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Valacyclovir as Initial Treatment for Acute Retinal Necrosis: A Pharmacokinetic Modeling and Simulation Study

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Abstract

Purpose—Acute retinal necrosis (ARN) is a feared complication of infectious retinitis most commonly caused by varicella zoster virus (VZV). We performed a pharmacokinetic modeling and simulation study by integrating the existing understanding of physiology with previously published data to evaluate the vitreal penetration of oral valacyclovir for the treatment of ARN, under various dosing scenarios.

Method—We compared different oral valacyclovir dosing regimens with intravenous acyclovir. The vitreous compartment was modeled as a peripheral compartment, and paired serum and vitreal acyclovir concentrations were obtained from previously published data of adult patients with ARN undergoing vitrectomy. The efficacy threshold for vitreal acyclovir concentrations was based on the previously reported IC₅₀ values for VZV.

Results—Based on the minimum vitreal acyclovir concentrations ($C_{\min}$) relative to the mean IC₅₀ for VZV, valacyclovir 1.5 g every 8 hours performed similarly to intravenous acyclovir 700 mg every 8 hours, with the minimum concentration ($C_{\min}$) exceeding the mean IC₅₀ after the second dose. In contrast, the standard dosing regimen for herpes zoster, valacyclovir 1 g every 8 hours, performed inferiorly to the intravenous acyclovir regimen throughout the dosing interval.

Conclusions—Modeling and simulation data support oral valacyclovir for the treatment of ARN, although the required dosing exceeds the recommended FDA dose size for herpes zoster.

Keywords

Infection; inflammation; pharmacology; retina

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

Acute retinal necrosis (ARN) is a feared complication of infectious retinitis most commonly caused by varicella zoster virus (VZV).¹ HIV infection and pregnancy are predisposing conditions, although ARN can occur in immunocompetent patients.²

The goals of antiviral therapy for ARN are to prevent retinal detachment in the affected eye and to reduce the risk of involvement of the unaffected eye.³ Intravenous acyclovir has been the recommended initial treatment for ARN, with a dose of 10 mg/kg every 8 hours, for a duration of 5–10 days, followed by an additional 6–12 weeks of oral acyclovir therapy.⁴ These recommendations are based on observational data and anecdotal clinical experience, and no prospective trial has formally evaluated acyclovir dosing regimens for treatment of ARN.⁴

Valacyclovir, the L-valyl ester of acyclovir, is absorbed via active oligopeptide transporters in the small intestine and quickly metabolized to form acyclovir in a reaction independent of cytochrome p-450.^{5,6} The absolute bioavailability of acyclovir after oral administration of valacyclovir is 54.5%, and indications approved by the Food and Drug Administration (FDA) include herpes labialis, genital herpes, and herpes zoster.⁷ Observational data suggest that oral valacyclovir could also be an effective initial therapy for ARN, which could be administered on an outpatient basis.^{8–11} In these non-randomized studies, patients with ARN were treated initially with valacyclovir in doses ranging between 1 g 3 times daily and 2 g 3 times daily. No instances of disease progression were noted among patients treated with valacyclovir, and the median time to resolution was similar to earlier studies of ARN patients treated with intravenous acyclovir.

We performed a pharmacokinetic modeling and simulation study using previously published data to evaluate the vitreal penetration of oral valacyclovir for the treatment of ARN, under various dosing scenarios. We compared simulated vitreal acyclovir concentrations after oral valacyclovir administration with the acyclovir concentration corresponding to 50% reduction in viral replication (IC₅₀) for VZV.

Materials and methods

Pharmacokinetic model

To construct the model of acyclovir distribution into the vitreous humor, we first selected pharmacokinetic parameters for the central volume of distribution (V_{central}) and total systemic clearance (CL_{std}) fixed at the literature estimates for acyclovir.¹² The absorption rate constant (K_a) and oral bioavailability (F) were fixed at literature estimates for valacyclovir after 1 g oral administration.^{7,13} Acyclovir is mainly eliminated through the renal pathway, and the effect of creatinine clearance or age on CL has been previously established.^{12,14} We included the age effect on CL in our pharmacokinetic model to improve the model prediction as follows:

$$CL = CL_{\text{std}} - 0.1 \cdot (\text{age} - 30)$$

where CL_{std} is the standard clearance at the age of 30 years old.

The vitreal acyclovir concentrations were modeled using a peripheral compartment, determined by the retinal blood flow (Q_v), hematocrit (HC), and vitreal volume of distribution ($V_{vitreal}$) (Figure 1):

$$\frac{dA_v}{dt} = Q_v \times (1 - HC) \times \left(C - \frac{C_v}{K_p} \right)$$

where C is the serum total concentration, K_p is the vitreous humor to serum partition coefficient, A_v is the amount of acyclovir in vitreous humor, and C_v is the vitreal concentration which equals to $A_v / V_{vitreal}$. During the model development, we assumed that the acyclovir in vitreous humor was mainly distributed through retinal blood flow and that the distribution between vitreous humor and aqueous humor had a negligible impact on vitreal concentration kinetics.

Paired serum and vitreal acyclovir concentrations were obtained from previously published data of adult patients with ARN undergoing vitrectomy, with each patient contributing both serum and vitreal acyclovir concentration data.¹⁵ In order to maximize the information content from this single sample per subject of vitreal acyclovir concentrations, a naïve-pooled approach was used.¹⁶ We estimated K_p in the two-compartment model using the observed vitreal acyclovir concentrations. A proportional error model best described the residual variability for both serum and vitreal acyclovir concentrations.

Pharmacodynamic target

Preclinical data were reviewed to identify the efficacy threshold for vitreal acyclovir concentrations based on the IC_{50} values for VZV. The mean IC_{50} value for VZV strains isolated from clinical samples was 3.65 μ M, corresponding to 0.82 μ g/mL (given a molecular mass of 225.21 g/mol), with the maximum IC_{50} value of 6.28 μ M (1.41 μ g/mL).¹⁷ We chose the minimum vitreal acyclovir concentration during the dosing interval (C_{min}), in relation to the mean VZV IC_{50} , for the definition of pharmacodynamic target attainment (known as the inhibitory quotient).¹⁷

Dosing scenarios and simulations

We first evaluated an oral valacyclovir dosing regimen consistent with the FDA label guidelines for the treatment of herpes zoster (1 g 3 times daily). In addition, we evaluated the off-label dosing regimen previously reported in an observational case series of patients with ARN (2 g 3 times daily)⁸ and a dosing regimen intermediate of these two scenarios (1.5 g 3 times daily). We compared each of these oral dosing regimens with acyclovir 700 mg intravenously administered every 8 h, corresponding to a 10 mg/kg dose size for a 70 kg individual, the current standard-of-care dosing regimen.⁴ Prior studies have demonstrated that valacyclovir absorption is mainly mediated by transporters, and the bioavailability of valacyclovir is dose dependent. Thus, bioavailability was adjusted based on dose size according to previous publications.^{7,18–20} All modeling and simulation studies were performed using Phoenix NLME 1.4 (Certara, L.P., St. Louis, MO, USA).

Results

Pharmacokinetic model

A two-compartment model for valacyclovir was fitted to the observed serum and vitreal acyclovir concentration data. The pharmacokinetic parameters, adopted from previous publications for the serum compartment and estimated for the vitreal compartment, are shown in Table 1. The age-dependent predictions of serum and vitreal acyclovir concentrations are presented with the corresponding observations in Figure 2. The two-compartment model for acyclovir concentrations yielded an estimate of K_p of 0.255 (95% CI 0.207–0.303).

Dosing scenarios and simulations

The mean simulated vitreal acyclovir concentrations under different oral valacyclovir dosing scenarios are shown in Figure 3, with intravenous acyclovir included for comparison. All scenarios reached steady state C_{min} exceeding the threshold as defined by the mean IC_{50} for VZV. The mean simulated vitreal acyclovir concentrations after intravenous dosing fell between the valacyclovir dosing regimens of 1.5 g 3 times daily and 2 g 3 times daily.

Analysis model

Both the high-dose oral regimens achieved therapeutic vitreal acyclovir concentrations within the first 12 h of treatment, with a vitreal C_{min} at steady state that was 71% (1.40 mg/L) and 127% (1.86 mg/L) greater than the IC_{50} (0.82 mg/L) for the regimens of 1.5 g and 2 g every 8 h. In contrast, the FDA-approved valacyclovir dosing regimen for treatment of herpes zoster (1 g every 8 h) required 16 h of treatment to reach vitreal acyclovir concentrations above the target value, with a vitreal C_{min} at steady state (0.932 mg/L) that was only 14% greater than the IC_{50} (0.82 mg/L).

Discussion

In this modeling and simulation study, we integrated knowledge of ocular physiology into a pharmacokinetic model to evaluate valacyclovir dosing strategies as the initial treatment of ARN. The target acyclovir concentrations in the vitreous compartment, based on the mean acyclovir IC_{50} for VZV isolates, were achieved by each of the valacyclovir dosing scenarios during the first day of therapy. However, a dose of 1.5 g valacyclovir every 8 hours was required to achieve vitreal acyclovir concentrations that matched those attained by the intravenous acyclovir regimen (corresponding to the current standard of care).

Although this modeling and simulation study supports the off-label use of high-dose valacyclovir for initial treatment of ARN based on pharmacodynamics target attainment, we are unable to estimate the risk of toxicity as a consequence of increased acyclovir exposure. Based on the oral bioavailability of valacyclovir, the administration of 1.5 g of valacyclovir every 8 hours could be expected to have a similar safety profile to the standard intravenous dosing of acyclovir for a 70 kg individual (700 mg every 8 hours), although future work is needed to determine the safety in different patient populations (e.g., among adults with impaired renal function). Due to the sparse sampling scheme, we were unable to perform

population pharmacokinetic modeling to account for effects such as weight.¹² Future efforts to obtain acyclovir concentrations in vitreal samples at varying time points during the dosing interval and after varying days of treatment would improve the accuracy of this compartmental pharmacokinetic model.

In summary, we predict that high-dose valacyclovir would achieve the therapeutic target in the vitreous compartment during the first day of therapy for ARN, and vitreal acyclovir concentrations with high-dose valacyclovir regimens (either 1.5 g or 2 g every 8 h) would exceed the concentrations attained with intravenous acyclovir administration. These modeling and simulation studies support the accumulating clinical experience with oral valacyclovir as an option for the initial treatment of ARN.

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Figure 1.
Two compartment models for vitreal acyclovir concentrations during treatment of ARN.

Figure 2.

Predicted and observed acyclovir concentrations in serum (Figure 2a) and vitreous fluid (Figure 2b) during treatment of ARN. Black line: predicted serum and vitreal acyclovir concentrations; open circle: observed serum acyclovir concentrations; open cross: observed vitreal acyclovir concentrations. The different concentration time profile (solid lines) in each figure represents the prediction at different ages.

Figure 3.

Mean simulation of vitreal acyclovir concentrations under different dosing scenarios of oral valacyclovir, compared with intravenous acyclovir (10 mg/kg every 8 h). The two horizontal lines represent the mean and maximum IC_{50} for VZV.¹⁷ Black dotted: valacyclovir 2 g every 8 h; gray solid: valacyclovir 1.5 g every 8 h; black solid: valacyclovir 1 g every 8 h; red: acyclovir 10 mg/kg every 8 h.

Table 1

Pharmacokinetic parameters in the simulated effect compartment model of vitreal acyclovir concentrations.

Pharmacokinetic parameter	Typical value	Standard error
V_{central} (L)	49.6 [*]	—
CL_{std} (L/h)	19.7 [*]	—
K_a (1/h)	0.28 [*]	—
F (1 g)	54.5% (1 g dose size) [*]	—
	49.5% (1.5 g dose size) [*]	—
	47.5% (2 g dose size) [*]	—
V_{vitreal} (L)	0.004 [*]	—
Q_{retinal} (mL/h)	0.26 [*]	—
Hematocrit	Male: 47% [*]	—
	Female: 41% [*]	—
K_p	0.255	9.19%
Proportional error (serum)	0.203	15.3%
Proportional error (vitreal)	0.252	9.92%

^{*} Fixed.