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Bioavailability and metabolism of cidofovir following topical administration to rabbits.

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Abstract

The bioavailability and metabolism of the antiviral nucleotide analog cidofovir (HPMPC) were examined in New Zealand white rabbits following topical administration to normal and abraded skin. Male rabbits (four per group) received ^{14}C-cidofovir (100 μCi/kg) intravenously (1 mg/kg) as a solution or topically (2 mg/animal) as a 1% w/w gel containing hydroxyethylcellulose (HEC) with or without propylene glycol (PG). The same PG/HEC formulation was applied topically to an abraded skin site in a fourth group of animals. All radioactivity detected in plasma and skin was accounted for by cidofovir. Plasma concentrations of radioactivity declined multiexponentially following intravenous administration, with a terminal half-life of 5.4 h. For intact skin, the absolute bioavailabilities of the HEC and PG/HEC formulations were 0.2 and 2.1%, respectively. For abraded skin, the bioavailability for the PG/HEC gel was 41%. Radioactivity in kidneys was attributed to cidofovir (> 95%) and cyclic HPMPC. Concentrations in kidney following topical administration of cidofovir to normal skin were < 4% of those following intravenous dosing. Topical application of cidofovir to intact skin led to negligible systemic exposure to the drug. The topical bioavailability and hence the flux of cidofovir through intact skin was enhanced by the presence of PG in the formulation. Abrasion of the skin removed the principal barrier to absorption and led to significant systemic exposure to cidofovir. © 1997 Elsevier Science B.V.

Keywords: Cidofovir; Antiviral; Topical; Rabbit; Pharmacokinetics; Formulation

1. Introduction

Cidofovir (1-(*S*)-3-hydroxy-2-(phosphonomethoxy)propylcytosine; HPMPC; I) is an acyclic nucleotide analog with potent activity against a broad spectrum of herpesviruses (Bronson et al., 1990a). Unlike acyclovir and other nucleoside analogs currently used for clinical therapy of human herpesvirus infections, cidofovir is not dependent on phosphorylation by a virus encoded nucleoside kinase to exert its antiviral

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effect (Bronson et al., 1990b). Instead, the drug is phosphorylated to its active form (cidofovir-diphosphate) by cellular enzymes. In vitro studies in cultured human cell lines have suggested that the resulting active metabolites are cleared slowly from the intracellular space (Bronson et al., 1990b). These properties offer the advantage of decreased frequency of dosing and protection of uninfected cells.

Topical cidofovir has been shown to be effective in the treatment of cutaneous infections of herpes simplex viruses HSV-1 and HSV-2 in animal models (De Clercq and Holy, 1991; Bronson et al., 1989; Maugdal and De Clercq, 1991; Kern et al., 1995). In addition, acyclovir-resistant HSV-1 infection in humans proved responsive to treatment with topical cidofovir (Snoeck et al., 1993). A topical gel formulation of cidofovir is currently undergoing clinical evaluation in the treatment of cutaneous herpesvirus and human papillomavirus (HPV) infections.

The absorption of ^{3}H-cidofovir from a number of topical gel formulations has been studied in vitro using hairless mouse skin in vertical diffusion cells (Aspe et al., 1995). In this study, cidofovir flux was proportional to cidofovir concentration and unaffected by pH or the presence of isopropyl alcohol. There was some indication of an increase in cidofovir flux with increasing propylene glycol concentration. However, the effect of propylene glycol did not reach statistical significance. Percutaneous flux was enhanced approximately 400 fold by removal of the stratum corneum using a tape-stripping technique. This observation is consistent with the role of the stratum corneum as the principal barrier to dermal absorption.

Rabbits have traditionally been used to evaluate the topical toxicity of dermal products. The guinea pig is the only available model of genital herpesvirus infection, and absorption of cidofovir in this model has been estimated (Kern et al., 1995). However, the rabbit has proven to be less susceptible than guinea pigs to the systemic toxicity of cidofovir (Bischofberger et al., 1994). The present study was therefore designed to assess in vivo the effect of formulation on the systemic exposure to cidofovir following topical application to rabbits. In addition, the study was intended to evaluate the effect of skin abrasion on the absorption of cidofovir. Levels of cidofovir achieved in skin were examined to provide support for topical efficacy of the drug. Levels of drug in kidney and testes were examined since these are potential target organs for systemic toxicity. Determination of potential metabolites of cidofovir in residual tissues was performed using HPLC with radioactive flow detection.

2. Materials and methods

2.1. Materials

Cidofovir was synthesized by Gilead Sciences, [2-^{14}C]-cidofovir (lot # 109-101-055; 55 mCi/mmol) was obtained from Moravek (Brea, CA). Propylene glycol, USP was from Spectrum (Gardena, CA) and Natrosol® (hydroxyethylcellulose) was from B.F. Goodrich (Cleveland, OH). Disodium pyrophosphate, sodium fluoride, *p*-nitrophenylphosphate, phenylarsine oxide and sodium orthovanadate were obtained from Sigma (St. Louis, MO). Acetonitrile was obtained from Baxter (Muskegon, MI). Dibasic potassium phosphate and monobasic potassium phosphate were obtained from Mallinkrodt (St. Louis, MO). Standards for cidofovir-diphosphate, cidofovir-monophosphate and the deaminated analog (HPMPU) were synthesized at Gilead Sciences.

2.2. Animals

The in-life phase of the study was conducted in accordance with the recommendations of the 'Guide for the Care and Use of Laboratory Animals' (National Institutes of Health publication 86-23) and was approved by an Institutional Animal Care and Use Committee. A total of 16 male New Zealand white rabbits (2.7–3.6 kg) were used in the study (Millbrook Farm, Amherst, MA). Animals were housed in individual stainless-steel cages and were fed Purina Certified High Fiber Rabbit Diet® 5325 and tap water ad libitum. Animals were prepared for the study at 24 h prior to dosing by closely clipping the fur from the

dorsal area of the trunk and marking a 4 × 4 cm square. Where required, the skin in the test area was abraded using a brush with stiff, pointed, nylon bristles, by rubbing six times each in horizontal and vertical directions to achieve uniform moderate to severe erythema. Elizabethan collars were worn by all animals throughout the first 6 h of the study to prevent potential ingestion of the drug. All rabbits were fasted for 12–18 h prior to dosing. Animals designated for sacrifice at 6 h post-dose were fasted throughout the study. Food was returned ad libitum at 6 h post-dose to animals designated for sacrifice at 24 h post-dose.

2.3. Formulations

Cidofovir was formulated for intravenous administration as a sterile aqueous solution containing 10 mg/ml ^{14}C-cidofovir (specific activity 100 μCi/mg). Cidofovir was formulated for topical administration as two different clear, aqueous gels at pH 7.0 containing (a) 1% w/w ^{14}C-cidofovir (150 μCi/mg), 1% w/w hydroxyethylcellulose (HEC gel); or (b) 1% w/w ^{14}C-cidofovir (150 μCi/mg), 1% w/w hydroxyethylcellulose and 10% w/w propylene glycol (PG/HEC gel). Gel formulations contained a preservative and were stored at room temperature prior to use.

2.4. Study design

Four groups of four New Zealand white rabbits (groups 1–4) were used in the study. Group 1 received a single intravenous injection of 1.0 mg/kg of ^{14}C-cidofovir (0.1 ml/kg) via a marginal ear vein. Group 2 received a single topical application of 0.2 ml of 1% cidofovir HEC gel formulation (equivalent to 2 mg cidofovir/animal) applied to normal skin. Groups 3 and 4 received a single topical application of 0.2 ml of 1% cidofovir PG/HEC gel formulation (equivalent to 2 mg cidofovir/animal) applied to normal or abraded skin, respectively. Topical formulations were applied to the designated region of dorsal skin using a preweighed syringe and were spread over the entire area using a glass rod. Following application, formulations were held in contact with the skin for the initial 6 h of the study using Tegaderm® 1625 transparent dressing and Transpore surgical tape (3M Medical-Surgical Division, St. Paul, MN). At 6 h post-initiation, any residual formulation was rinsed from the site of application and the dressing using water and the rinse was retained for analysis. Urine and faeces were cage collected for the duration of the study. Blood samples (2.0 ml) were collected into heparinized tubes from the medial auricular artery (in the case of animals dosed intravenously, the ear on the opposite side to the catheter was used). For animals dosed intravenously, blood samples were obtained at 0 (pre-dose), 5, 15, 30, 45, 60 and 120 min post-dose from two animals/group designated for sacrifice at 6 h post-dose and at 2, 4, 6, 8, 12 and 24 h post-dose from two animals/group designated for sacrifice at 24 h. For animals dosed topically, blood samples were obtained at 0 (pre-dose), 0.5, 1, 2, 3 and 4 h post-dose from two animals/group designated for sacrifice at 6 h post-dose, and at 4, 6, 8, 12 and 24 h post-dose from two animals/group designated for sacrifice at 24 h. Blood samples were processed immediately for plasma and plasma samples were frozen and stored at ≤ -15°C until analyzed. Two animals from each group were euthanized at each of 6 and 24 h post-dose by injection of sodium pentobarbital and exsanguination. Following injection of 1000 U/kg heparin, each animal was exsanguinated by perfusion with a minimum of one blood volume of normal saline. Kidneys, testes and samples of skin ($\sim$ 10 g) from both the site of administration and a remote untreated site were removed from each animal. All tissues were trimmed of extraneous fat and analyzed with plasma samples for content of total radioactivity by oxidation.

2.5. Determination of total radioactivity

Where possible, duplicate aliquots of plasma (0.5 ml) and tissue samples (<0.5 g) were oxidized using a Model 307 Sample Oxidizer and radioactivity determined in a Model 2500 TR Liquid Scintillation Counter (Packard, Meriden, CT). Kidneys and testes were homogenized prior to oxidation. Dose solution samples (0.05 ml) were analyzed in triplicate. All residual tissues were stored at ≤ -15°C until analyzed further.

2.6. Determination of cidofovir and metabolites

2.6.1. Tissue extraction

The presence of cidofovir and potential metabolites of cidofovir in plasma, kidney and skin samples was determined by ion-exchange HPLC using radioactive flow detection. The extraction solution comprised 60% methanol and 40% of an aqueous solution of enzyme inhibitors (50 mM disodium pyrophosphate, 50 mM sodium fluoride, 2 mM sodium orthovanadate, 5 mM *p*-nitrophenylphosphate, 0.35 μM phenylarsine oxide). Tissue samples (1–3 g) were initially homogenized in a volume of extraction solution equivalent to twice the weight of tissue at 4°C, using an Ultra-Turrax homogenizer (Tekmar, Cincinnati, OH). The crude homogenates were further subjected to homogenization using a Virtis 50 ultrasonic cell disrupter (Baxter, McGaw Park, IL) for 2–5 min. The homogenates were centrifuged at 4000 rpm for 30 min at 4°C. The supernatants were transferred to Ultrafree MC 10 000 MW cut-off centrifugal filter units (Millipore, Bedford, MA) and centrifuged at 14 000 rpm for 15 min. The filtrates were injected directly onto the HPLC. This extraction method was validated by addition of authentic standards of the phosphorylated metabolites of cidofovir to kidney homogenate prior to extraction. The phosphorylated metabolites remained intact (> 90%) during the process.

2.6.2. Radiochromatography of extracted samples

The HPLC system comprised a Model P4000 solvent delivery system with a Model AS3000 auto injector and a Model UV1000 UV detector (Spectra Physics, San Jose, CA). The column was a SAX 10 Partisil anion exchange column (250 × 4.6 mm) (Whatman, Clifton, NJ) equipped with a Brownlee AX-300 Newguard guard column (7 μm, 15 × 3.2 mm), (Alltech, Deerfield, IL). The mobile phases used were: (A) 5 mM potassium phosphate, pH 5.5; (B) 700 mM potassium phosphate, pH 5.5. The gradient was linear from 100% mobile phase A to 100% mobile phase B over 25 min, followed by mobile phase B for 5 min, returning to mobile phase A for 10 min. The total cycle time was 40 min. The flow rate was 1.0 ml/min and the column temperature was maintained at 45°C by a column oven. Detection was by a Model A-500 Radiomatic FLO-One/Beta liquid scintillation detector (Packard, Meriden, CT), using ULTIMA-FLO™AP (Packard) as scintillation fluid. The injection volume was 100 μl/sample. Data were acquired and stored by the FLO-ONE data acquisition system.

2.7. Pharmacokinetic analysis

Pharmacokinetic analyses were performed using concentrations of total radioactivity in plasma. Data for intravenous and oral formulations were analyzed by application of non-compartmental methods using PCNONLIN (Statistical Consultants, Lexington, KY). Additional pharmacokinetic parameters were calculated by standard methods (Rowland and Tozer, 1989). The absolute bioavailability of topical formulations was calculated as $100 \times [(AUC(0-\infty)_{topical}/Dose_{topical})]/[(AUC(0-\infty)_{intravenous}/Dose_{intravenous})]$. In cases where no terminal phase could be projected, $AUC(0\text{-}t_{last})_{topical}$ was substituted for $AUC(0\text{-}\infty)_{topical}$ in the above equation, where t_{last} is the time of the last quantifiable plasma concentration. The apparent maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were obtained by visual inspection.

3. Results

3.1. Plasma concentrations of total radioactivity

All radioactivity in plasma following intravenous or topical administration of ^{14}C-cidofovir was attributable to unchanged cidofovir. Total radioactivity was therefore an accurate representation of cidofovir levels. The time course of total radioactivity present in the plasma of rabbits following intravenous injection of ^{14}C-cidofovir is compared in Fig. 1 to the concentrations observed following each of the topical treatments. Plasma concentrations of radioactivity following intravenous administration were quantifiable for the entire 24 h of the study (the limit of detection was approximately 1 ng-eq/ml). Plasma levels were

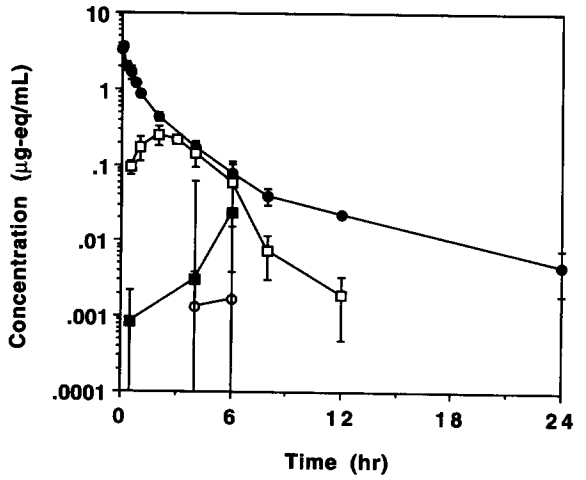

Fig. 1. Plasma concentration profile of total radioactivity following administration of ^{14}C-cidofovir to rabbits (●, intravenous; ○, topical HEC formulation on normal skin; ■, topical PG/HEC formulation on normal skin; □, topical PG/HEC on abraded skin).

quantifiable at only two or three time points following topical application of either the HEC or the PG/HEC gel formulation to normal skin. However, following topical application of the PG/HEC formulation to abraded skin, significant plasma levels were observed for the first 12 h of the study.

3.2. Pharmacokinetics and bioavailability

Table 1 summarizes the pharmacokinetic parameters for intravenous ^{14}C-cidofovir and the three topical treatments, based on total radioactivity. Plasma levels following intravenous dosing were described by a multiexponential decline with a terminal half-life of 5.4 h. The clearance of total radioactivity was 0.265 l/h per kg and the steady state volume of distribution was 0.692 l/kg. There were insufficient data to project a terminal elimination phase following topical administration of cidofovir formulations to normal skin, and the corresponding AUC values were projected only to the last quantifiable concentration. The relatively complete plasma concentration profile obtained following topical administration of cidofovir to abraded skin demonstrated a clear terminal phase (half-life 2.61 h) and allowed calculation of an AUC(0-∞) value. The difference in MRT values for intravenous dosing (2.61 h) and application to abraded skin (3.19 h) suggests rapid absorption of the topical drug across the skin when the stratum corneum is removed. The absolute bioavailability of the two topical formulations applied to normal skin were 0.2 and 2.1% for the HEC and PG/HEC gels, respectively, suggesting that bioavailability was enhanced slightly by the pres-

Table 1
Pharmacokinetics and bioavailability of intravenous and topical ^{14}C-cidofovir in rabbits[a]

Parameter	Intravenous	Topical		
		HEC gel	PG/HEC gel	
		Normal skin	Normal skin	Abraded skin
Dose (mg/kg)	1.0	0.67	0.62	0.66
AUC(0−t_{last}) (μg h/ml)	—	0.006	0.052	—
AUC(0−∞) (μg h/ml)	3.77	—	—	1.01
C_{max} (μg/ml)	3.55	0.002	0.023	0.249
T_{max}	—	6.0	6.0	2.0
MRT (h)	2.61	—	—	3.19
CL (l/h per kg)	0.265	—	—	—
V_{ss} (l/kg)	0.692	—	—	—
Bioavailability (%)	—	0.2	2.1	40.7
Urinary recovery at 6 h (%)	32.9	0.195	0.115	18.3
Urinary recovery at 24 h (%)	77.5	0.560	1.99	21.6

[a] Data are the mean of two animals per time point.

ence of PG. However, the absolute bioavailability of the PG/HEC gel applied to abraded skin was 41%.

3.3. Urinary recovery of total radioactivity

The mean ± S.D. urinary recoveries of the radioactive dose are summarized in Table 1 for intravenous and topical administration. Recovery of the intravenous dose was 32.9% at 6 h and 77.5% at 24 h. The estimated absolute bioavailabilities of the HEC formulation applied to normal skin were 0.6% at 6 h and 0.7% at 24 h (mean bioavailability 0.7%). The estimated absolute bioavailabilities of the PG/HEC formulation applied to normal skin were 0.4% at 6 h and 2.6% at 24 h (mean bioavailability 1.5%). The estimated absolute bioavailability of the PG/HEC topical treatment applied to abraded skin was 55.6% at 6 h and 27.9% at 24 h (mean bioavailability 41.8%). These values are in good agreement with the plasma bioavailability data. Recovery in faeces was less than 0.1% in all animals (data not shown).

3.4. Tissue distribution of total radioactivity

Fig. 2 compares the concentrations of total radioactivity present at 6 and 24 h postdose in kidney, testes and skin (treated versus untreated for topical formulations) for the four cidofovir treatments. Concentrations in kidney at 6 h after intravenous administration of ^{14}C-cidofovir (46.2 μg-eq/g) were more than 140 fold higher than those in untreated skin and 370 fold higher than those in testes.

The percent of the administered ^{14}C-cidofovir dose recovered in testes at 24 h postdose was less than 0.02% in all animals (data not shown). Recovery of the intravenous dose at 24 h postdose was much higher in kidney (7.69%) than in untreated skin (0.35%). At 24 h after topical administration of either formulation of cidofovir to normal skin, the recovery of dose was highest in the administration site rinse; recovery in the rinse was almost two fold greater for the PG/HEC formulation (80.9%) than for the HEC formulation. In contrast, recovery of the dose in treated normal skin at 24 h was highest for the HEC formulation (7.79%). Recovery of radioactivity in kidney at 24 h after topical administration of either formulation to normal skin was low (0.09 to 0.31%), suggesting minimal systemic exposure to the drug. At 24 h after topical administration of the PG/HEC formulation to abraded skin, the highest recovery was again in the administration site rinse (52.0%). However, significant amounts of radioactivity were also recovered at 24 h postdose in kidney (3.04%), indicating substantial systemic absorption of cidofovir in these animals.

3.5. Analysis of tissues for cidofovir, cyclicHPMPC and metabolites

There were no detectable impurities in the commercial radioactive materials, based on analysis by HPLC with radioactive flow detection. Fig. 3 shows a representative radiochromatogram of an extracted sample of treated skin obtained from a rabbit at 6 h after topical administration of ^{14}C-cidofovir in a PG/HEC gel. Unchanged cidofovir was the only species detected in skin samples, regardless of the treatment.

Fig. 4 shows a representative radiochromatogram of an extracted sample of kidney obtained from a rabbit at 6 h after intravenous administration of ^{14}C-cidofovir. Unchanged cidofovir accounted for $>95\%$ of the radioactivity in kidneys of animals given intravenous cidofovir or animals with abraded skin given the topical PG/HEC formulation. The remaining radioactivity eluted as an unidentified metabolite (retention time 7.6 min). This metabolite peak eluted from the anion exchange column before cidofovir and did not coelute with authentic standards of the purported phosphorylated metabolites of cidofovir (cidofovir-phosphate, cidofovir-diphosphate) or the potential deaminated analog, HPMPU. In addition, the unidentified peak did not appear to coelute with an authentic standard of cidofovir-phosphocholine, which is known to be an intracellular metabolite of cidofovir (Bronson et al., 1990b). The unknown metabolite accounted for approximately 4.2 and 3.6% of the radioactivity in kidney at 6 and 24 h, respectively, after intravenous administration of ^{14}C-cidofovir.

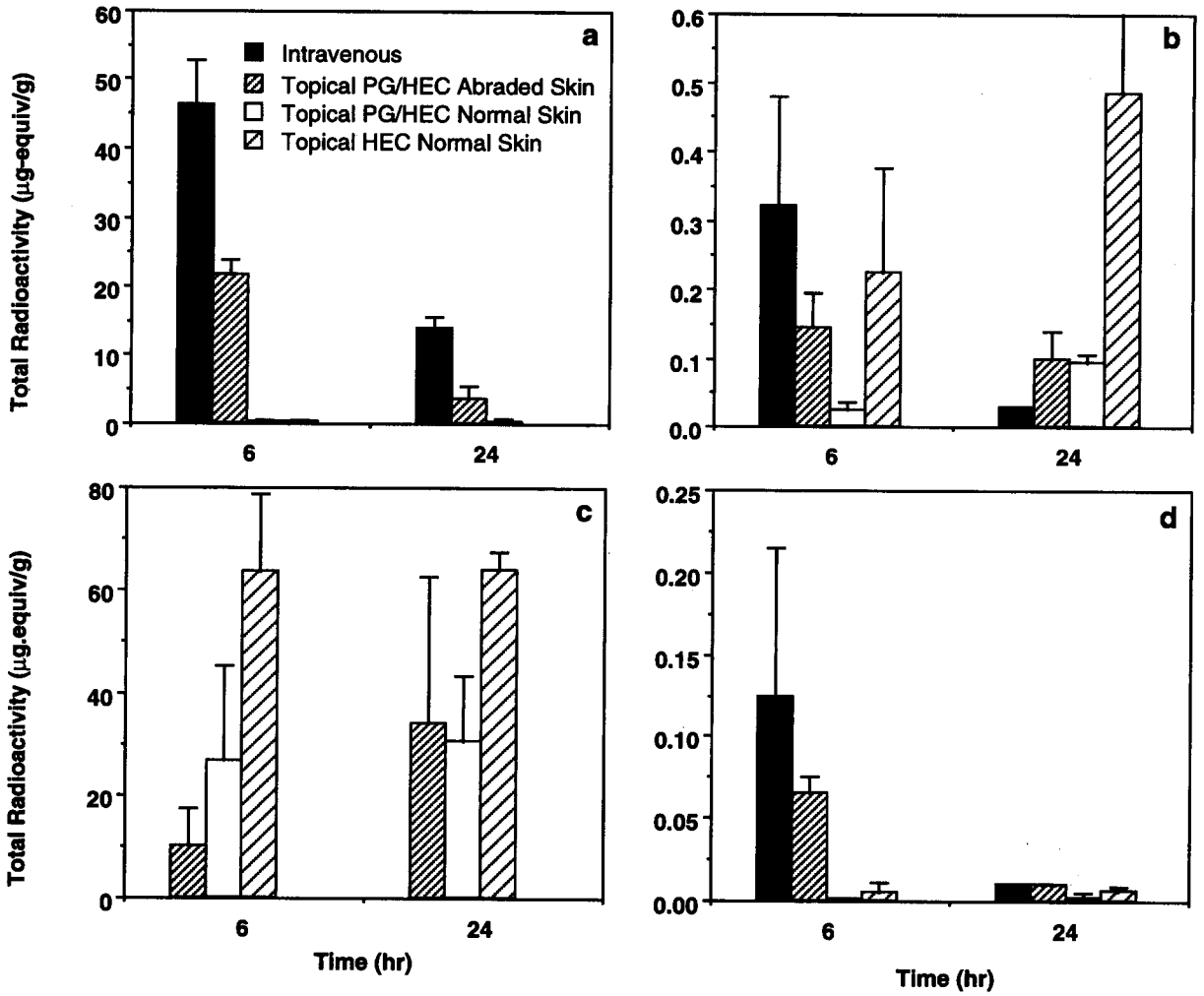

Fig. 2. Concentrations of total radioactivity in tissues at 6 and 24 h after administration of ^{14}C-cidofovir to rabbits: (a) Kidney; (b) untreated skin; (c) treated skin; (d) testes. Data are the mean for two animals per time point.

The same metabolite accounted for 1.2 and 2.5% of the radioactivity in kidney at 6 and 24 h, respectively, after topical administration of ^{14}C-cidofovir PG/HEC gel to abraded skin. This metabolite appeared to coelute with cyclic HPMPC, the cyclic analog of cidofovir. It has been demonstrated previously that cyclic HPMPC can be formed from cidofovir-diphosphate or cidofovir-phosphocholine by chemical degradation (Cundy et al., 1996c). This suggests that the cyclic HPMPC observed in the present study may have been produced ex vivo by degradation of phosphorylated metabolites of cidofovir. Concentrations of radioactivity in kidney following topical administration of cidofovir to normal skin were too low to examine further.

4. Discussion

The high bioavailability of topical cidofovir across abraded skin is entirely consistent with in vitro observations using tape-stripped skin (Aspe et al., 1995). Cidofovir is a dianion at physiologi-

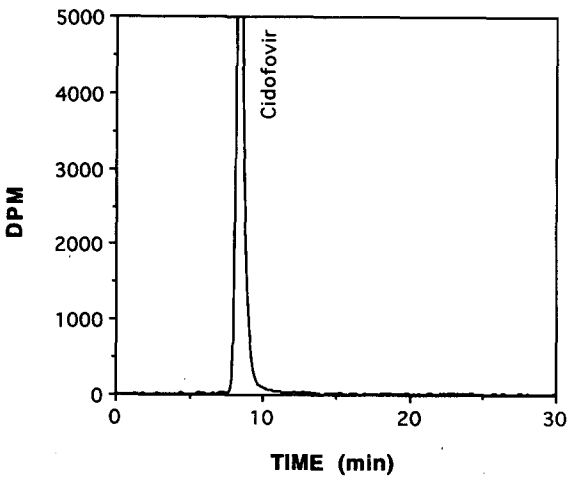

Fig. 3. Representative radiochromatogram of an extracted skin sample obtained from the site of application at 6 h after topical administration of ^{14}C-cidofovir as PG/HEC gel to normal skin.

cal pH and, in the presence of an intact stratum corneum, the highly polar molecule displays low permeability. Despite this low permeability, the antiviral activity of cidofovir against cutaneous viral infections indicates that a limited amount of drug is able to penetrate the skin and reach the dermal cells. Analogous permeability limitations are probably responsible for the low oral bioavailability of cidofovir (Wachsmann et al., 1994). The systemic bioavailability of topical cidofovir has been estimated previously in a model of genital herpes in guinea pigs (Kern et al., 1995). Recovery of radioactivity in urine following topical administration of ^{14}C-cidofovir in a 1% gel formulation containing propylene glycol was 3.5% compared to 87.5% following intravenous administration. Cidofovir was not detected in plasma following topical administration.

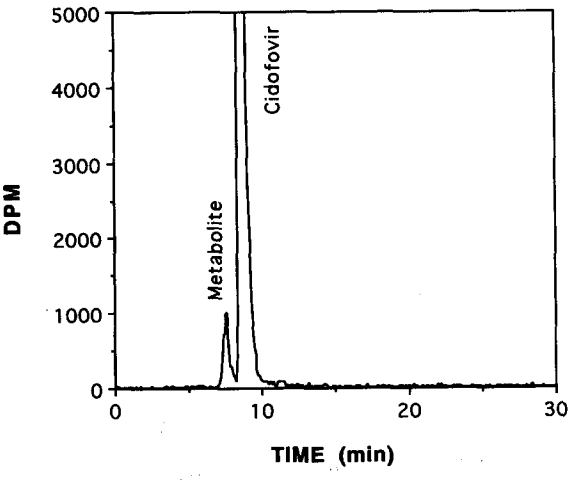

Fig. 4. Representative radiochromatogram of an extracted rabbit kidney sample obtained at 6 h after intravenous administration of ^{14}C-cidofovir.

Propylene glycol is one of a limited number of acceptable penetration enhancers employed in topical formulations and it has been shown to enhance the percutaneous penetration of a number of drugs, including the antiviral acyclovir (Okamato et al., 1990). In the present study, the addition of propylene glycol to the HEC formulation resulted in a 10-fold increase in the AUC and C_{max} values for cidofovir. Although these differences are based on a small number of samples, the urinary recovery data also support an increase in dermal flux of cidofovir in the presence of PG. As expected with the loss of the stratum corneum, the bioavailability of cidofovir applied to abraded skin was substantially higher. The levels of radioactivity observed in treated skin are highly dependent on the efficiency with which the residual formulation was removed prior to analysis. The fact that considerably more drug was recovered from skin at the site of administration of the HEC gel than the PG/HEC gel may therefore be an indication of the relative extent of adhesion of the two formulations to the surface of the skin.

All radioactivity present in skin at 24 h after intravenous or topical administration of ^{14}C-cidofovir was attributable to cidofovir. However, it is possible that the effective intracellular concentrations of radioactivity in this tissue were low and phosphorylated metabolites may have been present at levels too low to quantify.

The pharmacokinetics of cidofovir in humans and other species suggest that active tubular secretion plays a major role in the renal clearance of cidofovir (Cundy et al., 1995, 1996a). However, the plasma clearance of intravenous cidofovir in rabbits determined in the present study

(0.27 l/h per kg) was close the published value for glomerular filtration in this species (0.26–0.28 l/h per kg) (Shiba et al., 1990; Korner, 1963). Although there is no evidence of net tubular secretion, the high concentrations of cidofovir achieved within kidney cells following intravenous administration in this and other studies (Cundy et al., 1996b) are consistent with active uptake of the drug into proximal tubule cells. The pharmacokinetics of intravenous cidofovir in rabbits are otherwise consistent with observations in other animal species. Estimation of the initial volume of distribution of cidofovir by extrapolation of plasma concentration data to zero time (0.26 l/kg) suggests that the drug was rapidly distributed into extracellular fluid. The steady state volume of distribution of cidofovir was 0.66 l/kg, consistent with distribution beyond extracellular fluid. However, this apparent volume may not reflect the true distribution of cidofovir, since the drug is selectively accumulated within the kidney.

In summary, the addition of propylene glycol to an HEC gel formulation of cidofovir led to an increase in topical bioavailability of the drug. Application of the drug to abraded skin led to greatly enhanced systemic exposure compared to normal skin. For cutaneous viral infections such as HPV and HSV, where the stratum corneum is intact, the PG formulation should result in higher steady state concentrations of cidofovir in the epidermis and greater efficacy. The increased systemic concentrations of cidofovir produced by the PG formulation should not produce significant systemic toxicity, since the total dose applied topically will be much lower than the dose currently employed for intravenous therapy of cytomegalovirus infections.

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