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Intraocular acyclovir levels after subconjunctival and topical administration

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SUMMARY Substantial levels of acyclovir were detected in the aqueous and vitreous of New Zealand rabbits at various time intervals following subconjunctival injection. Intravitreal penetration of acyclovir after topical application was poor.

Acyclovir is an antiviral agent that possesses substantial activity and specificity against most members of the herpes simplex virus family with the possible exception of cytomegalovirus.¹ Acyclovir shows little toxicity toward uninfected human cells.² This preliminary study was designed to evaluate the intraocular levels of the drug at different time intervals following subconjunctival injection and topical administration. To the best of our knowledge no other report describes intraocular penetration of acyclovir following subconjunctival administration or vitreous levels after topical application of acyclovir.

Materials and methods

A total of 47 New Zealand white rabbits, weighing approximately 2 kg each, were divided into three groups for this study.

Part A. The animals were anaesthetised with an intravenous injection of ketamine hydrochloride. A single 25 mg injection of acyclovir sodium (0.5 ml of a 50 mg/ml (50 g/l) solution) was given under the bulbar conjunctiva of one eye of each rabbit. At 1, 3, 5, and 24 hours after subconjunctival injection aqueous and vitreous samples were removed and immediately refrigerated at -27°C . Each sample of aqueous was obtained with a 30-gauge needle inserted through clear cornea. Vitreous samples were aspirated with a 23-gauge needle placed 2 mm behind the limbus. Levels of acyclovir were determined by radioimmunoassay.³

Part B. The experiment was repeated with a 2.5 mg injection of acyclovir (0.5 ml of a 5 mg/ml (5 g/l)

solution) under the bulbar conjunctiva of one eye of each rabbit. Aqueous (0.1 ml) and vitreous (0.1 ml) samples were obtained in the same fashion as in part A at 0.5, 1, 2, 3, and 22 hours after subconjunctival injection.

Part C. One eye from each of 10 rabbits was treated with 3% acyclovir ointment. A 1 cm ribbon of the ointment was placed in the inferior cul de sac of each eye every five hours for 25 hours. A total of six applications were given to each eye. At 1, 2, and 3 hours after the last application of acyclovir vitreous samples were obtained and immediately refrigerated at -27°C . Acyclovir levels were determined by radioimmunoassay.

Results

Part A. Clinically the rabbits showed crystallisation of acyclovir after subconjunctival injection. The crystals dissolved within 18 hours. Minimal conjunctival reaction followed the injection. Relatively high aqueous (Table 1) and vitreous (Table 2) levels of acyclovir were detected after subconjunctival injection.

Part B. Subconjunctival crystallisation of acyclovir was not detected in this group. Substantial aqueous (Table 3) and vitreous (Table 4) levels of acyclovir were obtained.

Part C. Vitreous levels following topical application of the drug were negligible (Table 5).

Discussion

Acyclovir, 9-(2-hydroxyethoxymethyl)guanine, is also called acycloguanosine.^{4,5} In-vitro acyclovir is

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Table 1 Acyclovir levels in rabbit aqueous humour

Time (h)	Aqueous humour samples		
	Sample	Concentration	
		$\mu\text{g/ml}$	μM
1-0	A1	258.84	1150.38
	A2	533.13	2369.43
	A3	137.83	612.59
3-0	A4	104.42	464.07
	A5	297.42	1321.86
	A6	199.32	885.87
5-0	A7	71.50	316.23
	A8	102.49	455.50
	A9	82.55	366.88
24-0	A10	2.08	9.25
	A11	3.43	15.24
	A12	1.72	7.62

Samples were obtained after rabbits received a subconjunctival injection of 25 mg (0.5 ml) of acyclovir sodium salt.

Table 2 Acyclovir levels in rabbit vitreous humour

Time (h)	Vitreous humour samples		
	Sample	Concentration	
		$\mu\text{g/ml}$	μM
1-0	V1	2.31	10.27
	V2	4.73	21.03
	V3	1.61	7.17
3-0	V4	23.02	102.30
	V5	34.79	154.62
	V6	65.95	293.09
5-0	V7	15.44	68.62
	V8	32.58	144.78
	V9	0.21	0.95
24-0	V10	0.13	0.57
	V11	0.22	0.99
	V12	0.31	1.32

Samples were obtained after rabbits received a subconjunctival injection of 25 mg (0.5 ml) of acyclovir sodium salt.

active against DNA viruses of the herpes group.^{4,6} Because acyclovir is activated in vivo only by virus-specific enzymes, it is non-toxic to uninfected cells.²

In-vitro acyclovir has been found to be effective against several members of the herpes virus family. Minimum inhibitory concentrations (MIC) of acyclovir have been reported as 0.2, 0.4, 1.0, 1.5, and 16.3 $\mu\text{g/ml}$ (mg/l) for herpes simplex virus type I (HSV I), herpes simplex virus type II (HSV II), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) respectively.⁴ The ID₅₀ (50% inhibitory dose) in herpes virus isolated from human infections was 0.15 SD0.09 μM , 1.62 SD0.76 μM , and 3.75 SD1.30 μM for HSV I, HSV II, and VZV. Two CMV isolates had ID₅₀s of 100 and 160 μM , while four other isolates showed no plaque reduction at 200 μM .²

Table 3 Acyclovir levels in rabbit aqueous humour

Time (h)	Aqueous humour samples		
	Sample	Concentration	
		$\mu\text{g/ml}$	μM
0.5	A1	1.13	5.04
	A2	2.98	13.20
	A3	>45.00	>200.00
1-0	A4	>45.00	>200.00
	A5	16.00	71.10
	A6	9.36	41.60
2-0	A7	4.04	17.90
	A8	7.87	35.00
	A9	9.41	41.80
3-0	A10	3.27	14.50
	A11	5.59	24.90
	A12	9.19	40.09
22-0	A13	<0.56	<2.50
	A14	<0.56	<2.50

Samples were obtained after rabbits received a subconjunctival injection of 2.5 mg (0.5 ml) acyclovir.

Table 4 Acyclovir levels in rabbit vitreous humour

Time (h)	Vitreous humour samples		
	Sample	Concentration	
		$\mu\text{g/ml}$	μM
0.5	V1	6.28	27.90
	V2	0.90	3.98
	V3	0.62	2.76
1-0	V4	0.95	4.23
	V5	1.17	5.21
	V6	2.70	12.00
2-0	V7	1.43	6.36
	V8	<0.56	<2.50
	V9	1.30	5.78
3-0	V10	1.88	8.39
	V11	1.36	6.06
	V12	0.92	4.09
22-0	V13	<0.56	<2.50
	V14	<0.56	<2.50

Samples were obtained after rabbits received a subconjunctival injection of 2.5 mg (0.5 ml) acyclovir.

Topical application of acyclovir resulted in vitreous levels well below the therapeutic range for members of the HSV family. Subconjunctival injection with 25 mg of the sodium salt of acyclovir produced, in most instances, aqueous and vitreous levels sufficient to inhibit members of the HSV family with the possible exception of CMV. The vitreous acyclovir levels remained in therapeutic proportions for at least three hours after injection. Therapeutic aqueous levels for HSV I and HSV II were present at 18 hours after injection, but vitreous levels were subtherapeutic for all members of the HSV family except HSV I. The variation in acyclovir levels probably resulted in part from an uneven absorption

Table 5 Acyclovir levels in rabbit vitreous humour

Time (h)	Vitreous humour samples		
	Sample	Concentration	
		$\mu\text{g/ml}$	μM
1-0	V1	<0.02	<0.10
	V2	<0.03	<0.10
	V3	<0.02	<0.10
2-0	V4	0.03	0.12
	V5	<0.02	<0.10
3-0	V6	0.02	0.10
	V7	<0.02	<0.10
	V8	0.04	0.18
	V9	<0.02	<0.10
	V10	0.02	0.10

Samples were obtained after rabbits received a topically applied 1 cm ribbon of 3% acyclovir every five hours for a total of six applications over a 25-hour period.

due to crystallisation from the subconjunctival injection. This occurred only with the higher dose of acyclovir.

The second part of the experiment (subconjunctival injection of 2.5 mg of acyclovir) produced aqueous levels in excess of the MIC for all members of the HSV family except CMV for at least three hours after injection. Negligible levels of acyclovir were detectable 22 hours after injection. Vitreous levels were therapeutic for HSV I, HSV II, VZV, and EBV, but not CMV during the first three hours after injection.

Patients with herpes simplex retinitis have had substantial visual loss and retinal damage.⁷⁻¹¹ A recent communication¹² has suggested an association between acute retinal necrosis and HSV infection. HSV has been demonstrated in the anterior chamber in iritis, keratouveitis, and disciform corneal oedema with associated iritis.¹³⁻¹⁵ Herpes virus particles also have been detected in an iridectomy specimen removed from a patient with herpetic uveitis, deep keratitis, and secondary glaucoma.¹⁶ Our findings indicate that subconjunctival injection of acyclovir may provide effective drug levels for the primary or adjunctive treatment of deep herpetic disease such as retinitis, keratouveitis, iritis, and possibly acute retinal necrosis. Caution must be exercised, how-

ever, in making recommendations based on data obtained only from rabbit eyes. Subconjunctival acyclovir infection should avoid toxic reactions reported after parenteral administration.

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