

Pharmacokinetics of oral acyclovir (Zovirax) in the eye

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SUMMARY Patients due for cataract extraction received 5 doses of 400 mg acyclovir (Zovirax) orally during the 24 hours prior to surgery. Aqueous humour levels of acyclovir (mean 3.26 μM) were well above the normal ED₅₀ range for herpes simplex virus type 1, and showed a significant correlation with plasma concentrations (mean 8.74 μM). There was also a correlation between the age of the patient and the concentration of acyclovir in the plasma. Oral acyclovir was well tolerated.

Acyclovir (9-(2-hydroxyethoxymethyl)guanine) is a potent antiviral agent (Zovirax) against herpes simplex virus types 1 and 2.^{1,2} It acts selectively against the virus without eliciting any substantial toxic effect on uninfected cells. The first stage in the phosphorylation of acyclovir to its active triphosphate form is carried out by the virus-coded thymidine kinase but not by normal cellular enzymes. Acyclovir triphosphate selectively inhibits the viral DNA polymerase.³

Topical acyclovir was first demonstrated to be clinically effective in the treatment of superficial herpetic keratitis by Jones *et al.*⁴ Subsequent studies have shown it to be at least as effective⁵⁻⁷ as or more effective⁸⁻¹² than idoxuridine and adenine arabinoside and generally equivalent to trifluorothymidine.¹³ The intraocular penetration of acyclovir is superior to that of other antiviral agents, and statistically and biologically significant concentrations of acyclovir have been found in the aqueous humour following topical application of the ophthalmic ointment to patients about to undergo cataract surgery.¹⁴

Anecdotal evidence¹⁵ suggests that systemic therapy with intravenous acyclovir is also effective in the treatment of herpetic keratitis, and therapeutic concentrations of the drug have been demonstrated in the plasma following oral administration.¹⁶⁻¹⁸ Nevertheless, as an indication of the possible role of systemic therapy in the treatment of herpetic keratitis, especially the deeper forms of infection, it is necessary to determine the concentrations of acyclovir achieved in the aqueous humour after oral dosing. In this study

we have investigated the penetration of orally administered acyclovir into the aqueous humour of patients undergoing cataract surgery.

Patients and methods

Twenty patients due for cataract extraction, aged over 18 years and who gave their informed consent,

Table 1 *Acyclovir concentrations in plasma and aqueous humour following oral administration*

Patient number	Sex	Age (years)	Acyclovir concentration (μM)	
			Plasma	Aqueous humour
1	F	75	10.47	4.63
2	F	71	8.37	3.99
3	F	70	12.34	3.26
4	M	59	2.80	1.10
5	F	82	9.57	3.98
6	M	80	10.10	4.84
7	F	67	7.34	3.05
8	F	82	6.12	2.53
9	F	86	14.56	2.47
10	M	79	14.62	5.39
11	F	76	9.10	2.77
12	M	40	6.80	1.83
13	M	81	8.60	4.50
14	M	59	6.20	1.79
15	F	88	8.20	3.73
16	F	65	4.60	2.35
17	F	62	7.95	—
18*	M	49	<0.01	<0.2
19*	M	69	0.08	<0.2
20*	F	70	<0.01	<0.2

*Patients 18, 19, 20 were untreated controls.

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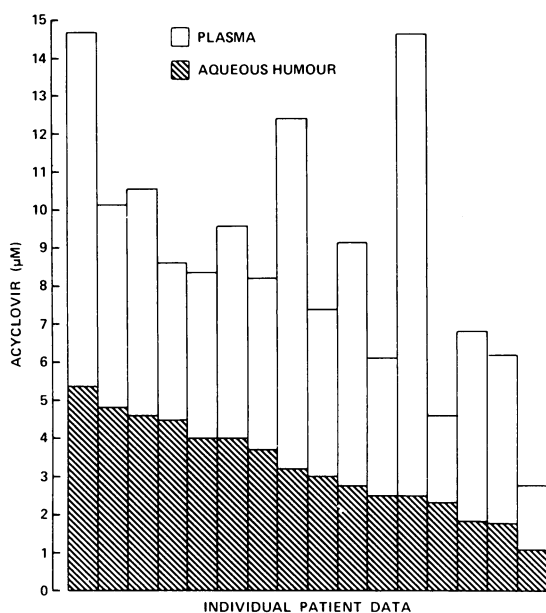


Fig. 1 Comparison of aqueous humour and plasma concentrations of acyclovir in individual patients following oral administration.

were included in the study. Patients with impaired renal function, recent history of gastrointestinal disorder, or pre-existing corneal disease or uveitis were excluded. Seventeen patients received oral acyclovir (400 mg) 5 times in 24 hours, the last dose being given 2 hours before surgery. The remaining 3

patients did not receive the drug and provided control samples to standardise the drug assay procedure.

All patients were fasted for 8 to 10 hours before cataract surgery, which was performed under general or local anaesthesia. No premedication was given in order to avoid possible interference in absorption of acyclovir. Surgery was carried out by the standard procedure with limbal based conjunctival flap and ab-externo approach. After adequate haemostasis to avoid contamination of the samples with blood, 0.1 to 0.15 ml aqueous humour was aspirated via a 25 gauge needle into a disposable tuberculin syringe. A sample (10 ml) of heparinised venous blood was obtained at the same time, centrifuged, and the plasma transferred to a fresh tube. All specimens were immediately frozen at -20°C and stored for subsequent analysis by the Department of Clinical Pharmacology, Wellcome Research Laboratories. Acyclovir concentrations were determined by radioimmunoassay.¹⁹

Results

Sufficient volumes of aqueous humour for analysis were obtained from 16 patients receiving acyclovir. Patient details and the concentrations of acyclovir found in the plasma and aqueous humour are given in Table 1. Substantial levels of acyclovir, with a mean concentration of $3.26 \pm 1.24 \mu\text{M}$, were detected in the aqueous humour, while the mean concentration of drug achieved in the plasma was $8.69 \pm 3.16 \mu\text{M}$.

A comparison of individual patient data (Fig. 1) suggested that there may be a linear relationship between the levels of acyclovir in the aqueous

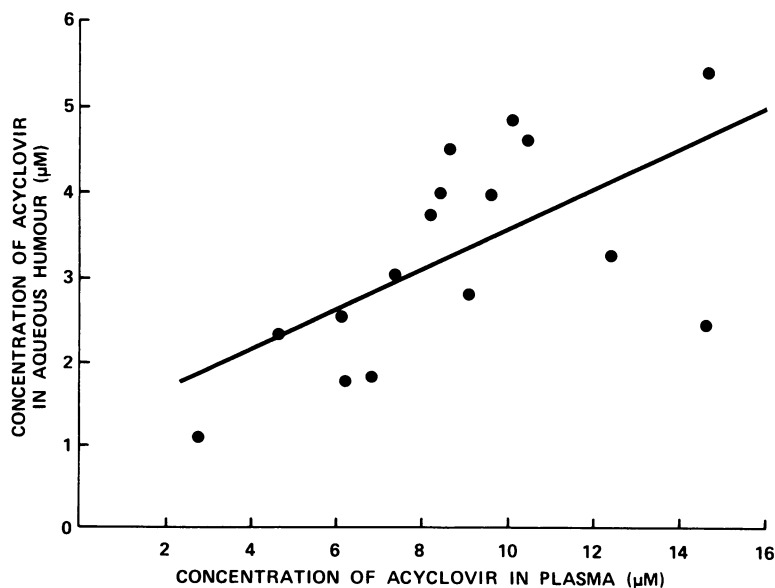


Fig. 2 Correlation between the concentration of acyclovir in the aqueous humour and plasma.

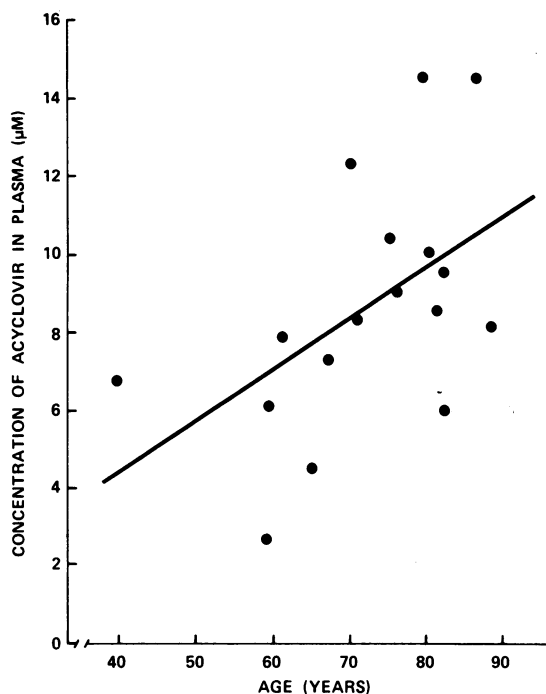


Fig. 3 Correlation between the concentration of acyclovir in the plasma and the age of the patient.

humour and the plasma. Linear regression analysis (Fig. 2) showed a significant correlation ($r=0.62$, $p<0.01$) between plasma and aqueous concentrations of the drug, the equation of best fit being:

Acyclovir in aqueous humour (μM) = $1.20 + 0.24 \times$ acyclovir in plasma (μM).

The age of the patients included in the study ranged from 40 to 88 years, and in general higher plasma concentrations of acyclovir, following the same oral dosing regimen, were found in older patients. Analysis (Fig. 3) demonstrated a significant correlation ($r=0.52$, $p<0.05$) between the age of the patient and the level of acyclovir detected in the plasma.

Oral acyclovir was well tolerated and no adverse reactions were reported.

Discussion

Substantial levels of acyclovir were detected in the aqueous humour following oral administration of the drug. The levels achieved were approximately half those found by Poirier *et al.*¹⁴ (mean of 25 patients $7.5 \mu\text{M}$) after topical administration of acyclovir ointment. However, both the mean aqueous humour concentration of acyclovir ($3.26 \mu\text{M}$) and the lowest individual value ($1.10 \mu\text{M}$) recorded in this study are well in excess of the mean ED_{50} s of $0.15 \mu\text{M}^{20}$ and

$0.18 \mu\text{M}^{21}$ reported for clinical isolates of herpes simplex virus type 1.

The plasma levels of acyclovir achieved in this study are somewhat higher than those reported previously^{17,18} following oral administration and appear to be related to the age of the patient. The principal route of drug clearance is through the kidney,²² and the increased plasma levels found in older patients are probably a reflection of decreasing renal function with age. The maximum plasma level observed was, however, considerably lower than the concentrations of drug routinely achieved by intravenous dosing²³ and therefore well within safety limits.

Direct viral invasion and replication may be implicated as the cause of deep stromal keratitis and uveitis. Herpes-like particles have been demonstrated in the stroma in deep herpetic keratitis,²⁴ and virus has recently been isolated from the cornea in chronic stromal keratitis.²⁵ Herpes virus has also been detected in the iris²⁶ and aqueous humour.^{27,28} The good intraocular penetration of orally administered acyclovir may therefore be of value in the treatment of the deeper forms of herpetic eye infection.

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