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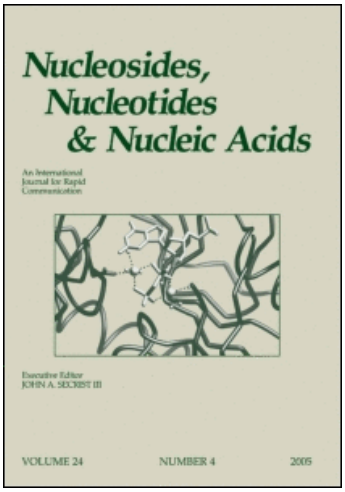

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PHARMACOKINETICS OF SALICYLATE ESTER PRODRUGS OF CYCLIC HPMPC IN DOGS

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PHARMACOKINETICS OF SALICYLATE ESTER PRODRUGS OF CYCLIC HPMPC IN DOGS

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ABSTRACT

A series of aryl ester prodrugs of cyclic HPMPC have been synthesized and their physicochemical properties, pharmacokinetics and metabolism have been evaluated. Chemical stability was dependent on the orientation of the exo-cyclic ligand; the equatorial isomers were 5.4 to 9.4 fold more reactive than the axial isomers. The oral bioavailability of cyclic HPMPC from the aryl ester prodrugs ranged from 11.2% for *o*-pentylphenyl cyclic HPMPC to 46.3% for butylsalicylyl cyclic HPMPC. Cyclic HPMPC was the major metabolite observed for all the salicylyl ester prodrugs. Cidofovir accounted for 2 to 12% of the total plasma AUC for butyl-, cyclohexyl- and phenethyl-salicylyl esters of cyclic HPMPC. Intact prodrug or the corresponding monosalicylyl esters of cidofovir each accounted for less than 10% of the total AUC for salicylyl ester prodrugs.

INTRODUCTION

Cidofovir ((S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine; HPM PC) is a potent inhibitor of herpesvirus replication in cultured cells and in various animal models (1). Cidofovir (Vistide®) was approved for first line therapy of cytomegalovirus retinitis in patients with AIDS (2). Cyclic HPMPC(1-[((S)-2-hydroxy-2-oxo-1,4,2 dioxaphosphorinan 5-yl) methyl]cytosine) is a cyclic analog of cidofovir with similar in vivo and in vitro antiviral activity against HSV-2 to that of cidofovir (3). Cyclic HPMPC is selectively converted to cidofovir within

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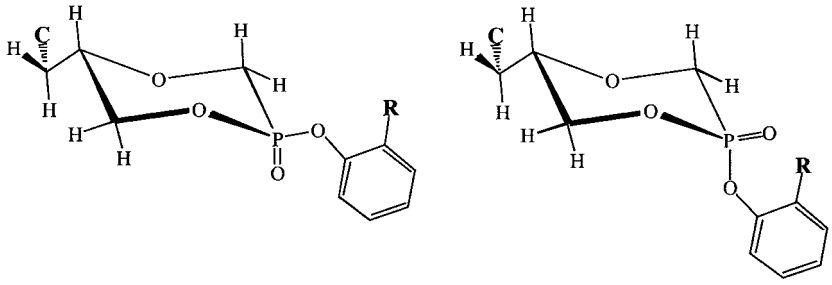
cultured cells in vitro (3). Cyclic HPMPC was significantly less nephrotoxic than cidofovir following repeated intravenous administration to rats, rabbits and monkeys (3). Cyclic HPMPC appeared to have an improved therapeutic index compared to cidofovir. The oral bioavailability of cyclic HPMPC is low: 3.5, 21.9 and 3.1% in rats, dogs and humans. As a result of the low oral bioavailability of cyclic HPMPC in animals and humans, a series of novel prodrugs were designed to enhance the intestinal permeability of the drug.

Material and Method

The concentrations of cyclic HPMPC and cidofovir in plasma samples were determined by ion-pair reverse-phase HPLC with fluorescence derivatization. The concentrations of cyclic HPMPC prodrugs and salicylyl HPMPC monoesters in plasma samples were determined by reverse-phase HPLC with UV detection. All data were analyzed using non-compartmental methods by PCNONLIN (4).

RESULTS AND DISCUSSIONS

Chemical stability was dependent on the orientation of the exo-cyclic ligand; the equatorial isomers were 5.4 to 9.4 fold more reactive than the axial isomers. (5). Axial isomers of salicylyl cyclic HPMPC prodrugs were selected for in vivo



Equatorial **Axial**

R	
$COOCH_2CH_3$	Ethylsalicylyl
$COO(CH_2)_3CH_3$	Butylsalicylyl
$COO(CH_2)_4CH_3$	Pentylsalicylyl
$COO(CH_2)_5CH_3$	Hexylsalicylyl
$COOCH_2CH(C_2H_5)(CH_2)_3CH_3$	2-Ethylhexylsalicylyl
$COOC_6H_5$	Phenylsalicylyl
$COOCH_2CH_2C_6H_5$	Phenethylsalicylyl
$COOC_6H_{11}$	Cyclohexylsalicylyl

Scheme.

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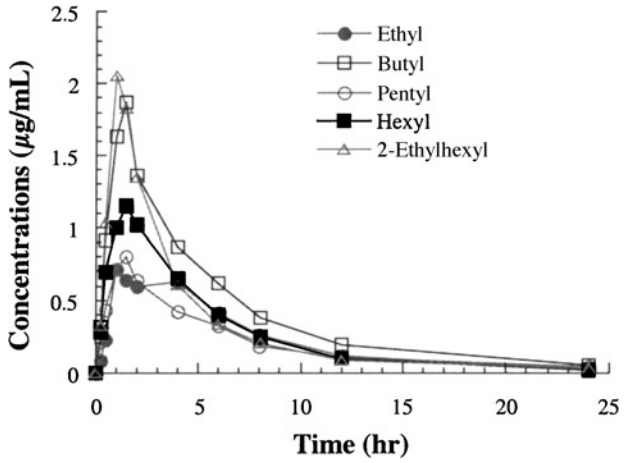

Figure 1. Concentrations of cyclic HPMPC in plasma following oral administration of alkylsalicylyl cyclic HPMPC prodrugs to dogs.

evaluation. Both isomers of butylsalicylyl cyclic HPMPC were evaluated for comparison. Figure 1 shows the plasma concentration of cyclic HPMPC following oral administration of its salicylate prodrugs. Oral bioavailability of cyclic HPMPC from its alkylsalicylyl ester prodrugs ranged from 18.5% for the ethylsalicylyl

Table 1. Oral Bioavailability of Salicylyl Cyclic HPMPC Prodrugs in Beagle Dogs. (Values are Mean)

Compound	Formulation (dose)	% BA as * Cyclic HPMPC	Cmax (μg/mL)	Tmax (hr)
Ethylsalicylyl cyclic HPMPC	PEG 400 (7.9 mg/kg)	18.5 ± 5.78	0.67 ± 0.24	1.90 ± 1.25
Butylsalicylyl cyclic HPMPC	20% PEG 400 in citric acid			
Axial isomer	(pH 2.2) (8 mg/kg)	46.3 ± 8.97	1.57 ± 0.46	1.50 ± 0.35
Equatorial isomer	(8 mg/kg)	36.4 ± 9.26	1.61 ± 0.45	0.60 ± 0.22
Pentylsalicylyl cyclic HPMPC	40% PEG 400 in citric acid (pH 2.2) (9.2 mg/kg)	22.4 ± 5.53	0.75 ± 0.18	1.60 ± 0.22
Hexylsalicylyl cyclic HPMPC	20% PEG 400 in citric acid (pH 2.2) (8 mg/kg)	30.5 ± 4.83	0.97 ± 0.27	1.40 ± 0.42
2-Ethylhexylsalicylyl cyclic HPMPC	20% PEG 400 in citric acid (pH 2.2) (10 mg/kg)	34.4 ± 4.83	2.10 ± 0.62	1.20 ± 0.27
Phenylsalicylyl cyclic HPMPC	PEG 400 (9.3 mg/kg)	27.8 ± 6.16	2.70 ± 0.51	1.40 ± 0.42
Phenethylsalicylyl cyclic HPMPC	20% PEG 400 in citric acid (pH 2.2) (8 mg/kg)	35.3 ± 3.37	0.85 ± 0.15	1.50 ± 0.35
Cyclohexylsalicylyl cyclic HPMPC	20% PEG 400 in citric acid (pH 2.2) (8 mg/kg)	22.7 ± 4.43	0.98 ± 0.36	0.90 ± 0.22

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cyclic HPMPC to 46.3% for the butylsalicylyl cyclic HPMPC [Table 1]. Cyclic HPMPC was the major metabolite for all of the salicylyl ester prodrugs of cyclic HPMPC. Cidofovir accounted for less than 10% of the total AUC. Intact prodrug or salicylyl HPMPC monoester were also detected in plasma and each accounted for less than 10% of the total AUC. The oral bioavailability of cyclic HPMPC from the two stereoisomers of butylsalicylyl cyclic HPMPC were not significantly different ($P > 0.05$). The extent of conversion to cidofovir was similar for both isomers. No prodrug or monoester was generated from the equatorial isomer while both species were detected for the axial isomer. Salicylyl ester prodrugs successfully delivered cyclic HPMPC to the systemic circulation with minimal exposure to cidofovir. This approach may allow oral delivery of cyclic HPMPC while minimizing cidofovir-related toxicity.

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