51 ml/h per kg at 1 mg/kg, 182 ± 21 ml/h per kg at 3 mg/kg, and 169 ± 22 ml/h per kg at 10 mg/kg by non-compartmental analysis for intravenous dosing. Volume of distribution and clearance were independent of dose in this range. The AUC was proportional to dose for intravenous dosing (Fig. 3) with r^2 for linear regression forced through zero = 0.98. Oral dosing demonstrated poor bioavailability (estimated at < 5.3% by comparison of oral and intravenous AUC values in identical subjects (Table 1 and Fig. 2)). Subcutaneous dosing demonstrated good bioavailability by AUC in comparison with intravenous dosing (98.5 ± 9.8%; Table 1 and Fig. 2B, Fig. 2C).

Urinary data (Table 2) supported these findings and demonstrated that most of the compound was excreted unchanged in the urine within 24 h of dosing. By comparison of total urinary recov-

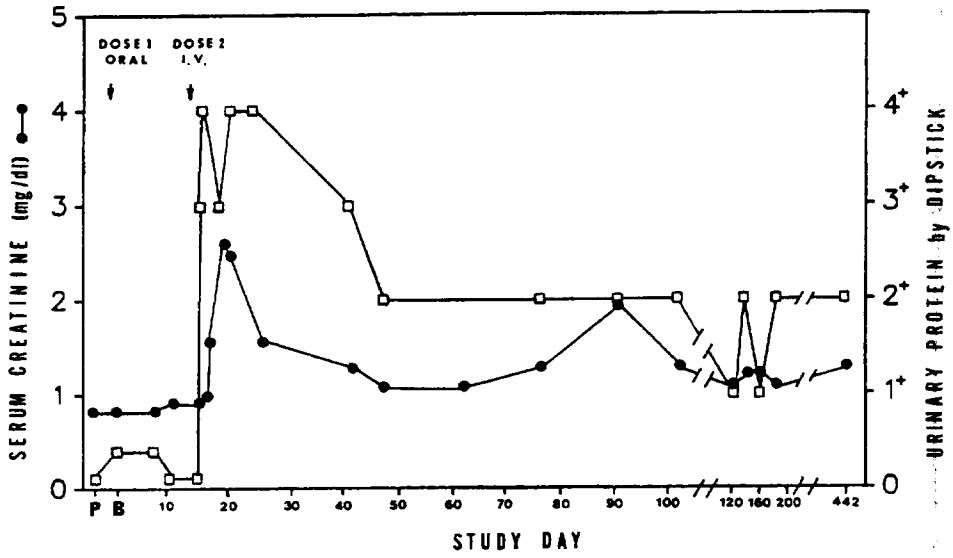

Fig. 1. Nephrotoxicity in Patient 16 following administration of HPMPC orally and intravenously on study days 1 and 15, respectively. P, predose lab evaluation on study day −10; B, baseline lab evaluation the day of first dosing.

ery of parent drug from 0 to 24 h, bioavailability of subcutaneous HPMPC was essentially equivalent to that of intravenous infusion (82.4 ± 8.3% for s.c. compared with 79.4 ± 11.9% for intravenous recovery of parent drug in urine during this time period; Table 2). Oral administration gave poor bioavailability, with only 2.4 ± 0.3% recovery of parent drug in urine (Table 2). The urinary collection was incomplete from subject 16, whose serum bioavailability data would imply a high urinary recovery of drug after oral administration, and from subject 18 after intravenous dosing; consequently, these results were excluded from the analysis.

The influence of HPMPC on the pharmacokinetics of zidovudine was examined in the subjects who were on stable doses of zidovudine prior to the study. The results of two subjects that did not give analyzable pharmacokinetic curves were not included in analysis. No consistent effect of HPMPC on the AUC of zidovudine was seen following any route (Fig. 4). The observed changes in zidovudine AUC following HPMPC administration were similar to the average intra-individual variability for zidovudine AUC found from comparing the zidovudine AUC values of subjects prior to receiving HPMPC or placebo (22 ± 11%).

4. Discussion

HPMPC is the first antiviral nucleotide analog to be evaluated in humans. This drug has shown promising activity against CMV in preclinical studies and was especially remarkable for having a prolonged intracellular half-life due to its phosphorylated anabolites, HPMPC-monophosphate and HPMPC-diphosphate (Ho et al., 1992).

The decline in concentration over time following intravenous dosing was non-linear, in agreement with the one other published study of cidofovir pharmacokinetics (Cundy et al., 1995). Furthermore, both the present study and the one by Cundy et al. (1995) show a similar increase in the terminal half-lives with increasing dosage. We cannot exclude one or more further phases of elimination occurring after the serum levels declined below the limit of quantitation (220 ng/ml).

The maximal tolerated subcutaneous dose was established as 3 mg/kg by the development of transient local fibrosis and the unacceptable volume needed for administration of higher doses.

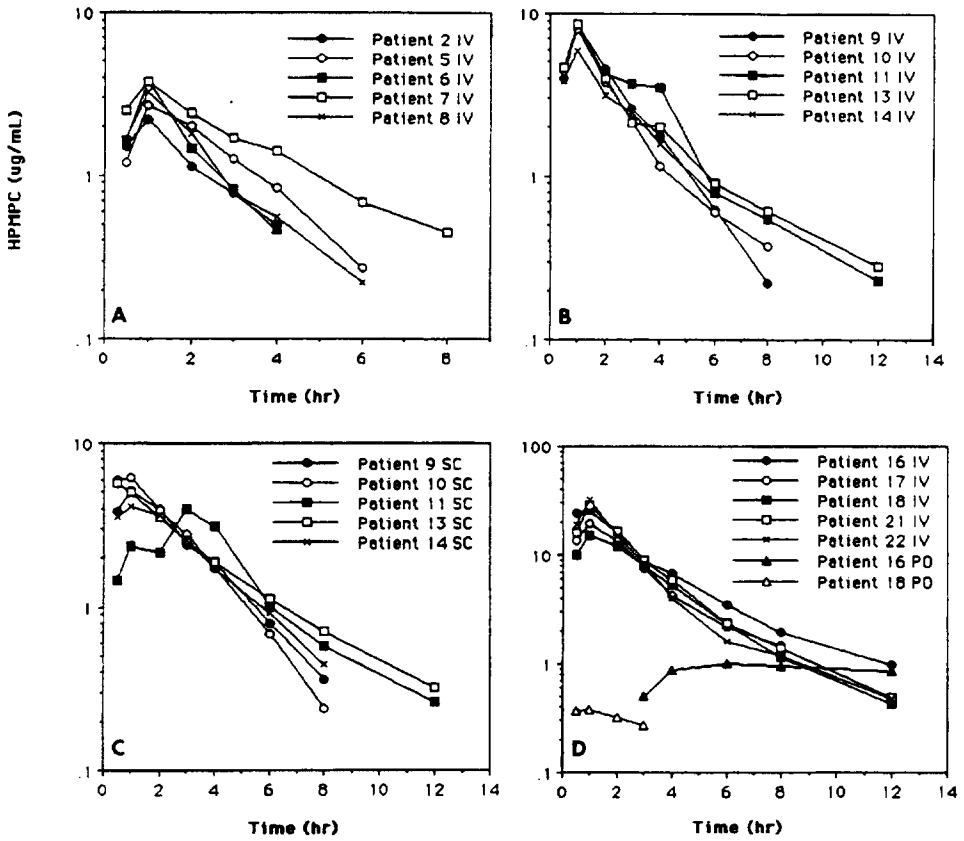

Fig. 2. Pharmacokinetics of HPMPC. (A) 1 mg/kg tier, drug administered i.v.; (B) 3 mg/kg tier, drug administered i.v.; (C) 3 mg/kg tier, drug administered s.c.; (D) 10 mg/kg tier, drug administered i.v. and p.o. No drug levels above the limit of quantification were found for 3 of 5 subjects given drug p.o. at the highest (10 mg/kg) dosage tier.

Intravenous dosing was limited at 10 mg/kg by the development of nephrotoxicity in 1 of 5 subjects.

The subcutaneous bioavailability was 98.5 ± 9.8% (Table 1) as assessed by comparison of AUC values following subcutaneous and intravenous administration. The subcutaneous bioavailability was 103.7 ± 9.8% as assessed by recovery of parent drug in urine (82.4 ± 8.3% for recovery of parent drug after s.c. administration compared with 79.4 ± 11.9% for i.v. administration). Oral bioavailability was poor in most subjects (3.9 ± 2.7% by comparison of total urinary recovery of parent drug after oral versus intravenous dosing), although one subject had an oral bioavailability of 20%. This generally poor oral bioavailability probably represents poor passage of HPMPC through the intestinal wall due to the charged phosphonate on the molecule.

It is not clear why one subject had such a large oral bioavailability, but this subject's C_{max} following oral HPMPC administration was quite delayed (Patient 16, Fig. 2D). Furthermore, this subject also had the highest AUC for zidovudine in our study. We feel this argues for an altered physiology underlying the increased bioavailability in this particular subject. Zidovudine is thought to be absorbed solely by non-specific (and hence, non-saturable) mechanisms (Chan et al., 1993) and probably this is also the means for HPMPC absorption.

The observed nephrotoxicity in one subject was remarkable for being prolonged and biphasic, involving both glomerular (proteinuria) and tubular

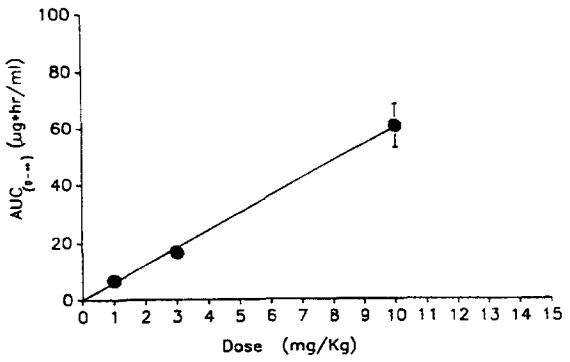

Fig. 3. Dose proportionality of AUC of HPMPC following intravenous administration. Each data point represents the mean ± standard deviation of AUC values of subjects within the dosage tier (n = 5). The regression line is forced through the origin (r^2 = 0.98).

(Fanconi-like syndrome) dysfunction. We feel that this toxicity is due to HPMPC and not due to other concurrent conditions or medications for three reasons: (1) the close temporal relationship between the nephrotoxicity and drug administration, (2) the exposure/toxicity relationship (this subject had the highest AUC values for both the oral and intravenous doses) and (3) similarities in our subject's course to toxicities observed in preclinical animal testing of this drug. Also, the identical toxicity has been reported in other trials of HPMPC (Polis et al., 1995). The nephrotoxicity appeared to be associated with the intravenous dose, but the moderate exposure to HPMPC from the previous oral dose could have created subclinical toxicity that was exacerbated or unmasked by the second dose. This unmasking could be due to the higher drug exposure from intravenous relative to oral dosing or due to drug accumulation in the kidney with multiple doses. Indeed, the importance of frequency of HPMPC dosing is demonstrated in another clinical trial of HPMPC in which regimens corresponding to 3, 5, or 10 mg/kg per week were associated with at least 2+ proteinuria in 2 of the 4 subjects in each group, while all 9 subjects with less intense exposures did not have 2+ proteinuria (Polis et al., 1995).

The nephrotoxicity seen following HPMPC is strikingly similar to experimental puromycin aminonucleoside (PAN) nephrotoxicity in animals (Stonard et al., 1987). Both compounds are nucleoside analogs that require phosphorylation for activity. Both PAN and HPMPC produce glomerular and tubular toxicity, with proteinuria being a prominent feature (Stonard et al., 1987). This damage is biphasic with a similar time course for both drugs (Anderson et al., 1991). In animals, the late toxicity represents development of irreversible focal glomerulosclerosis and interstitial tubular damage. Thus, we suspect that the observed nephrotoxicity in our subject will not be

Table 1
Summary of serum pharmacokinetic data

	1 mg/kg[a]	3 mg/kg		10 mg/kg	
	i.v.	i.v.	s.c.	i.v.	p.o.[b]
AUC(0-t_{last}) (μg/h per ml)	6.8 ± 2.4	16.7 ± 2.0	16.4 ± 1.1	61.0 ± 7.9	<3.8 ± 2.9
AUC(0-∞)(μg/h per ml)	7.7 ± 2.6	17.9 ± 2.3	17.9 ± 1.5	64.2 ± 8.8	
AUMC(0-∞)(μg/h^2 per ml)	23.8 ± 13.8	64.7 ± 19.0	64.8 ± 15.9	224.7 ± 544.6	
MRT (h)	2.2 ± 0.5	3.0 ± 0.8	3.1 ± 0.6	2.9 ± 0.3	
Cltot(ml/h per kg)	164 ± 51	182 ± 21	186 ± 13	169 ± 22	
Vd_{SS} (ml/kg)	341 ± 61	609 ± 189	572 ± 94	482 ± 81	
$t_{1/2}$ of terminal phase (h)	1.7 ± 0.4	2.5 ± 0.9	2.3 ± 0.7	2.9 ± 0.7	
T_{max} (h)	1	1.2 ± 0.4	0.9 ± 0.2	1	
C_{max} (μg/ml)	3.1 ± 0.6	7.2 ± 1.8	4.7 ± 1.3	23.9 ± 5.6	
Bioavailability (%)	–	–	98.5 ± 9.8	–	<5.3 ± 2.9

[a] Mean of five patients ± S.D.
[b] Only two patients with detectable levels. For the other three patients, results based on the HPMPC limit of detection were substituted.

Table 2
Summary of urine pharmacokinetic data

Group		K (h^{-1})[a]	K_e(h^{-1})[b]	F_u (%)[c]	Rel. bioav.[d]
i.v.	1 mg/kg	0.237 ± 0.058	0.214 ± 0.062	91.9 ± 20.2	–
	3 mg/kg	0.235 ± 0.060	0.184 ± 0.071	79.4 ± 11.9[e]	–
	10 mg/kg	0.281 ± 0.038	0.277 ± 0.211	105.9 ± 52.1[e]	–
s.c.	3 mg/kg	0.205 ± 0.027	0.169 ± 0.038	82.4 ± 8.3	105.6 ± 15.5
p.o.	10 mg/kg	0.123 ± 0.044	–	2.4 ± 0.3	3.9 ± 2.7

[a] Mean of five subjects ± S.D. except where indicated otherwise.
[b] Renal excretion rate constant.
[c] The fractional amount of parent drug recovered in the urine over 24 h calculated as the quantity of parent drug in urine (0–24 h) divided by total quantity given.
[d] Ratio of recovery of parent drug in urine by a given route relative to that following intravenous administration.
[e] Mean of four subjects ± S.D.

completely reversible. Of note, the one subject in other HPMPC trials with a rise in serum creatinine continued to experience a further rise in serum creatinine 3 months after cessation of HPMPC (Polis et al., 1995).

The mechanism for both puromycin aminonucleoside and the observed HPMPC toxicity is unclear. The toxicity develops in kidneys directly infused with PAN via the renal artery without toxicity in the contralateral kidney, implying direct toxicity rather than being immune mediated (Hoyer et al., 1972). The lack of protection from PAN nephrotoxicity by local irradiation (Eddy et al., 1991), anti-lymphocyte globulin (Eddy et al., 1991) and cyclosporin (Nahman and Cosio, 1990) also implies direct toxicity. The subject in whom HPMPC nephrotoxicity was observed was severely immunocompromised, also arguing against a mechanism mediated by T-helper cells. The rapidity of onset, lack of other systemic manifestations, and lack of nephritis argues against a serum sickness mechanism in either PAN or HPMPC.

That serious toxicity was observed only in the subject with highest exposure of both oral and intravenous HPMPC and the dose dependence of toxicity in preclinical experience with HPMPC (K. Cundy, personal communication) implies that toxicity has a dependence either upon peak serum level, total drug exposure, or repeated exposure to some threshold level of drug. In PAN toxicity, subcutaneous administration typically requires several doses to produce chronic toxicity, while a single intravenous dose produces both acute severe nephrotic syndrome followed by chronic progressive focal glomerulosclerosis. In both HPMPC and puromycin toxicity, renal accumulation of drug to a disproportionate extent may be involved in producing organ-selective toxicity. This could be similar to the mechanism of β-lactam toxicity (Tune et al., 1989). Renal exposure to HPMPC could be minimized by both careful dosing regimens and agents to block renal uptake of drug, such as the use of cilastatin or probenecid to block β-lactam toxicity.

In summary, we have characterized the pharmacokinetics, bioavailability and tolerance of 1, 3, and 10 mg/kg of HPMPC in HIV-infected subjects. The AUC values of HPMPC were dose-proportional for the dosage range observed. Subcutaneous bioavailability was good, essentially equivalent to that of the intravenous route, but the development of transient local fibrosis and the volumes needed for subcutaneous dosing precluded dosing higher than 3 mg/kg. Oral bioavailability was poor (estimated to be $< 5\%$ by either analysis of serum AUC values of drug or recovery of parent compound in urine). The drug was predominantly eliminated renally and the nephrotoxicity in one subject was the only serious adverse event observed. This subject had a significant lag period prior to oral absorption and also had the highest AUC for zidovudine. We found no consistent effect on zidovudine by concomitant HPMPC.

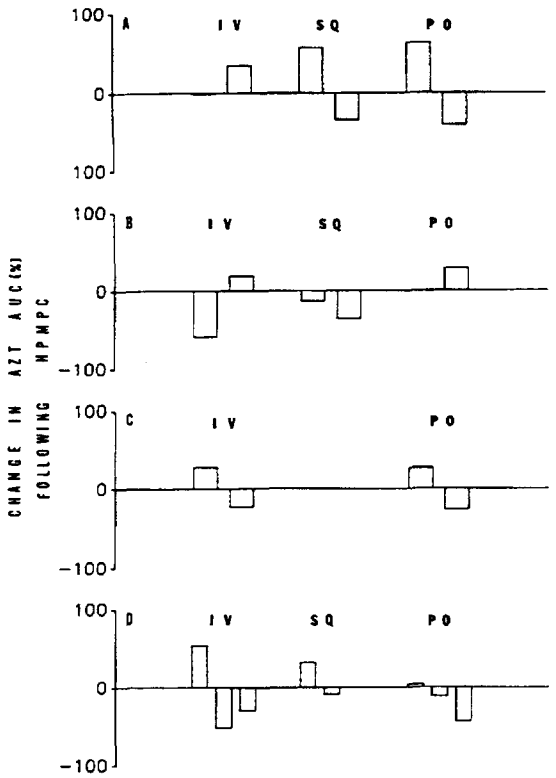

Fig. 4. Change in AZT AUC following HPMPC administration. Each bar represents the percentage change in AZT AUC following HPMPC administration in an individual subject. Subjects received (A) 1 mg/kg HPMPC, (B) 3 mg/kg HPMPC, (C) 10 mg/kg HPMPC and (D) placebo. IV, intravenous; SQ, subcutaneous; PO, oral.

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