Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2013; **68**: 1635–1641
doi:10.1093/jac/dkt064 Advance Access publication 28 March 2013

Intraocular penetration of penciclovir after oral administration of famciclovir: a population pharmacokinetic model

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Received 17 October 2012; returned 21 December 2012; revised 20 January 2013; accepted 29 January 2013

Objectives: We developed a population model that describes the ocular penetration and pharmacokinetics of penciclovir in human aqueous humour and plasma after oral administration of famciclovir.

Methods: Fifty-three patients undergoing cataract surgery received a single oral dose of 500 mg of famciclovir prior to surgery. Concentrations of penciclovir in both plasma and aqueous humour were measured by HPLC with fluorescence detection. Concentrations in plasma and aqueous humour were fitted using a two-compartment model (NONMEM software). Inter-individual and intra-individual variabilities were quantified and the influence of demographics and physiopathological and environmental variables on penciclovir pharmacokinetics was explored.

Results: Drug concentrations were fitted using a two-compartment, open model with first-order transfer rates between plasma and aqueous humour compartments. Among tested covariates, creatinine clearance, co-intake of angiotensin-converting enzyme inhibitors and body weight significantly influenced penciclovir pharmacokinetics. Plasma clearance was 22.8 ± 9.1 L/h and clearance from the aqueous humour was 8.2×10^{-5} L/h. AUCs were 25.4 ± 10.2 and 6.6 ± 1.8 μg·h/mL in plasma and aqueous humour, respectively, yielding a penetration ratio of 0.28 ± 0.06. Simulated concentrations in the aqueous humour after administration of 500 mg of famciclovir three times daily were in the range of values required for 50% growth inhibition of non-resistant strains of the herpes zoster virus family.

Conclusions: Plasma and aqueous penciclovir concentrations showed significant variability that could only be partially explained by renal function, body weight and comedication. Concentrations in the aqueous humour were much lower than in plasma, suggesting that factors in the blood–aqueous humour barrier might prevent its ocular penetration or that redistribution occurs in other ocular compartments.

Keywords: ophthalmic viral infections, antiviral therapy, pharmacokinetic modelling

Introduction

Ocular herpes zoster (herpes zoster ophthalmicus) is a viral infectious disease, which represents 15%–25% of all cases of zoster; it is due to reactivation of latent varicella zoster virus (VZV) in the first branch of the trigeminal nerve. Short- and long-term ocular complications, such as uveitis, scleritis, stromal keratitis, neurotrophic keratitis and glaucoma, occur in 50%–70% of untreated patients and may potentially lead to vision loss.[1–3] Indeed, ophthalmic herpes zoster can cause pathological changes in the ocular structures via several mechanisms: direct viral invasion, secondary inflammation, alterations of autoimmune mechanisms and neurotrophic disorders.[1] If instituted within 72 h of the rash, systemic antiviral therapies reduce the incidence of ocular complications.[4]

Famciclovir is an orally administered pro-drug of the antiviral agent penciclovir; it is a nucleoside analogue active against VZV, herpes simplex virus type I (HSV-1) and II (HSV-2) and Epstein–Barr virus (EBV). After oral administration, famciclovir is quickly deacetylated by intestinal and hepatic esterases and oxidized

in the liver to penciclovir, and little or essentially no parent compound is recovered from blood or urine.[5,6] The absolute oral bioavailability of penciclovir is between 70% and 75% and the time to reach maximum concentrations ranges between 0.5 and 0.75 h after the dose.[7] Penciclovir is extensively distributed and <20% bound to plasma proteins over the therapeutic concentration range. It is mainly eliminated via the kidneys, by glomerular filtration and tubular secretion, with an elimination half-life of ~2 h in young healthy volunteers.[5,8]

The longer intracellular half-life of penciclovir triphosphate and its lower potential toxicity, in addition to the emergence of cases of aciclovir-resistant strains, allows it to be an efficacious alternative to valaciclovir and aciclovir for the treatment of ophthalmic herpes zoster.[9] Vitreous concentrations within the inhibitory range for HSV and VZV have been reported in a small study.[10] However, the pharmacokinetic characteristics of penciclovir penetration in the human eye are still unknown.

The aim of the present study was to characterize the population pharmacokinetics of penciclovir in plasma and aqueous humour, and estimate its penetration into the eye after oral administration of famciclovir. The population approach served to quantify inter-individual variability and to identify potential influential covariates.

Methods

Study data

Fifty-three adult patients undergoing cataract surgery were included. Three patients provided drug level data that were used to determine the limit of quantification of penciclovir in the aqueous humour and the sampling schedule for the 50 subsequently included patients. Inclusion criteria were age ≥18 years and Karnofsky score ≥60. Exclusion criteria were pregnancy or breastfeeding, immunosuppression, shingles, ocular infection or inflammation, retinal detachment and intraocular injection of silicone oil. A single dose of 500 mg of famciclovir was administered to each patient at various times prior to cataract surgery (range 1.1–18.5 h). The compound was administered to fasting patients in the presence of their usual medication. A median of 3 (range 1–5) plasma samples and a single aqueous humour sample were collected in each patient between 1 and 19 h after drug intake. The Ethics Committee of Geneva University Hospitals approved the protocol and all patients gave written informed consent regarding participation in the study.

Analytical method

Blood samples were collected into heparinized tubes from the forearm and plasma was obtained after immediate centrifugation of the samples (3000 **g** at 4°C for 10 min). Aqueous humour samples (100 μL) were directly transferred into polypropylene tubes. Plasma and aqueous humour samples were stored at −20°C until analysis.

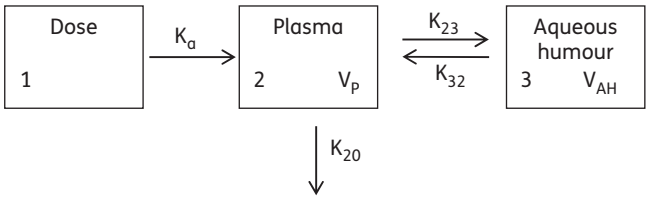

Figure 1. Structural pharmacokinetic model for penciclovir plasma (P) and aqueous humour (AH) concentrations.

Penciclovir analysis in aqueous humour and plasma was performed as previously described.[11] Briefly, plasma samples were purified by solid-phase extraction using Oasis®MCX (30 mg) cartridges, a polymeric mixed-mode cation exchange and reversed-phase sorbent. Ganciclovir, an antiviral drug structurally related to penciclovir, was used as an internal standard. Owing to the low protein content, aqueous humour samples were directly injected onto the HPLC system and no internal standard was added.

The chromatographic equipment consisted of an Agilent 100 Series LC system (Agilent, Paolo Alto, USA) with a quaternary pump, a vacuum degasser, an autosampler, a thermostated column compartment and a fluorescence detector. Chromatographic conditions were the same for the two biological fluids. Separation was performed by gradient

Table 1. Derived pharmacokinetic parameters

Parameter	Definition	Formula
$t_{1/2P}$ (h)	elimination half-life from plasma	$\ln(2)/K_{20}$
CL_P (L/h)	plasma clearance	$K_{20}\ V_P$
AUC_P (μg·h/L)	area under the curve in plasma	dose/CL_P
$t_{1/2AH}$ (h)	elimination half-life from aqueous humour	$\ln(2)/K_{32}$
CL_{AH} (L/h)	clearance from aqueous humour	$K_{32}\ V_{AH}$
AUC_{AH} (μg·h/L)	AUC in aqueous humour	(dose/CL_{AH}) (K_{23}/K_{20})
P_{ratio}	coefficient of penetration into aqueous humour	($K_{23}\ V_P$)/($K_{32}\ V_{AH}$)

Table 2. Demographic characteristics of the study population

Characteristic	
Sex ($n=53$), *n* (%)	
male	22 (42)
female	31 (58)
Age (years) ($n=53$)	
mean ± SD	77.3 ± 13.3
median (range)	81 (30–98)
Body weight (kg) ($n=49$)	
mean ± SD	69.6 ± 15.8
median (range)	68 (47–146)
BMI (kg/m^2) ($n=42$)	
mean ± SD	25.7 ± 4.4
median (range)	25.1 (18.4–44.1)
CL_{CR} (mL/min) ($n=38$)	
mean ± SD	57.5 ± 32.2
median (range)	48.8 (24.4–163.4)
Comedication, *n* (%)	
anti-inflammatory agents	17 (32)
ACE inhibitors	15 (28)
diuretics	16 (30)
β-blockers	10 (19)
proton pump inhibitors	12 (23)

Table 3. Final population pharmacokinetic parameters for penciclovir in 53 patients and validation from 2000 bootstrapped samples

	Population model ($n=53$ patients)		Bootstrap validation ($n=2000$ samples)		
Parameters	estimate	SE (%)[a]	mean	SE (%)[a]	95% CI
K_a (h^{-1})	1.86	—	1.86	—	—
K_{20} (h^{-1})	0.25	4	0.25	4	0.23–0.27
K_{23} (h^{-1})	2.59×10^{-7}	9	2.50×10^{-7}	9	2.00×10^{-7}–2.90×10^{-7}
K_{32} (h^{-1})	0.41	9	0.40	9	0.33–0.47
V_P (L)	86.2	6	87.2	5	79.1–98.0
V_{AH} (L)	2.0×10^{-4}	—	2.0×10^{-4}	—	—
θ_{CLCR} (h^{-1})[b]	0.07	29	0.07	31	0.03–0.12
$\theta_{ACE\ inhibitors}$ (h^{-1})[b]	0.06	32	0.04	35	0.01–0.08
θ_{BW}[c]	1.01	18	1.08	18	0.70–1.44
ω (K_{20}) (CV %)[d]	21	48[f]	20	47[f]	15–24
ω (V_P) (CV %)[d]	14	110[f]	17	83[f]	4–27
σ_P (CV %)[e]	24	61[f]	22	60[f]	15–30
σ_{AH} (CV %)[e]	28	48[f]	28	47[f]	23–35

Final model:
$TVK_{20}=K_{20}+\theta_{CLCR}\times(CL_{CR}-48.8)/48.8-\theta_{ACE\ inhibitors}\times$ACE inhibitors
$TVV_P=V_P\times[1+\theta_{BW}\times(BW-68)/68]$
TV, typical population value; P, plasma; AH, aqueous humour; K_a, mean absorption rate constant; K_{20}, mean apparent elimination rate constant; K_{23}, mean apparent distribution rate constant from P to AH; K_{32}, mean apparent elimination rate constant from AH to P; V_P, mean apparent volume of distribution in plasma; V_{AH}, mean apparent volume of distribution in the aqueous humour; CL_{CR}, creatinine clearance (with median value of 48.8 mL/min); BW, body weight (with median value of 68 kg).
[a]Standard errors of the estimates (SE), defined as SE/estimate and expressed as percentages.
[b]Relative influence of CL_{CR} and ACE inhibitor intake (0/1) on K_{20}.
[c]Relative influence of BW on V_P.
[d]Estimate of between-subject variability, expressed as CV %.
[e]Estimate of residual variability, expressed as CV %.
[f]Standard errors of the CVs, taken as $\sqrt{}$(SE/estimate) and expressed as a percentage.

elution on a Zorbax SB-aqC18 (100 mm×2.1 mm) column with a mobile phase consisting of a mixture of acetonitrile and 50 mM phosphate buffer containing 5 mM sodium octanesulfonate, pH 2.0, at a flow rate 0.3 mL/min. Detection was fluorimetric with emission and excitation wavelengths set at 360 and 253 nm, respectively. The column temperature was fixed at 20°C. Twenty microlitres was injected onto the HPLC system.

The limit of quantification (LOQ) was 0.1 μg/mL [coefficient of variation (CV) 8.8%] for plasma and 0.05 μg/mL for aqueous humour (CV 5.5%). Measured concentrations <LOQ were set to LOQ/2 for pharmacokinetic modelling ($n=7$ in plasma and $n=1$ in aqueous humour).

Population pharmacokinetic analysis

The time courses of penciclovir concentrations in plasma and aqueous humour were fitted using non-linear mixed-effect modelling (NONMEM) and the relationship between parameter estimates and available covariates was investigated.

Basic model

A two-compartment, open model with first-order transfer rates between plasma and aqueous humour was used to describe the pharmacokinetics of penciclovir (Figure 1). Basic estimated parameters were the absorption rate constant (K_a), the elimination rate constant (K_{20}), the transfer rate constants between plasma and aqueous humour (K_{23} and K_{32}) and the volume of distribution in plasma (V_P). The volume of distribution of the aqueous humour (V_{AH}) was fixed to 200 μL according to the true physiological intracameral volume.[12] Due to its small volume, aqueous humour incorporates extremely reduced amounts of drug from plasma and consequently does not affect the concentration–time profile in plasma. Elimination from the aqueous humour could not be distinguished from redistribution to the plasma compartment, and bidirectional first-order exchange between plasma and aqueous humour was thus chosen to describe penciclovir flow across the blood–aqueous barrier.[13]

The following parameters were derived from the final individual Bayesian estimates: penciclovir clearance (CL), AUC and elimination half-life ($t_{1/2}$) in plasma and aqueous humour (Table 1). The penetration of penciclovir in the eye was described by the penetration coefficient (P_{ratio}), defined as AUC_{AH}/AUC_P. This coefficient reflects the aqueous-to-plasma concentration ratio that occurs transiently when the concentration in the aqueous humour reaches its peak value. As no intravenous famciclovir was administered, volumes of distribution, CLs and AUCs represent apparent values.

The inter-individual variability in the population parameters was modelled assuming exponential error models, using $\theta_i=\theta\cdot\exp(\eta_i)$, where θ_i is the pharmacokinetic parameter of the ith individual, θ is the average population value and η_i is a random effect, assumed to be normally distributed with a mean of zero and a variance ω^2. Residual (intra-individual) variability was estimated for plasma and humour data and modelled using an exponential error model of the form $C_{ij,obs}=C_{ij,pred}\exp(\varepsilon_{ij})$, with $C_{ij,obs}$ and $C_{ij,pred}$ representing observed and predicted concentrations of the ith subject at time j, respectively, and ε_{ij} the residual error, assumed to be normally distributed with a mean of zero and a variance σ^2.

Table 4. Mean and inter-individual variability of parameters derived from the final model

	$t_{1/2P}$ (h)	CL_P (L/h)	AUC_p (μg·h/mL)	$t_{1/2AH}$ (h)	CL_{AH} (L/h)	AUC_{AH} (μg·h/mL)	P_{ratio}
Mean ± SD	2.9 ± 0.8	22.8 ± 9.1	25.4 ± 10.2	1.7	8.2×10^{-5}	6.6 ± 1.8	0.28 ± 0.06
CV %	28%	40%	40%	—	—	28%	22%
Range	1.7–5.3	8.9–56	8.9–56.2	—	—	3.8–12.2	0.18–0.54

Covariate model

Available covariates were age, body weight, body mass index (BMI), creatinine clearance (CL_{CR}), gender and comedication. Only comedications likely to influence renal elimination or drug absorption were tested. CL_{CR} was estimated according to the Cockcroft–Gault equation.[14] Dichotomous variables were coded 0/1 and missing CL_{CR} and body weight were set to median values. Analyses of covariate effects were performed in two main steps: (i) the relationships between individual parameters and covariates were first analysed with the non-parametric Mann–Whitney test for categorical covariates and the Spearman correlation coefficient for continuous covariates (software SYSTAT version 10, Systat Software Inc., Chicago, IL, USA); and (ii) significant covariates ($P < 0.05$) were then integrated in the population model using linear or non-linear functions as appropriate, centred on the median value.

Parameter estimation and model selection

NONMEM®[15] (version 7.2, NM-TRAN, version II) was used with the FOCE INTERACTION method to fit the data. The minimum objective function value (ΔOF) provided by NONMEM® (-2 log likelihood, approximate χ^2 distribution) was used to discriminate between models using the likelihood ratio test. A model was considered superior to another nested model when the OF value was reduced by at least 3.84 points ($P < 0.05$). Covariate analysis comprised forward selection of influential factors followed by backward deletion. Covariates were retained in the final model at the statistical level of $P < 0.01$. Model assessment was based on diagnostic plots (goodness-of-fit plots and normalized prediction distribution errors) along with standard errors and correlation matrix of parameter estimates, size of residual errors and η shrinkage.

Model validation

The stability and performance of the final population pharmacokinetic model were validated by the bootstrap method using 2000 bootstrap samplings with replacement. The final population pharmacokinetic model was fitted repeatedly to the 2000 bootstrapped samples and pharmacokinetic parameters were calculated for each dataset. The mean, standard error and 95% CI of each parameter obtained with the bootstrapped data were then compared with the corresponding parameters obtained with the original dataset. The statistical analysis was performed using Perl-speaks-NONMEM version 3.2.4 (http://psn.sourceforge.net/). The final model was also validated using visual predictive check (VPC). Using the parameter values of the final population pharmacokinetic model, we simulated data for 1000 individuals and generated 2.5th, 50th and 97.5th percentiles. The observed concentrations were plotted against the 95% prediction interval ($PI_{95\%}$) of the simulated dataset at each timepoint and visually compared. Figures were generated using GraphPad Prism (version 4.00 for Windows, GraphPad Software, San Diego, CA, USA; www.graphpad.com).

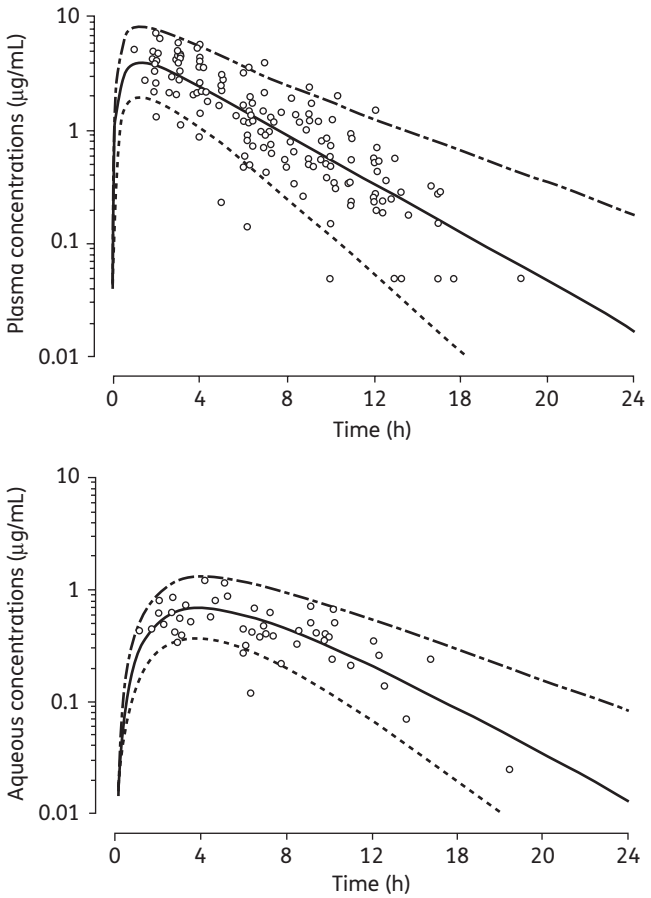

Figure 2. Penciclovir plasma (top panel) and aqueous humour (bottom panel) concentrations (circles) after a 500 mg oral dose of famciclovir in 53 patients. Continuous lines represent population predictions for an 81-year-old person with a body weight of 68 kg and a CL_{CR} of 48.8 mL/min (median values in the study sample). Broken lines show the $PI_{95\%}$ obtained from a simulated dataset of 1000 subjects.

Results

A total of 164 plasma samples and 53 aqueous humour samples were collected. Penciclovir concentration ranged from 0.05 to 7.26 μg/mL in plasma and from 0.025 to 1.21 μg/mL in aqueous humour. Demographic characteristics of the study sample are described in Table 2.

A two-compartment model with first-order transfer rates adequately described the pharmacokinetics of penciclovir in aqueous humour and plasma. Because of a lack of data in the

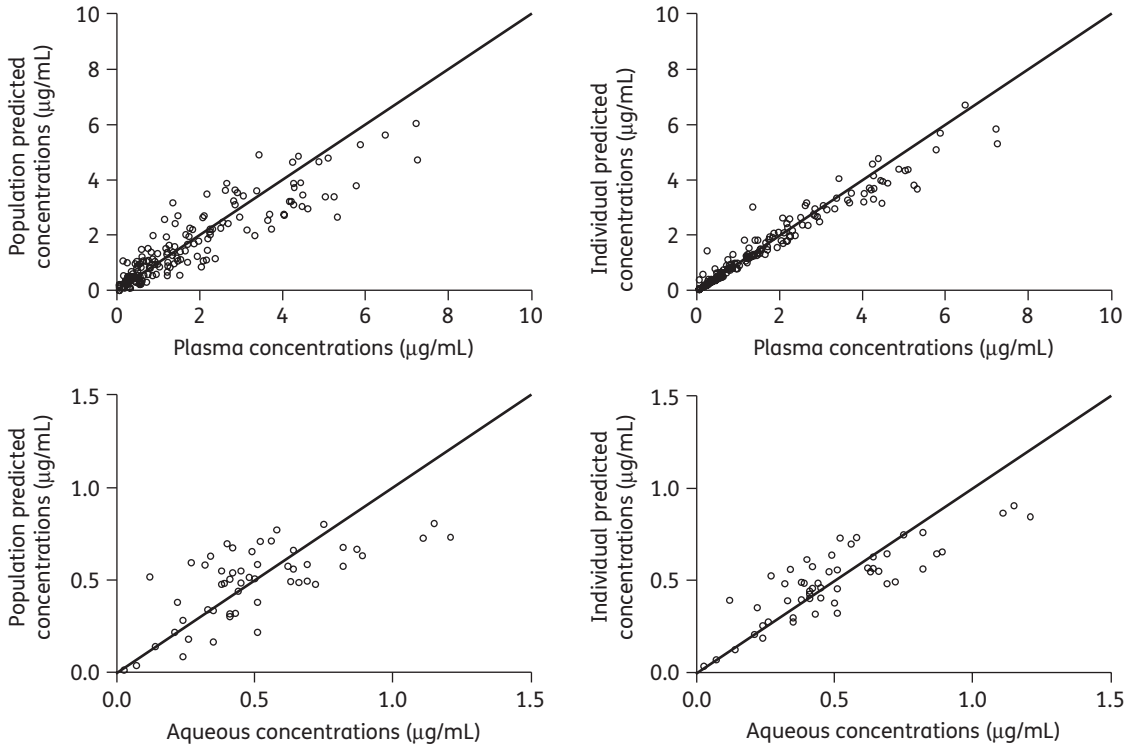

Figure 3. Goodness-of-fit plots. Penciclovir plasma (top panels) and aqueous humour (bottom panels) population (left-hand panels) and individual (right-hand panel) predictions versus observed concentrations in 53 patients.

absorption phase, the absorption rate K_a could not be adequately estimated and was fixed to 1.86 h^{-1} according to the literature.[16] Assignment of inter-individual variability on K_{20} ($\Delta OF = -205$; $P < 0.0001$) and V_P ($\Delta OF = -66.5$; $P < 0.0001$) improved the fit, but data did not support the estimation of inter-individual variability on K_{23} or K_{32}, in keeping with a single observation per patient in the aqueous humour. Incorporating covariance between K_{20} and V_P slightly improved the fit ($\Delta OF = -7.3$; $P < 0.01$).

The statistical preliminary covariate analysis identified a significant effect of age, CL_{CR} and co-intake of an angiotensin-converting enzyme (ACE) inhibitor on K_{20}, as well as body weight, BMI, age and sex on V_P ($P < 0.001$). All these covariates, except for BMI (with an effect statistically not different from body weight), were further tested for significance in the model.

In univariate analyses, a significant influence of age ($\Delta OF = -24.1$; $P < 0.001$), CL_{CR} ($\Delta OF = -11.1$; $P < 0.001$) and ACE inhibitors ($\Delta OF = -5.0$; $P < 0.05$) on K_{20} was observed. Sex and body weight did not significantly influence penciclovir elimination ($\Delta OF < -0.7$). The inclusion of a body weight effect on V_P improved the fit ($\Delta OF = -19$; $P < 0.001$), but no other variable showed any influence on this parameter. Multivariate analysis identified CL_{CR} and co-intake of an ACE inhibitor as significant predictors of penciclovir elimination and an influence of body weight on V_P ($\Delta OF = -50.2$; $P < 0.0001$ compared with the model without any covariates). The age effect on K_{20} did not remain significant, as it was correlated to CL_{CR}. Correlation between K_{20} and V_P did not remain statistically significant either after inclusion of the covariates. Penciclovir elimination (K_{20}) was reduced by 41% in patients with severe renal impairment (CL_{CR} 20 mL/min) compared with those with a normal renal function (CL_{CR} 120 mL/min), which is further decreased by 17% and 29%, respectively, in the presence of an ACE inhibitor. Upon body weight doubling, doubling of the volume of distribution is expected. Significant covariates explained 15% and 34% of the variability in K_{20} and V_P, respectively. The final population pharmacokinetic parameters and results from the bootstrap analysis are presented in Table 3. Secondary parameters derived from the final model are summarized in Table 4. The mean P_{ratio} from plasma to aqueous humour was 28%, with individual values ranging from 18% to 54%. Goodness-of-fit plots and VPC are depicted in Figures 2 and 3.

Simulated concentration–time profiles in plasma and in aqueous humour after 500 mg of oral famciclovir three times daily are depicted in Figure 4. Average minimal and maximal concentrations (μg/mL) at steady-state were, respectively, 0.43 ($PI_{95\%}$ 0.053–1.99) and 4.47 ($PI_{95\%}$ 2.1–9.6) in plasma and 0.28 ($PI_{95\%}$ 0.08–0.84) and 0.83 ($PI_{95\%}$ 0.42–1.62) in aqueous humour.

Discussion

The present study describes for the first time the penetration and pharmacokinetics of penciclovir in the aqueous humour after oral administration of famciclovir. Over recent years, particular interest in the intraocular penetration of anti-infectious agents administered orally has arisen from the growing incidence of ocular infections resulting from the increasing number of transplant and HIV patients. Oral administration is easy to perform and may make it possible, according to the physico-chemical characteristics of the molecule, to obtain therapeutic concentrations in

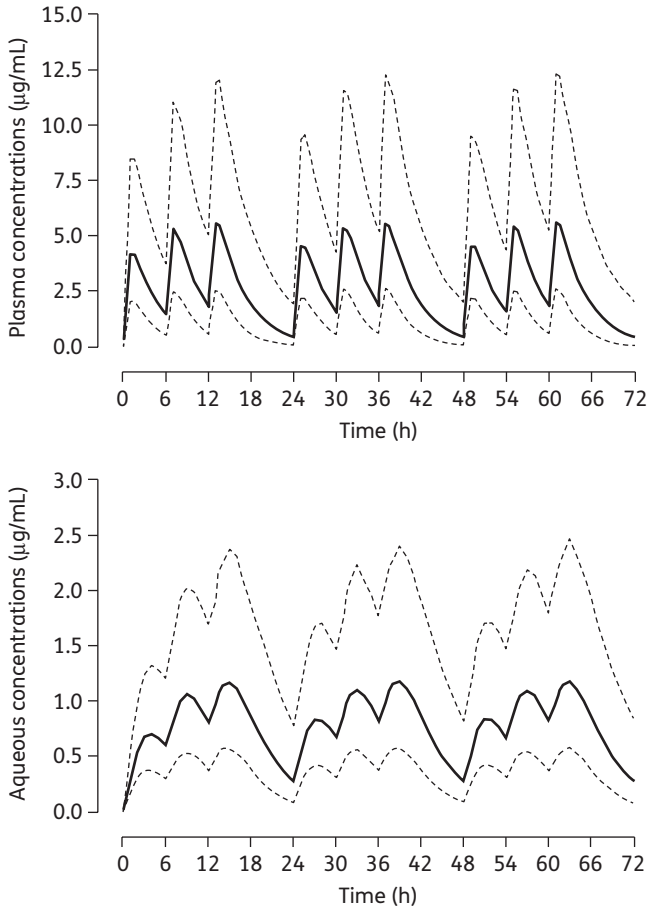

Figure 4. Simulations of penciclovir in plasma (top panel) and in the aqueous humour (bottom panel) after 500 mg of famciclovir three times daily (6, 12 and 24 h) for an 81-year-old person with a body weight of 68 kg and a CL_{CR} of 48.8 mL/min (median values in the study sample). The continuous line represents the population predictions and the broken lines show the $PI_{95\%}$.

aqueous humour. The favourable pharmacokinetic profile of penciclovir compared with aciclovir and valaciclovir (higher oral bioavailability, higher intracellular triphosphate concentration and prolonged intracellular half-life) makes it a suitable alternative for the treatment of various types of infections caused by viruses of the herpes simplex family.[17]

The estimates of penciclovir plasma CL, volume of distribution and half-life are in good agreement with previously reported values.[16] As expected, penciclovir elimination is markedly affected by renal function.[18] In addition, a significant influence of co-administered ACE inhibitors was observed. The well-known effect of these drugs on the filtration pressure might explain this finding. The observed ACE effect might also have corrected a potential bias in the estimation of true renal function, which might have been over- or under-estimated by the Cockcroft–Gault approximation in some patients. In line with reported data, penciclovir is extensively distributed and its volume of distribution is affected by body weight.[5]

Penciclovir exhibits several characteristics favourable to good intraocular penetration: small molecular weight, low protein binding and high volume of distribution. The average penetration ratio of penciclovir in the eye was 28%, with a CV of 22% reflecting variability in penciclovir volume of distribution. This penetration ratio is similar to the 28% (CV 32%) and 24% (CV 25%) reported for penciclovir[10] and aciclovir[19] in the vitreous humour, respectively. The much lower exposure in the aqueous humour than in plasma suggests that penciclovir distribution to this liquid might be regulated by efflux transport systems in the blood–aqueous barrier that limit the ocular bioavailability of systemically administered drugs.[20] Maximal concentrations in the aqueous humour were reached ~4 h after drug intake, whereas plasma peak levels were obtained in <1 h. This delay was dependent on the rate constant from aqueous humour to plasma, whereas the concentration decrease in aqueous humour paralleled that in plasma at later times (flip-flop kinetics, with $K_{32} > K_{20}$). The apparent CL from aqueous humour of 1.37 μL/min is compatible with the reported rate of aqueous humour secretion (1–3 μL/min) in humans.[21] This might suggest that penciclovir is mainly eliminated from the eyes by the humour turnover.

Simulations of multiple doses of famciclovir based on the final model show that no accumulation occurs in plasma or in the aqueous humour. Owing to marked inter-individual variability, a wide range of concentrations in plasma and the aqueous humour can be observed. Higher concentrations in the aqueous humour can be expected in overweight patients and in those presenting an impaired renal function in particular, but other as yet unknown factors influencing drug intraocular penetration might also be involved.

Studies have demonstrated that oral administration of 500 mg of famciclovir three times daily leads to satisfactory and sustained intracellular triphosphate concentrations and represents an effective regimen in the treatment of cutaneous or ophthalmic shingles.[9,22,23] However, no clear relationship has been established to date between penciclovir plasma levels, intracellular triphosphate concentrations and antiviral efficacy. The concentration of penciclovir required for inhibiting virus growth in cell culture by 50% (IC_{50}) varies considerably depending on assay type and infecting virus, with the IC_{50} ranging from 0.02 to 0.9 μg/mL for HSV-1, from 0.06 to 4.4 μg/mL for HSV-2, from 0.8 to 4 μg/mL for VZV and from 1.5 to 3.1 μg/mL for EBV.[24–26] Based on such *in vitro* data, our model predicts that plasma concentrations are within the range of inhibitory concentrations for susceptible virus. Aqueous concentrations are within the range of IC_{50} values reported for HSV-1, HSV-2 and EBV and in the lower range of IC_{50} values reported for VZV. Based on data from Chong *et al.*,[10] vitreous penciclovir concentrations of patients receiving 500 mg of famciclovir three times a day were within the range of simulated aqueous humour concentrations in Figure 4 (same dosing regimen). Therefore, penciclovir concentrations in aqueous and vitreous humours are expected to be similar and within the range of the IC_{50} for HSV-1, HSV-2, EBV or VZV, which are also involved in herpetic anterior uveitis or acute retinal necrosis. Similar results were observed in different studies comparing aqueous and vitreous humour levels of different antibiotics after oral administration in humans. For example, after oral administration of 400 mg of ofloxacin, aqueous and vitreous humour levels were 1.54 ± 0.27 and 1.77 ± 0.24 μg/mL, respectively.[27] Human aqueous and vitreous humour levels of ciprofloxacin following oral

administration of 1000 mg of ciprofloxacin were 0.59 ± 0.06 and 0.64 ± 0.06 μg/mL, respectively.[28]

Limitations of the present study need to be acknowledged. First, the sample size was relatively modest and the statistical power was limited, in particular with respect to the possible role of comedication. Second, sample characteristics (a majority of elderly patients, with impaired renal function and several comedications) might not allow generalization of the results to all patients for whom penciclovir treatment is intended. Third, the fact that a single aqueous humour sample was collected per patient prevented more precise investigation of variability associated with transfers into and out of the aqueous humour.

In conclusion, famciclovir oral administration results in variable plasma and ocular concentrations that are partially explained by renal function, co-administration of ACE inhibitors and body weight. The penetration ratio of penciclovir in the aqueous humour is 28% (CV 22%), with peak concentration reached ~4 h after drug intake. Average concentrations of penciclovir in the aqueous humour after multiple dosing of 500 mg of famciclovir three times daily are in the range of IC_{50} values for non-resistant herpes zoster virus and in the low range of IC_{50} values for varicella zoster virus, but the relationship between concentrations in the aqueous humour and efficacy needs to be further investigated.

Funding

This study was supported using internal funds.

Transparency declarations

None to declare.

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