Brief Report

Shedding a Light on Acyclovir Pharmacodynamics: A Retrospective Analysis on Pharmacokinetic/Pharmacodynamic Modelling of Acyclovir for the Treatment of Varicella Zoster Virus Infection in Immunocompromised Patients: A Pilot Study

Geeske F. Grit [1], Anne-Grete Märtson [2], Marjolein Knoester [3], Marlous L. Toren-Wielema [1] and Daan J. Touw [1,*]

[1] Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands
[2] Antimicrobial Pharmacodynamics and Therapeutics, University of Liverpool, Liverpool L69 3BX, UK
[3] Department of Medical Microbiology and Infection Prevention, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands
* Correspondence: d.j.touw@umcg.nl; Tel.: +31-50-361-4071

Abstract: Background: Acyclovir and valacyclovir are used for the treatment and prophylaxis of infections with herpes simplex virus (HSV) and varicella zoster virus (VZV). The aim of this study is to provide insight into the pharmacodynamics (PD) of (val)acyclovir. Methods: Patients were retrospectively selected, based on therapeutic drug monitoring for acyclovir, to create a population pharmacokinetic (PK) model in Pmetrics. This PK model was used to develop a PK/PD model to study the effect of acyclovir levels on VZV viral load in plasma in immunocompromised patients. Results: Immunocompromised patients with known VZV viral loads in plasma were included for PK/PD modelling ($N = 4$, with 23 measure points); they were part of the population of 43 patients used for PK model building. The PK/PD model described the data well ($r^2 = 0.83$). This is a hopeful first step in clarifying the pharmacodynamics of acyclovir; however, the data in this study are limited. Conclusions: Our preliminary PK/PD model can be used in further research to determine the effect of acyclovir levels on VZV viral load.

Keywords: pharmacokinetics; pharmacodynamics; acyclovir; PKPD modeling; varicella zoster virus

1. Introduction

Acyclovir (ACV) and valacyclovir (VCV) are antiviral agents used for treatment and prophylaxis of infections with herpes simplex virus (HSV) and varicella zoster virus (VZV) [1,2]. VCV is a prodrug of ACV and has improved oral bioavailability, compared to oral acyclovir [2]. The susceptibility to ACV is highest for herpes simplex virus type 1 (HSV-1), followed by herpes simplex virus type 2 (HSV-2) and VZV [3]. Susceptibility is defined as 50% inhibitory concentration (IC_{50}) or as 50% effective concentration (EC_{50}), indicating the in vitro ACV concentration, which reduces plaque numbers or viral copies by 50%, compared to control-infected cells [4,5]. The in vitro IC_{50} of ACV for HSV-1 and HSV-2 varies between 0.02–0.9 and 0.03–2.2 mg/L, respectively. The in vitro IC_{50} for VZV ranges from 0.8 to 4.0 mg/L [3].

Currently, it is unclear which pharmacodynamic (PD) target should be achieved for effective treatment with ACV or VCV. Various studies used different PD targets [6–11], e.g., ACV concentration 50% of time > IC_{50}, or minimal ACV concentration (C_{min}) > IC_{50} [6,7]. The referred studies do not provide clear evidence to support these PD targets [12–15]. However, it is assumed that the efficacy of ACV is related to time-dependent killing [16].

This study aims to provide insight into the pharmacodynamics of ACV. A population (pop) PK model was created to predict ACV levels, and a PK/PD model was developed to study the effect of ACV levels on plasma VZV viral load.

2. Materials and Methods

2.1. Population Selection

Patients of the University Medical Center Groningen (UMCG), Groningen, The Netherlands, treated with oral VCV and/or intravenous (IV) ACV for an HSV or VZV infection and who had measured ACV levels between 1 January 2018 and 1 December 2021, were included in this retrospective study. Patients on dialysis and/or who had objected to the use of their medical data were excluded from analysis. The Medical Ethics Review Board of the UMCG declared that this study did not need Medical Research Involving Human Subjects Act (WMO) approval (METc2021/029).

2.2. ACV Levels and VZV Viral Loads Analysis

The serum concentration of ACV was measured, as described previously [17]. The analysis of the VZV viral loads in plasma is based on Hawrami et al. [18] and is included in the Supplementary Methods. The measured VZV viral loads (cycle threshold (Ct) values) were converted to $\log_{10}$ viral copies/mL. The calibration line of the Epstein–Barr virus (EBV) was used, since no calibration line of VZV was available. EBV was chosen because this is also a human herpes virus. The viral load was considered undetectable when no signal was found or Ct value was > 39.99. By this, the lower limit of detection was 1.4 $\log_{10}$ copies/mL.

2.3. PK Model

A pop PK model of (val)acyclovir was developed and fitted to our patient data (method included in the Supplementary Methods). The models were analysed by comparing goodness-of-fit plots, r^2 of individual and population predictions, Akaike information criterion (AIC), Bayesian information criterion (BIC) and -2 Log likelihood values. ACV levels < 0.1 mg/L and levels with unclear ACV administration times were excluded.

2.4. PK/PD Model

A PK/PD model was developed in Pmetrics, version 1.9.7. for RStudio (version 1.4.1106, Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA, USA) [19]. The model code is provided in the Supplementary Methods. Of our population, immunocompromised patients (chemotherapy, under immunosuppressants, hematologic disorders) with at least two positive VZV viral load measurements in plasma were included in the PK/PD model. The individual posterior prediction PK parameters were calculated from the final PK model and were used as covariates for creating the PK/PD model.

The base PK/PD model was as follows:

$$\frac{\Delta X_1}{\Delta t} = B(1) \times F - K_a \times X_1 \tag{1}$$

$$\frac{\Delta X_2}{\Delta t} = K_a \times X_1 - K_e \times X_2 \tag{2}$$

Equations (1) and (2) describe the rate of change of the ACV amount in the compartments. X_1 is the ACV amount in the gut (mg) and X_2 is the ACV amount in the central compartment (mg). B(1) is the input of VCV. F is the bioavailability of VCV. K_a is the absorption rate constant (h^{-1}). K_e is the elimination rate constant (h^{-1}).

The following equation was used for the PK/PD model [20]:

$$\frac{\Delta X_3}{\Delta t} = \text{initial condition} - K_{kmax} \times \frac{\left(\frac{X_2}{V}\right)^{Hk}}{\left(\frac{X_2}{V}\right)^{Hk} + EC_{50}{}^{Hk}} \times X_3 \tag{3}$$

Equation (3) describes the change in VZV viral load in plasma ($\log_{10}$ viral copies/mL). The initial condition (IC) is the VZV viral load (viral copies/mL) at time = 0. K_{kmax} is the maximal rate of drug-induced viral kill ($\log_{10}$ viral copies/mL/h). X_2/V is the ACV concentration in plasma (mg/L). The EC_{50} is the concentration of acyclovir that induces 50% of the maximal rate of kill (mg/L). Hk is the slope function. The parameter distribution used for prediction in mean and median was tested.

3. Results

3.1. Patient Population

The PK/PD model was fitted to immunocompromised patients with both ACV levels and VZV plasma viral loads ($N = 4$ with 23 measure points). The patient characteristics are shown in Table 1. These 4 patients were part of a heterogeneous population who were included for PK model building ($N = 43$ with 96 ACV concentration data points). Patient characteristics of this population ($N = 43$) are described in Table S1.

Table 1. Patient characteristics for pharmacokinetic/pharmacodynamic modelling ($N = 4$). Mean $AUC_{24\,h}$ is calculated between first and last viral load measurement.

Patient Number	Age (Years)	eGFR (mL/min/1.73 m^2)	First Measured VZV Viral Load (Log_{10} Copies/mL)	Last Measured VZV Viral Load (Log_{10} Copies/mL)	Mean AUC_{24h} (h × mg/L)
1	2	143	3.1	Undetectable	29
2	60	131	5.4	2.6	66
3	36	26	3.1	2.8	215
4	69	73	2.8	Undetectable	120

VZV: varicella zoster virus; AUC_{24h}: area under the curve for 24 h; eGFR: estimated glomerular filtration rate.

3.2. PK Modelling

The final PK model was a one-compartment model with linear elimination without covariates, since a two-compartment model, as well as including covariates, did not improve the model. The PK parameters are described in Table 2. The final model adequately described the patient data. The individual posterior prediction goodness-of-fit plot resulted in an $r^2 = 0.95$ (Figure S1). The individual PK parameters of the final PK model were used as covariates in the PK/PD model.

Table 2. PK parameters of final PK model ($N = 43$).

PK Parameter	Mean	Median	SD	Shrinkage
Ke (h^{-1})	0.274	0.235	0.191	43.0%
V (L)	44.298	52.173	16.351	47.6%
Ka (h^{-1})	0.601	0.557	0.385	59.1%
FA	0.443	0.438	0.226	52.3%

PK: pharmacokinetic; K_e: elimination rate constant; V: volume of distribution; K_a: absorption rate constant; FA: bioavailability of valacyclovir; SD: standard deviation.

3.3. PK/PD Modelling

PD parameters of the PK/PD model are shown in Table 3. The individual posterior prediction goodness-of-fit plot resulted in an $r^2 = 0.83$ (Figure 1a). The individual VZV viral load vs. time plots (Figure 1b) showed that the predicted viral load curve is comparable with the observed viral loads.

Table 3. PD parameters of final PK/PD model (*N* = 4).

PD Parameter	Mean	Median	SD
K_{kmax} ($\log_{10}$ copies/mL/h)	0.040	0.020	0.044
Hk	6.29	3.27	5.29
IC (copies/mL)	6442	4661	6029
EC_{50} (mg/L)	10.50	8.37	10.91

PD: pharmacodynamic; K_{kmax}: the maximal rate of drug-induced viral kill; Hk: the slope function; IC: initial condition; EC_{50}: acyclovir concentration inducing half maximal rate of kill; SD: standard deviation.
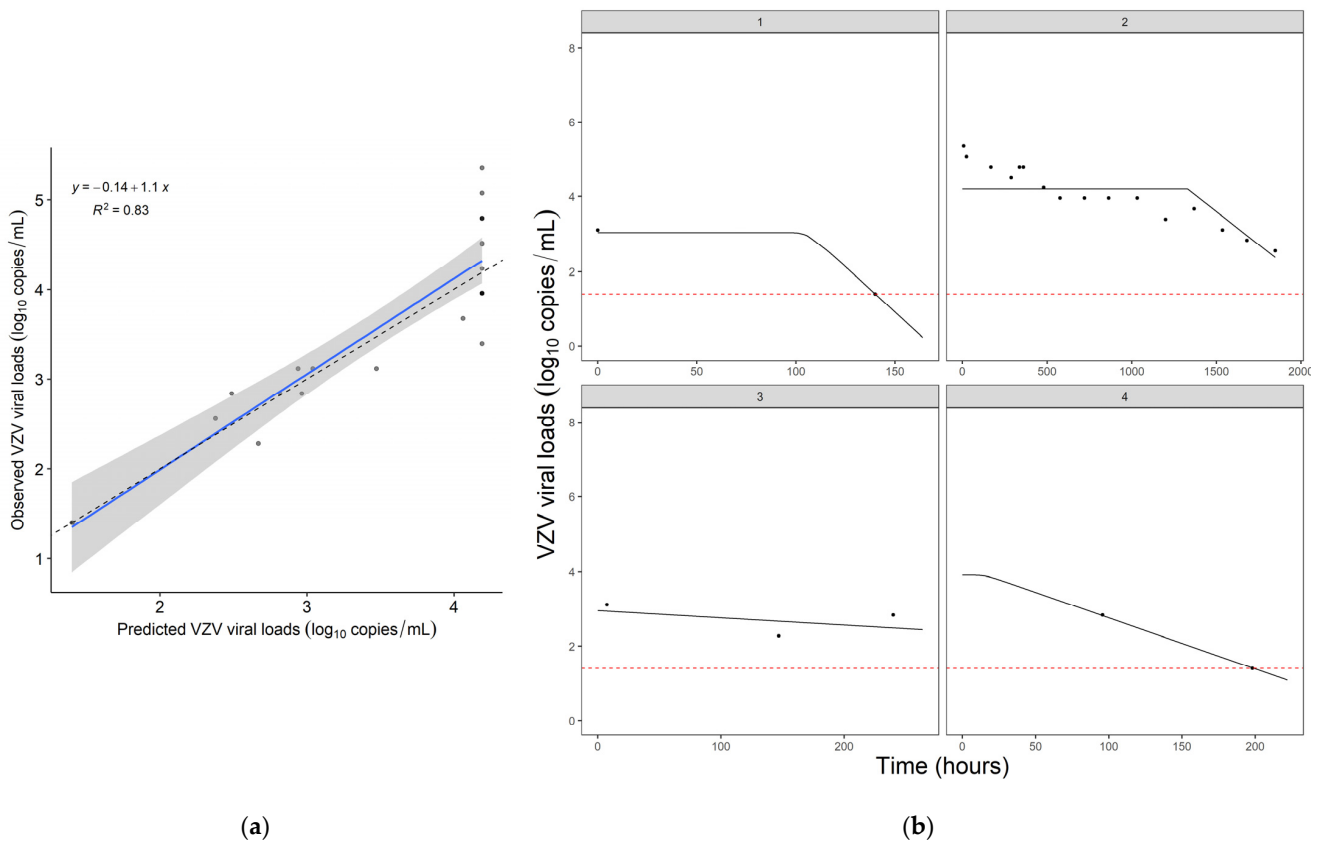

(**a**)   (**b**)

Figure 1. Results of PK/PD model of the effect of acyclovir on VZV viral loads in plasma (*N* = 4) (**a**) Individual posterior predictions goodness-of-fit plot of mean of final PK/PD model. The solid line represents the linear regression of the observed and predicted viral loads, the dashed line represents a reference line for y = x and the black dots display the observed VZV viral loads (**b**) Individual VZV viral load ($\log_{10}$ copies/mL) vs. time (hours) plots. The black dots represent the observed viral loads, the black line displays the individual predicted plot and the dotted line is the limit of detection. PK: Pharmacokinetic; PD: pharmacodynamic; VZV: varicella zoster virus.

4. Discussion

Currently, there is no clear understanding of the pharmacodynamics of acyclovir. Therefore, it is important to develop a PK/PD model to evaluate the dose–concentration–response relationship for optimal treatment. To our knowledge, this is the first study that describes a PK/PD model of ACV in the treatment of VZV. First, a PK model was created to describe and predict ACV levels. The effect of ACV concentration on viral load was investigated by developing a PK/PD model. Some studies have already given a small insight into the pharmacodynamics of acyclovir. Safrin et al. concluded that there is a strong association between EC_{50} and clinical response after treatment of HSV-infected immunocompromised patients [5]. Moreover, IC_{50} values are already incorporated in dosing guidelines: a higher ACV or VCV dose is recommended to treat VZV than to treat HSV [2], since the IC_{50} of

VZV is higher [3]. Furthermore, a significant dose–response relationship has previously been found for 1×250 mg VCV, 1×500 mg VCV and 1×1000 mg VCV for suppression of recurrent genital herpes, suggesting a concentration–response relationship [16]. However, the efficacy of ACV was associated with time-dependent killing in a study where ACV 400 mg twice daily was shown to be significantly more effective (lower rate of recurrence of genital herpes) than VCV 500 mg once daily, despite ACV maximal concentration (C_{max}) and area under the curve (AUC) being higher for VCV 500 mg once daily [16].

Our results are limited by the small sample size: only four patients were included in the PK/PD model. However, we used all available data in The Netherlands. No other hospital in the Netherlands we contacted measured ACV levels. The PK/PD model was derived from a similar modelling study on ganciclovir and cytomegalovirus conducted in our department [20]. Another drawback of this study is that the converted viral loads in $\log_{10}$ copies/mL are an estimate of the VZV viral load, since the calibration line of EBV was used. However, we used the relative differences between viral loads and, therefore, the reliability of our PK/PD model is unlikely to be affected.

Despite these limitations, our PK/PD model provides a good first step in clarifying the pharmacodynamics of ACV, inviting other researchers to study the effect of ACV levels on VZV viral load. In this way, evidence-based PD targets can be determined to improve exposure and potentially accelerate viral clearance. We would like to call on hospitals internationally to share available data.

Supplementary Materials: The following supporting information can be downloaded at: https: //www.mdpi.com/article/10.3390/pharmaceutics14112311/s1, Supplementary methods: VZV viral loads analysis, PK model, PK model code; Table S1: Patient characteristics for population pharmacokinetic modelling; Figure S1: Individual posterior predictions goodness-of-fit plot of final pharmacokinetic model.

Author Contributions: Conceptualization, G.F.G., M.L.T.-W., D.J.T.; data curation, G.F.G., A.-G.M.; writing—original draft preparation, G.F.G.; writing—review and editing, A.-G.M., M.K., M.L.T.-W., D.J.T. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Ethical review and approval were waived for this study by the Medical Ethics Review Board of the UMCG due to the retrospective inclusion of patients with existing data (METc2021/029, 11 March 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Aciclovir 250 mg Powder for Solution for Infusion. Available online: https://www.medicines.org.uk/emc/product/6175/smpc (accessed on 17 September 2022).
2. Valaciclovir 500 mg Film Coated Tablets. Available online: https://www.medicines.org.uk/emc/product/4349/smpc (accessed on 17 September 2022).
3. Brunton, L.L.; Hilal-Dandan, R.; Knollmann, B.C. Antiviral Agents (Nonretroviral). In *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 13rd ed.; Acosta, E.P., Ed.; McGraw-Hill: New York, NY, USA, 2017; Chapter 62.
4. Duan, R.; de Vries, R.D.; Osterhaus, A.D.; Remeijer, L.; Verjans, G.M. Acyclovir-resistant corneal HSV-1 isolates from patients with herpetic keratitis. *J. Infect. Dis.* **2008**, *198*, 659–663. [CrossRef] [PubMed]
5. Safrin, S.; Elbeik, T.; Phan, L.; Robinson, D.; Rush, J.; Elbaggari, A.; Mills, J. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob. Agents Chemother.* **1994**, *38*, 1246–1250. [CrossRef] [PubMed]
6. Sampson, M.R.; Bloom, B.T.; Lenfestey, R.W.; Harper, B.; Kashuba, A.D.; Anand, R.; Benjamin, D.K., Jr.; Capparelli, E.; Cohen-Wolkowiez, M.; Smith, P.B. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. *Pediatr. Infect. Dis. J.* **2014**, *33*, 42–49. [CrossRef] [PubMed]

7. Abdalla, S.; Briand, C.; Oualha, M.; Bendavid, M.; Béranger, A.; Benaboud, S.; Tréluyer, J.M.; Zheng, Y.; Capito, C.; Demir, Z.; et al. Population Pharmacokinetics of Intravenous and Oral Acyclovir and Oral Valacyclovir in Pediatric Population to Optimize Dosing Regimens. *Antimicrob. Agents Chemother.* **2020**, *64*, e01426-20. [CrossRef] [PubMed]

8. Tod, M.; Lokiec, F.; Bidault, R.; De Bony, F.; Petitjean, O.; Aujard, Y. Pharmacokinetics of oral acyclovir in neonates and in infants: A population analysis. *Antimicrob. Agents Chemother.* **2001**, *45*, 150–157. [CrossRef] [PubMed]

9. Zeng, L.; Nath, C.E.; Blair, E.Y.; Shaw, P.J.; Stephen, K.; Earl, J.W.; Coakley, J.C.; McLachlan, A.J. Population pharmacokinetics of acyclovir in children and young people with malignancy after administration of intravenous acyclovir or oral valacyclovir. *Antimicrob. Agents Chemother.* **2009**, *53*, 2918–2927. [CrossRef] [PubMed]

10. O'Leary, C.K.; Jones, C.; Bryant, P.A.; Abo, Y.N.; Osowicki, J.; Gwee, A. Feasibility of Continuous Infusions of Acyclovir. *Pediatr. Infect. Dis. J.* **2020**, *39*, 830–832. [CrossRef] [PubMed]

11. Cies, J.J.; Moore, W.S., 2nd; Miller, K.; Small, C.; Carella, D.; Conley, S.; Parker, J.; Shea, P.; Chopra, A. Therapeutic drug monitoring of continuous-infusion acyclovir for disseminated herpes simplex virus infection in a neonate receiving concurrent extracorporeal life support and continuous renal replacement therapy. *Pharmacotherapy* **2015**, *35*, 229–233. [CrossRef] [PubMed]

12. Saiag, P.; Praindhui, D.; Chastang, C. A double-blind, randomized study assessing the equivalence of valacyclovir 1000 mg once daily versus 500 mg twice daily in the episodic treatment of recurrent genital herpes. *J. Antimicrob. Chemother.* **1999**, *44*, 525–531. [CrossRef] [PubMed]

13. Spruance, S.L.; Tyring, S.K.; DeGregorio, B.; Miller, C.; Beutner, K. A large-scale, placebo-controlled, dose-ranging trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. *Arch. Intern. Med.* **1996**, *156*, 1729–1735. [CrossRef] [PubMed]

14. Kimberlin, D.W.; Lin, C.Y.; Jacobs, R.F.; Powell, D.A.; Corey, L.; Gruber, W.C.; Rathore, M.; Bradley, J.S.; Diaz, P.S.; Kumar, M.; et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* **2001**, *108*, 230–238. [CrossRef] [PubMed]

15. Rabalais, G.P.; Nusinoff-Lehrman, S.; Arvin, A.M.; Levin, M.J. Antiviral susceptibilities of herpes simplex virus isolates from infants with recurrent mucocutaneous lesions after neonatal infection. *Pediatr. Infect. Dis. J.* **1989**, *8*, 221–223. [PubMed]

16. Reitano, M.; Tyring, S.; Lang, W.; Thoming, C.; Worm, A.M.; Borelli, S.; Chambers, L.O.; Robinson, J.M.; Corey, L. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: A large-scale dose range-finding study. *J. Infect. Dis.* **1998**, *178*, 603–610. [CrossRef] [PubMed]

17. Märtson, A.; van Hateren, K.; van den Bosch, G.; van der Werf, T.; Touw, D.; Alffenaar, J.C. Determination of ganciclovir and acyclovir in human serum using liquid chromatography-tandem mass spectrometry. *J. Appl. Bioanal.* **2018**, *4*, 175–186. [CrossRef]

18. Hawrami, K.; Breuer, J. Development of a fluorogenic polymerase chain reaction assay (TaqMan) for the detection and quantitation of varicella zoster virus. *J. Virol. Methods* **1999**, *79*, 33–40. [CrossRef]

19. Neely, M.N.; van Guilder, M.G.; Yamada, W.M.; Schumitzky, A.; Jelliffe, R.W. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. *Ther. Drug Monit.* **2012**, *34*, 467–476. [CrossRef] [PubMed]

20. Märtson, A.G.; Sturkenboom, M.G.G.; Knoester, M.; van der Werf, T.S.; Alffenaar, J.C.; Hope, W. Standard ganciclovir dosing results in slow decline of cytomegalovirus viral loads. *J. Antimicrob. Chemother.* **2022**, *77*, 466–473. [CrossRef] [PubMed]