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Efficacy of A-73209, a potent orally active agent against VZV and HSV infections

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Summary

A-73209 is a novel oxetanocin derivative with potent in vitro and in vivo activity against VZV, HSV-1, and HSV-2. A-73209 was two logs more potent than acyclovir against five thymidine kinase positive (TK^+) strains of VZV in vitro (mean EC_{50} 0.01 vs. 1.22 μg/ml). The activity of A-73209 was one log more potent than acyclovir against TK^+ HSV-1 strains in vitro ($EC_{50} = 0.03$ vs. 0.32 μg/ml). A-73209 yielded a mean EC_{50} of 2.2 μg/ml compared to a mean EC_{50} of 0.37 μg/ml for acyclovir against a panel of TK^+ HSV-2 strains in vitro. The in vitro activity of A-73209 against thymidine kinase negative or deficient strains of VZV, HSV-1 and HSV-2 was much lower than for the corresponding TK^+ strains. A-73209 produced efficacy superior to acyclovir against lethal systemic or intracerebral HSV-1 infections in mice. The greater efficacy of A-73209 relative to acyclovir was especially apparent with oral dosing. Against HSV-2 infections in mice, the efficacy of A-73209 ranged from equal to 1.7 times less active relative to acyclovir with oral dosing. A-73209 was orally bioavailable in mice, with maximal serum concentrations well in excess of in vitro inhibitory concentrations. A-73209 appears to be a potent and selective agent against varicella-zoster virus and herpes simplex virus infections.

HSV-1; HSV-2; VZV; Oxetanocin; Therapy

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Introduction

A-73209, 1-([2′*R*, 3′*R*, 4′*S*]-3′,4′-bis(hydroxymethyl)-2′-oxetanyl)-5-methyluracil, is a novel nucleoside analog of the oxetanocin family, a class of nucleoside compounds that inhibit viral DNA synthesis. Carbocyclic nucleoside analoges have demonstrated potential as broad spectrum antiviral agents (Norbeck et al., 1990; Field et al., 1990). The oxetanocins have potent and specific activity against herpesviruses both in vitro (Sakuma et al., 1991) and in vivo (Nishiyama et al., 1988). The oxetanocins, unlike acyclovir, contain an oxetanosyl-*N*-glycoside in the sugar moiety.

Several nucleoside analogs have shown promising activity against herpesvirus. The carbocyclic nucleoside analoges cyclobutyl-A and cyclobutyl-G have shown potent activity against HSV-1, HSV-2, EBV, CMV, and VZV, as well as against HIV (Clement and Kern, 1991). The in vitro activity of the cyclobutyl compounds was superior to acyclovir vs. EBV and VZV (Clement and Kern, 1991). BV-araU [1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil] demonstrated superior potency against HSV-1 and VZV as compared to acyclovir. The in vivo activity of BV-araU was superior or equivalent to acyclovir vs. HSV-1 infections in mice (Machida, Ijichi and Takezawa, 1992; Machida, Ijichi and Ashida, 1990). (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) is in development, having recently shown efficacy vs. experimental HSV-1 keratitis infection (Maudgal and De Clercq, 1991a) and various other herpes virus infections (De Clercq, 1993). The acyclic nucleoside analog [9-(2-phosphonylmethoxyethyl)adenine] (PMEA) has demonstrated activity against HSV-1, HSV-2 and HIV, including strains that are thymidine kinase deficient. PMEA has shown efficacy against both TK^+ and TK^- strains in experimental HSV-1-induced keratitis (Maudgal and De Clercq, 1991b). Penciclovir, an analog of acyclovir, has potent and selective activity against HSV-1, HSV-2 and VZV (Boyd et al., 1987). Preclinical trials have suggested that the in vivo antiviral effect of penciclovir is of longer duration than acyclovir (Boyd et al., 1988). Famciclovir is a prodrug of penciclovir with oral bioavailability and activity against HSV-1, HSV-2, and VZV (Vere Hodge et al., 1989). Both penciclovir, famciclovir, and BW-256, a valine ester prodrug of acyclovir with greater bioavailability, are undergoing clinical trials.

Acyclovir is the current standard treatment for herpes simplex virus infections. There is a high response rate during therapy, but relapses are common after treatment termination, presumably due to reactivation of latent virus (Molin et al., 1991; Mindel, 1991). Treatment of HSV-1 or HSV-2 infection is difficult and the infections are potentially life-threatening in immunocompromised patients (Tang and Shepp, 1992; Hardy, 1992). Acyclovir, used to treat reactivation of VZV in adults (Collins, 1988), was approved recently for treatment of varicella in children. However, the benefits of therapy are considered modest (Balfour et al., 1992).

In this study we investigated the in vitro antiviral activity and the in vivo therapeutic efficacy of A-73209. In vitro studies utilized several strains of VZV,

HSV-1 and HSV-2, and in vivo investigations utilized several murine models of HSV-1 and HSV-2 infection. In addition, the pharmacokinetic characteristics of A-73209 were investigated and correlated with in vivo efficacy.

Materials and Methods

A-73209. A-73209 was synthesized at Abbott Laboratories as described previously (Norbeck et al., 1991). The structure is shown in Fig. 1.

Viruses. The origin and preparation of wild type HSV-1 and HSV-2 isolates have been described previously (Kern et al., 1978). The Ellen and OKA strains of VZV and the CMV strains were obtained from American Type Culture Collection, Rockville, MD. The isolate DKG was obtained from the diagnostic virology laboratories of the Children's Hospital of Alabama. The ACV-resistant mutants of HSV-1, HSV-2 and VZV were obtained from Dr. Jack Hill and Dr. Karen Biron, Burroughs Wellcome, Research Triangle Park, NC. The virus stocks for HSV were prepared in primary rabbit kidney cells, while stocks for CMV and VZV were prepared in low passaged human foreskin fibroblast cells. The VZV pools contained cell associated virus.

Determination of in vitro EC_{50} values. The in vitro potency (50% effective concentration) of A-73209 and acyclovir against HSV-1, HSV-2 and VZV was determined using human foreskin fibroblast cultures. Briefly, low passage human foreskin fibroblasts were seeded into 96-well plates 24 h prior to use at a concentration of 2.5×10^4 cells per ml in 0.1 ml of minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS). The cells were incubated for 24 h at 37°C in 5% CO_2. The medium was removed and MEM containing 2% FBS was added. Selected wells received appropriate

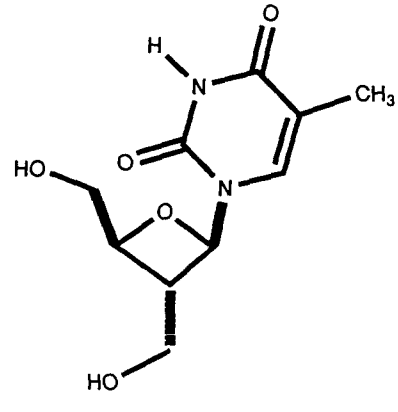

Fig. 1. Structure of A-73209, 1-([2′*R*, 3′*R*, 4′*S*]-3′,4′-bis(hydroxymethyl)-2′-oxetanyl)-5-methyluracil.

concentrations of agent which was then serially diluted 1:5.

After serial dilution of agent, 0.1 ml of the appropriate virus was added to each well, excluding the cell control which received 0.1 ml of MEM. For HSV-1 and HSV-2 assays, the virus concentration was 1000 PFUs per well. For the CMV and VZV assays, the virus concentration added was 2500 PFU per well. The plates were incubated at 37°C in a CO_2 incubator for 3 days for HSV-1 and HSV-2, 10 days for VZV, and 14 days for CMV. After the incubation period, the medium was aspirated and the cells were stained with 0.1% crystal violet for 30 min. The stain was then removed and the plates rinsed using tap water until excess stain was removed. The plates were dried at room temperature for 24 h and optical densities were determined at 620 nm in a Biotek microplater autoreader (Moran et al., 1985).

HSV-1 infection. Swiss mice (Sasco) 6–8 weeks old and weighing 16–20 g were housed 10 to a cage and given free access to food and water. Systemic HSV-1 infection was produced by intraperitoneal inoculation of approximately 8×10^3 plaque forming units (PFU) of HSV-1, strain 123. The inoculum was maintained frozen at −70°C and thawed just before use. Intracerebral infection was produced by direct intracranial inoculation of mice under anesthesia (Nembutanol, 0.2 ml of a 7 mg/ml solution). Approximately 6 PFU in 50 μl were inoculated to obtain a lethal infection. Medication was twice daily for a total of 3 days by either oral or intraperitoneal route. A single double strength loading dose (equal to the entire daily dose) was delivered 7 h post-inoculation, with additional single strength doses delivered 23, 31, 47, 55, 71, and 79 h post-inoculation. Mortality was monitored daily for 21 days. The dose required to obtain 50% survival (ED_{50}) was calculated using linear regression methods as described previously (Carter et al., 1983.). Mean survival time (MST) was calculated for mice that died during the 21 day observation period. There were 10–12 mice per dosage group. Due to anticipated acid sensitivity of A-73209, oral doses were preceeded by a 0.1 ml oral dose of Maalox.

HSV-2 infection. Systemic infections of Swiss mice were obtained following intraperitoneal inoculations of HSV-2 strains G, Jensen or MS. The inoculations were 3.8×10^3 PFU (Jensen), 2.4×10^5 PFU (G) or 9.5×10^5 PFU (MS). The dermal infection was produced in a 1 cm^2 section of mouse skin which had been cleared of hair by shaving. A 10 μl drop of virus suspension containing approximately 1×10^5 PFU of HSV-2 strain X-79 was evenly spread on the 1 cm^2 area using a moist cotton swab. Inoculation was produced by lightly abrading the skin 20 times with a 25-gauge needle. Mice were dosed orally with a double strength loading dose delivered 7 h post-inoculation, with additional doses delivered 23, 31, 47, 55, 71, and 79 h post-inoculation. The endpoints used to determine drug efficacy were MST, ED_{50} calculated at 21 days, and for the dermal trial, lesion severity. Lesions were examined daily and scored on a scale of 0 to 4 with 0 = no lesion, 1 = 1–2 mm lesions, 2 = 2–4 mm lesions, 3 = 4–6 mm lesions, and 4 = severe lesion covering

the entire infected area. Mean lesion scores are reported. There were 10–12 mice per dosage group.

Pharmacokinetic characteristics of A-73209. Strain CD1/ICR mice were dosed intraperitoneally (30 mg/kg) or orally (125 mg/kg) with A-73209 or acyclovir. Blood samples were collected individually from groups of mice at 0.25, 0.5, 0.75, 1, 2, 3, 6, 8, 12, and 24 h post dosing. Plasma was separated from chilled blood samples and stored frozen until analysis. A 0.2 ml aliquot of plasma was combined with 0.6 ml of acetonitrile. The samples were thoroughly mixed to precipitate the proteins, followed by centrifugation at $13\,000 \times g$ for 3 min. A constant volume (0.7 ml) of the supernatent was lyophilized to dryness followed by reconstitution of the sample with 0.2 ml water. A-73209 was separated from plasma contaminants on a 10 cm × 4.6 mm 5 μm ODS-AQ column with 1% THF in a water mobile phase at a flow rate of 0.5 ml/min with UV detection of the 100 μl injection volume at 266 nm. The method was linear over the concentration range 0–45 μg/ml with an estimated detection limit of 0.1 μg/ml. The plasma concentrations of each sample were calculated by the least squares linear regression analysis (unweighted) of the peak area of the spiked plasma standards vs. concentration. Area under the curve values were calculated by the trapezoidal method over the time course of the study. The relative availability ($F\%$) of the oral solution was calculated by dividing the AUC of the orally dosed animals by the AUC of the intraperitoneally dosed animals, with corrections made for differences between dose size.

Results

In vitro potency of A-73209 and acyclovir against herpes virus

In human foreskin fibroblast culture, A-73209 was approximately 2 logs more potent than acyclovir against each of five thymidine kinase positive (TK^+) strains of VZV (Table 1). The mean EC_{50} value for A-73209 was 0.01 μg/ml (range 0.003–0.03 μg/ml) compared to 1.22 μg/ml (range 0.6–2.7 μg/ml) for acyclovir. A-73209 was somewhat more potent than acyclovir against TK-deficient VZV strains (V860217-1-3 and 8908). A-73209 was four to 46 times more potent than acyclovir against TK^+ strains of HSV-1. Acyclovir and A-73209 had low activity against TK^- deficient or altered strains of HSV-1 (DM 2.1, SC 16-S1). Against TK^+ strains of HSV-2, A-73209 was overall less potent than acyclovir. A-73209 and acyclovir had weak activity against TK^- deficient strains of HSV-2 (8711). A-73209 was inactive against CMV or EBV.

Preliminary drug safety

A-73209 was not toxic to fibroblasts under the conditions of the assay as measured by either neutral red uptake or cell proliferation ($IC_{50} > 100$ μg/ml). A-73209 was non-mutagenic in the AMES test. Toxicity was not observed in mice given daily per oral (PO) doses of 500 mg/kg, or daily intraperitoneal (IP)

TABLE 1

Anti-herpesvirus activity of A-73209 and acyclovir in human foreskin fibroblast cell culture

Virus	strain	TK	EC_{50} (μg/ml)	
			A-73209[a]	acyclovir[a]
VZV	Ellen	+	0.003	0.60
	Oka	+	0.02	2.7
	DKG	+	0.03	1.0
	V8907	+	0.01	1.0
	V8602/5-1-1	+	0.008	0.80
	V8602/7-1-3	deficient	1.2	7.4
	V8908	deficient	3.0	23
HSV-1	E-377	+	0.05	0.20
	123	+	0.012	0.56
	SC 16	+	0.03	0.20
	SC 16-S1	altered	34	33
	DM 2.1	deficient	92	>100
	11893	altered	82	64
	11359	deficient	>100	>100
HSV-2	MS	+	5.7	0.60
	8705	+	0.50	0.30
	X-79	+	1.0	0.40
	JEN	+	0.50	0.20
	HEET	+	3.0	0.30
	SR	+	3.6	0.40
	G	+	0.88	0.39
	11680	altered	47	13
	12247	altered	81	>100
	8711	deficient	>100	>100
EBV	P3HR1		>100	7.2
			A-73209	ganciclovir
CMV	AD 169		>100	0.4
	Davis		>100	1.2
	Towne		>100	0.5

[a]The toxicity IC_{50} of A-73209 and acyclovir for human foreskin fibroblasts was >100 μg/ml by both neutral red uptake and cell proliferation assays.

doses of 400 mg/kg.

In vivo activity against HSV-1 infection in mice

With intraperitoneal dosing, A-73209 was four times more potent than acyclovir against lethal systemic HSV-2 infection (Table 2). A-73209 yielded an ED_{50} of 30 mg/kg · day compared to an ED_{50} of 128 mg/kg · day for acyclovir. With oral dosing, A-73209 was at least four times more potent than acyclovir against lethal systemic HSV-1 infection. Oral treatment with A-73209 produced an ED_{50} value of 142 mg/kg, while oral therapy with acyclovir was ineffective (ED_{50} > 500 mg/kg). Against a lethal intracerebral infection (Table 3), A-73209

TABLE 2

Efficacy of A-73209 and acyclovir against lethal systemic HSV-1 (123) infection in mice[a]

Compound	daily dose[b]	mean survival time (days)[c]	% survivors[d]	ED_{50} (mg/kg · day)
A-73209	200 mg/kg IP	12.0	90	
	50 mg/kg IP	9.8	60	30
	12.5 mg/kg IP	8.3	30	
Acyclovir	400 mg/kg IP	8.0	60	
	100 mg/kg IP	6.7	70	128
	25 mg/kg IP	6.4	0	
Untreated		6.6	0	
A-73209	500 mg/kg PO	2.0	90	
	250 mg/kg PO	8.3	60	142
	125 mg/kg PO	10.8	50	
Acyclovir	500 mg/kg PO	8.6	10	
	250 mg/kg PO	8.2	0	>500
	125 mg/kg PO	7.1	0	
Untreated		8.7	0	

[a]Mice were inoculated with 10 × LD_{50} (8.3×10^3 PFU) of HSV-1.
[b]Total daily dose was divided into two daily doses (bid).
[c]Surviving mice were excluded from calculation.
[d]Survivors, day 21 after inoculation.

yielded protective efficacy with oral dosing ($ED_{50} = 211$ mg/kg · day), while acyclovir was not effective with oral dosing ($ED_{50} > 500$ mg/kg · day).

TABLE 3

Efficacy of A-73209 and acyclovir against lethal intracerebral HSV-1 infection in mice

Compound	daily dose[b]	mean survival time (days)[c]	% survivors[d]	ED_{50} (mg/kg · day)
A-73209	500 mg/kg PO	11.5	80	
	250 mg/kg PO	11.0	70	211
	125 mg/kg PO	10.4	22	
Acyclovir	500 mg/kg PO	7.1	0	
	250 mg/kg PO	7.3	10	>500
	125 mg/kg PO	6.8	0	
Untreated		5.2		

[a]Mice were inoculated intracranially with 10 × LD_{50} (6.0×10^0 PFU) of HSV-1.
[b]Total daily dose was divided into two daily doses (bid), except on the day of inoculation when the mice received the daily amount in a single dose.
[c]Surviving mice were excluded from calculation.
[d]survivors, day 21 after inoculation.

TABLE 4

Efficacy of A-73209 and acyclovir against lethal systemic HSV-2 infection in mice

strain	IP ED_{50} (mg/kg · day)		PO ED_{50} (mg/kg · day)	
	A-73209	acyclovir	A-73209	acyclovir
G[a]	99	56	<125	<125
MS[b]	120	50	342	250
JEN[c]	>240	85	500	282

[a]Mice were inoculated with 100 × LD_{50} strain G (2.4×10^5 PFU).
[b]Mice were inoculated with 100 × LD_{50} strain MS (9.5×10^5 PFU).
[c]Mice were inoculated with 10 × LD_{50} strain JEN (3.8×10^3 PFU).

TABLE 5

Efficacy of A-73209 and acyclovir against lethal dermal HSV-2 infection in mice[a]

Compound	daily dose[b]	MST[c]	% survivors[d]	Mean peak lesion score[e]	ED_{50} (mg/kg · day)
A-73209	500 mg/kg PO	12.3	20	3.3	
	250 mg/kg PO	12.8	20	3.2	>500
	125 mg/kg PO	14.3	10	3.6	
Acyclovir	500 mg/kg PO	12.0	60	1.6	
	250 mg/kg PO	12.6	50	2.0	250
	125 mg/kg PO	10.8	40	2.4	
Vehicle		9.6	0	4.0	–

[a]Mice were inoculated with 10 × LD_{50} strain X (1.1×10^5 PFU).
[b]Total daily dose was divided into two daily doses (bid), except on the day of inoculation when the mice received the daily amount in a single dose.
[c]Surviving mice were excluded from calculation.
[d]Survivors, day 21 after inoculation.
[e]Based on a 0–4 scale; 0 = no disease, 1 = 1 lesion, 2 = scattered lesions, 3 = overlapping lesions, 4 = single confluent lesion.

TABLE 6

Pharmacokinetic evaluation of A-73209 and acyclovir in mice

Dose (mg/kg)	t_{max} (hrs)	C_{max} (μg/ml)	$t_{1/2}$ (hrs)	AUC(0–∞) (μg/ · h/ml)	$F\%$[a]
A-73209					
30 IP	0.25	43.26	3.21	82.94	
125 PO	1.00	47.61	9.54	191.93	55.5[a]
Acyclovir					
30 IP	0.25	23.89	1.51	49.10	
125 PO	0.25	5.44	4.93	9.55	4.6[a]

[a]Apparent availability based on IP dose – $[AUC_{PO}/AUC_{IP}]$.

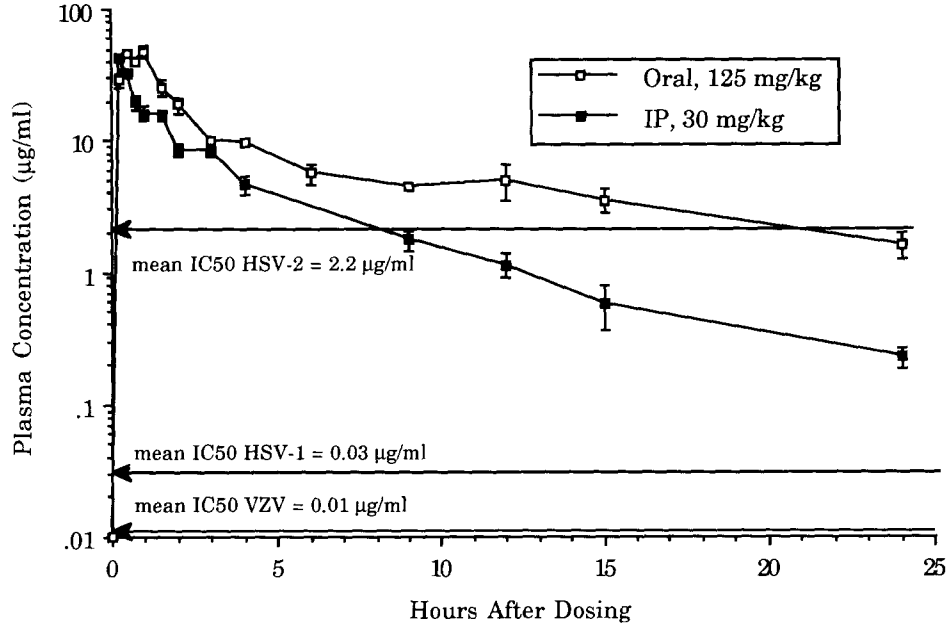

Fig. 2. Mean plasma concentrations of A-73209 in mice following a 125 mg/kg oral dose compared to in vitro EC_{50} values. There were five mice per time point.

In vivo activity against HSV-2 infection in mice

Against systemic HSV-2 infections, the efficacy of A-73209 ranged from equal to three times less effective than acyclovir. With IP dosing, the efficacy of acyclovir ($ED_{50}=50$ to 85 mg/kg) was greater than A-73209 ($ED_{50}=99$ to >240 mg/kg). With oral dosing, the activity of A-73209 ranged from approximately equal to 1.7 times less potent was acyclovir. In a lethal dermal HSV-2 infection of mice, A-73209 was about 2 times less potent than acyclovir with oral dosing as determined from animal survival and skin lesion scoring (Table 5).

Pharmacokinetics of A-73209

A-73209 showed approximately 50% oral availability in mice (Table 6). A 30 mg/kg IP dose yielded a plasma half-life of over 3 h, and a 125 mg/kg oral dose produced a plasma half-life of greater than 9 h. The C_{max} values of A-73209 in mouse were two to three logs greater than the in vitro EC_{50} (μg/ml) of susceptible strains of VZV and HSV-1 (Fig. 2).

Discussion

A-73209 provided effective therapy for herpes virus infections in several

mouse models. Protective activity of A-73209 was found with either IP or oral administration in a murine model of systemic HSV-1 infection. The efficacy of A-73209 against HSV-1 infection was superior to acyclovir by both routes. Oral administration of A-73209 was protective for intracerebral HSV-1 infection, while acyclovir, which has a low ability to cross the blood brain barrier (Biron et al., 1992), was ineffective. The efficacy of A-73209 in the intracerebral model of infection suggests that the compound crosses the blood brain barrier following oral dosing. Protective oral therapy of intracerebral HSV-1 infection in mice is difficult, and the efficacy of oral A-73209 therapy is encouraging. A-73209 administered orally or intraperitoneally was also protective against lethal systemic HSV-2 infection.

The efficacy of A-73209 following oral dosing in herpes virus infections is corroborated by the pharmacokinetic characteristics of the compounds. A-73209 yielded apparent availability of 50% in mice with a plasma half-life greater than 3 h. The plasma concentrations of A-73209 in mice were over 100-fold greater than the in vitro EC_{50} values for VZV and HSV-1 strains. A-73209 demonstrated less efficacy with IP dosing relative to acyclovir vs. systemic or dermal HSV-2 infection (Tables 4 and 5). Oral dosing narrowed the gap in efficacy between acyclovir and A-73209 vs. systemic HSV-2 infection. Efficacy was nearly equal for A-73209 and acyclovir vs. strain G, while strain Jensen appeared more resistant to A-73209. The efficacy of A-73209 and acyclovir were both limited against dermal HSV-2 infection.

There was a good correlation between in vitro activity and in vivo efficacy of A-73209 and acyclovir. In vitro A-73209 was superior to acyclovir vs. HSV-1, and this activity correlated with superior in vivo activity. Against several HSV-2 strains, A-73209 was not as active as acyclovir, and this result correlated with the relative in vivo efficacy of the two compounds. A-73209 demonstrated great superiority to acyclovir vs. VZV in vitro. Against five TK^+ strains of VZV, A-73209 was over 100-fold more potent than acyclovir, and this factor could result in effective therapy against VZV infections.

A-73209 and acyclovir likely have similar mechanisms of action. A-73209, had less activity against TK^- strains of VZV similar to other oxetanocins and acyclovir (Sakuma et al., 1991). Also, A-72309 and acyclovir were virtually inactive against TK^- or deficient strains of HSV-1 and HSV-2. This result suggests that A-73209 is phosphorylated to the monophosphate form by viral thymidine kinase. The in vitro activity of A-73209 appears to be superior to the acyclovir analoges penciclovir and famciclovir. A-73209 and BV-araU are 100- to 1000-fold more potent than acyclovir vs. VZV in vitro (Machida et al., 1990).

There is a clinical need for new and effective therapies against herpes virus infections. Herpes virus infection often occurs in immunocompromised patients including cancer and AIDS patients. Almost all of these infections result from reactivation of latent virus (Tang and Shepp, 1992). Treatment of HSV infections in AIDS patients often requires long term therapy, and there are reports of clinical resistance linked to prolonged treatment (Oliver et al., 1989;

Marks et al., 1989). VZV infections that occur in AIDS patients may become prolonged and serious (Linneman et al., 1990). Clinical benefit has been demonstrated for acyclovir therapy of varicella in children (Balfour et al., 1990), but the value of this approach is controversal. Shingles can be a painful and prolonged disease in adult patients, and effective therapy is required.

The correlation between in vitro potency, in vivo efficacy and pharmacokinetics suggests potential utility of A-73209 against VZV and HSV-1 infection. There is not a consistent and proven animal model for VZV infection and therapy, although there has been progress with a hairless guinea pig model (Myers and Stanberry, 1991; Myers et al., 1991). The simian zoster model is useful for agents that show activity vs. simian zoster virus; however, A-73209 dose not have in vitro activity against this virus (K. Soike, personal communication). A-73209 demonstrated approximately one log greater potency than acyclovir in vitro against HSV-1 and this potency correlated with superior in vivo activity. Against HSV-2, A-73209 was less active relative to acyclovir, and this correlated with in vivo efficacy. A-73209 demonstrated two logs greater potency than acyclovir against VZV virus in vitro. The pharmacokinetic performance of A-73209 relative to in vitro EC_{50} values (Fig. 2) suggests that A-73209 has potential use against varicella-zoster infections.

In summary, A-73209 demonstrated in vitro potency and protective efficacy in mouse models of herpes virus infection. The pharmacokinetic characteristics of A-73209 include high oral availability and long plasma elimination half-life. The relative in vitro and in vivo efficacy of A-73209 compared to acyclovir in vitro and in vivo suggest potential clinical efficacy and utility of A-73209 vs. herpes virus infections.

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