

Population pharmacokinetics of ribavirin in lung transplant recipients and examination of current and alternative dosing regimens

Eliza Milliken^{1†}, Auke E. S. de Zwart^{2†}, Jan-Willem C. Alffenaar³, Deborah J. E. Marriott⁴,
Annelies Riezebos-Brilman⁵, Ana Schteinman^{6,7}, Allan M. Evans⁸, Allan R. Glanville^{1,9},
Erik A. M. Verschuuren² and Stephanie E. Reuter ^{8,10*}

¹Faculty of Medicine, The University of Notre Dame, Sydney, Australia; ²University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands; ³University of Groningen, University Medical Centre Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands; ⁴Department of Microbiology, St Vincent's Hospital, Sydney, Australia; ⁵Department of Medical Microbiology, University Medical Centre Utrecht, University of Utrecht, Utrecht, The Netherlands; ⁶Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, Australia; ⁷St Vincent's Clinical School, UNSW Medicine, University of New South Wales, Sydney, Australia; ⁸School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia; ⁹Department of Thoracic Medicine, St Vincent's Hospital, Sydney, Australia; ¹⁰School of Medicine and Public Health, The University of Newcastle, Newcastle, Australia

*Corresponding author. University of South Australia, CEA-19, GPO Box 2471, Adelaide, SA 5001, Australia. Tel: +61-8-8302-1872; Fax: +61-8-8302-2389; E-mail: stephanie.reuter@unisa.edu.au  orcid.org/0000-0003-3888-7287

†Authors contributed equally to the work.

Received 18 June 2018; returned 24 August 2018; revised 29 September 2018; accepted 13 October 2018

Background: Ribavirin is used in the treatment of respiratory paramyxovirus infection in lung transplant recipients; however, its pharmacokinetic profile in the transplant population is unknown despite the potential for alterations due to underlying pathology. Furthermore, the ability of current regimens to meet exposure targets has not been established.

Objectives: This study examined the pharmacokinetics of ribavirin in a lung transplant population for which current and alternative dosing regimens were assessed.

Methods: Population pharmacokinetic modelling was conducted in NONMEM using concentration–time data from 24 lung transplant recipients and 6 healthy volunteers. Monte Carlo simulation was used to assess the ability of dosing regimens to achieve pre-specified target concentrations.

Results and conclusions: A three-compartment model with first-order elimination most adequately described ribavirin concentration–time data, with CL_{CR} and patient type (i.e. lung transplant) identified as significant covariates in the model. Simulations indicate that current regimens achieve efficacious concentrations within 24 h of treatment initiation that increase to supra-therapeutic levels over the treatment period. A regimen of 8 mg/kg q6h orally for 48 h followed by 8 mg/kg q24h orally for the remainder of the treatment period was predicted to result in >90% of patients exhibiting concentrations within the defined target range throughout the entire treatment course. Additional work to formally establish target therapeutic concentrations is required; however, this study provides a valuable first step in determining optimal ribavirin treatment regimens for paramyxovirus infections in the lung transplant population.

Introduction

Ribavirin is a guanosine analogue that is used in the treatment of paramyxovirus infections.¹ Historically, its primary respiratory indication has been treatment of respiratory syncytial virus (RSV) pneumonitis in paediatric and haematological malignancy or stem cell transplant populations.^{2–4} More recently its use has been extrapolated to pulmonary transplant patients and the treatment

of other paramyxoviruses, including human metapneumovirus (HMPV) and parainfluenza virus.^{5–7} Goals of treatment are to reduce morbidity and mortality from acute pneumonitis as well as reduce the incidence of the bronchiolitis obliterans syndrome or transplant-associated pathological airway destruction, which has been linked to infection with respiratory viruses.^{8,9} Both acute infection and bronchiolitis obliterans syndrome are major contributors to reduction in median survival post-thoracic transplantation

and improved antimicrobial strategies are paramount to mortality reduction.^{5,7,8} With the advent of new direct-acting antiviral agents for hepatitis C, the treatment of paramyxoviruses has taken over as a primary use for ribavirin. While ribavirin is available in aerosolized, intravenous and oral formulations, previous studies have focused mainly on the efficacy of aerosolized ribavirin, while only a single study has directly compared two types of formulations for paramyxovirus infections.^{10,11} Despite this, most international thoracic transplant centres have opted for less expensive and less cumbersome oral and intravenous preparations, which may have equal efficacy.^{11–13} Although ribavirin is in common use, its pharmacokinetics in the unique transplant population are not well understood. It is feasible that transplant recipients as a population may manifest deviations in the pharmacokinetic profile of antimicrobials and other drugs due to physiological changes induced by the transplant. Such changes include a high incidence of renal failure, polypharmacy (immunosuppressive regimens) and heavy corticosteroid exposure with associated alterations in hepatic metabolism. In cystic fibrosis patients, drug pharmacokinetics may be altered by abnormal gastrointestinal absorption; however, as total body fat and stomach contents influence the absorption and distribution of ribavirin, this may be an issue even in non-cystic fibrosis transplant recipients as the prevalence of malnutrition is high in this population.

Ribavirin is characterized by multi-compartmental pharmacokinetics with distribution of the drug into tissues and a characteristic long terminal half-life.¹⁴ The antiviral effect of ribavirin may be dependent on dosage and the resulting plasma concentrations of the drug; thus, its pharmacokinetic properties are critical to the identification of optimal treatment protocols.^{15–17} However, the evidence for a target effective plasma concentration is lacking, although the IC₅₀ for RSV replication has been estimated at 1.35–5.82 mg/L *in vitro*, and values for HMPV may be similar to those for RSV.^{18–20} Previous research has indicated that effective plasma concentrations are >2.5 mg/L; however, given the known association between plasma concentrations >3.5 mg/L and haemolytic anaemia,^{21–24} it is considered reasonable to propose a target therapeutic range of 2.5–3.0 mg/L, with outer limits of 1.5–4.0 mg/L.

Ribavirin dose regimens for pulmonary virus infections have been derived from hepatitis C treatment. In order to achieve early steady-state concentrations, treatment strategies for oral or intravenous administration typically comprise loading doses of 11 mg/kg q8h for the first 24 h of treatment, followed by a maintenance dose of 10 mg/kg q12h. Despite established clinical protocols, target attainment of these regimens has not been previously examined in lung transplant recipients, who may have altered pharmacokinetics due to changes in underlying physiology. In order to investigate this further, a population pharmacokinetic approach was used to examine the pharmacokinetic properties, and sources of variability, of ribavirin in lung transplant recipients and healthy normal volunteers. Utilizing this model, the ability of current and alternative dosing regimens to meet target concentrations was examined.

Patients and methods

Pharmacokinetic data were prospectively and retrospectively obtained from lung transplant recipients diagnosed with a paramyxovirus infection recruited from study centres at St Vincent's Hospital (Sydney, Australia) and

University Medical Centre Groningen (The Netherlands). Additional concentration–time data were extracted using Engauge Digitizer software (<http://markummitchell.github.io/engauge-digitizer>) from previously published work examining the pharmacokinetics of oral and intravenous ribavirin in healthy volunteers.²⁵

The study was reviewed and approved by the institutional Human Research Ethics Committees (St Vincent's Hospital Sydney Human Research Ethics Committee HREC/15/SVH/74 and Medisch Ethische Toetsingscommissie University Medical Centre Groningen METc 2015/452). Prospectively examined participants were fully informed of the study procedures and provided written informed consent prior to study initiation. For retrospective participants, given the nature of the study, the need for written informed consent was waived by the local ethics committee. The study was conducted in accordance with the study protocol, the Declaration of Helsinki and local ethics standards.

To be deemed eligible for study inclusion, lung transplant recipients were required to be >18 years of age and receiving ribavirin treatment for respiratory paramyxovirus infection. Patients receiving haemodialysis treatment were excluded from participation. No formal restrictions on time since transplantation were included as part of the eligibility criteria, but all patients were required to be stable since receipt of their transplant and not to have been transplanted for acute viral pneumonitis.

Study procedures

Patients were initiated on oral and/or intravenous ribavirin treatment according to local standard treatment protocols and blood samples for analysis of plasma ribavirin concentrations were collected at various times after dose administration.

St Vincent's Hospital protocol

Study participants were administered a mixed intravenous/oral ribavirin dosing regimen consisting of a loading dose of 11 mg/kg q8h intravenously as a 30 min infusion for the first 24 h, followed by a maintenance dose of 10 mg/kg q12h orally. Blood samples were collected immediately prior to the first dose, immediately after completion of the infusion and then 1, 2, 3, 4, 6 and 8 h after the start of the first infusion. Additional samples were also collected on the morning of days 4 and 7 immediately prior to dosing and then 2 h after dose administration.

University Medical Centre Groningen protocol

Patients were treated with oral ribavirin administered as a loading dose of 11 mg/kg q8h for the first 24 h, followed by a maintenance dose of 10 mg/kg q12h. As part of standard care, blood samples were collected for monitoring of plasma ribavirin concentrations at 1.5 h after administration of the first dose and then immediately prior to morning dose administration on days 2, 4, 7 and 10.

Healthy normal volunteer dataset

Ribavirin pharmacokinetics were examined in healthy normal volunteers, as previously described.²⁵ In brief, participants were administered single doses of 150 mg of 13C₃-ribavirin intravenously and 400 mg of ribavirin orally. Blood samples were collected immediately prior to dosing and then 0.083, 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 11, 13, 17, 25, 37, 49, 61, 73, 97, 121, 145 and 169 h after dose administration.

Biological sample analysis

Blood samples were processed immediately after collection and stored at –20°C until analysis. Plasma samples were analysed for ribavirin concentrations by the Department of Clinical Pharmacology and Toxicology of St Vincent's Hospital and the Department of Clinical Pharmacy and Pharmacology of University Medical Centre Groningen using validated LC

Table 1. Participant characteristics

	St Vincent's Hospital patients	University Medical Centre Groningen patients	Healthy volunteers
Count	11	13	6
Gender	7 male/4 female	5 male/8 female	6 male/0 female
Age (years), mean \pm SD (range)	46.1 \pm 14.3 (26–63)	53.2 \pm 14.4 (27–73)	36.8 \pm 5.34 (31–44)
Body weight (kg), mean \pm SD (range)	65.6 \pm 15.6 (47–105)	73.2 \pm 18.4 (42–120)	78.3 \pm 11.3 (58.7–89.9)
CL _{CR} (mL/min), mean \pm SD (range)	61.8 \pm 30.7 (20.1–126)	56.6 \pm 25.4 (25.1–111)	105 \pm 13.2 (86.8–120)
Time since transplantation (years), mean \pm SD (range)	7.39 \pm 4.85 (0.25–15.1)	4.06 \pm 3.06 (0.25–7.00) ^a	NA
Underlying disease	2 pulmonary hypotension/2 cystic fibrosis/1 interstitial lung disease/1 COPD/5 unknown	4 cystic fibrosis/4 COPD/3 α -1 antitrypsin deficiency/1 pulmonary fibrosis/1 pulmonary hypotension	NA

No significant differences were found in participant characteristic data, with the exception of CL_{CR}, which was significantly higher in healthy volunteers compared with the St Vincent's Hospital and University Medical Centre Groningen patient groups.

^an = 4.

tandem MS methodology.²⁶ Values for samples returning concentrations below the lower limit of quantification of the assay (0.2 mg/L) were not made available by the analytical laboratory; these samples were excluded from the pharmacokinetic dataset.

Population pharmacokinetics

Population pharmacokinetic modelling and simulation were conducted using NONMEM[®] VII (ICON Development Solutions, Ellicott City, MD, USA) software with an Intel Fortran compiler and Wings for NONMEM interface (<http://wfn.sourceforge.net>). Full details of the model development protocol and model diagnostics are available as [Supplementary data](#) at JAC Online; the pharmacokinetic methods are briefly described below.

One-, two- and three-compartment models with first-order absorption and elimination from the central compartment were fitted to plasma ribavirin concentration–time data. Models with more complex absorption characteristics based on a chain of absorption transit compartments were also investigated. The pharmacokinetic models were parameterized (where appropriate) as CL, volume of distribution of the central compartment (V_c), intercompartmental clearance(s) (CL_d), volume of distribution of the peripheral compartment(s) (V_p), absorption rate constant (K_a) and bioavailability (F). The model incorporated population parameter variability (comprising between-subject and between-occasion variability) and residual unexplained variability (comprising proportional and/or additive error).

Once the base structural model had been determined, the contributions of continuous (e.g. age, body weight, renal function) and categorical (e.g. gender, patient type) covariates to population parameter variability were assessed using a forward selection–backward elimination procedure.

Model selection was based on the objective function value (minus twice the log-likelihood of the data) as well as visual inspection of the standard diagnostic plots. A statistically significant ($P < 0.05$) improvement in the comparison of nested models was defined as a decrease in the objective function value of 3.84U (for 1 degree of freedom). The final population pharmacokinetic model was evaluated through visual predictive checks.

Monte Carlo simulation

To assess the ability of current and alternative dosing regimens to meet target ribavirin concentrations over a 14 day treatment course, the final population pharmacokinetic model was used to simulate datasets for a

representative patient population of 10000 individuals. Model simulation was conducted using R[®] Version 3.3.2 (R Foundation for Statistical Computing). Dosing regimens were assessed on the ability to meet the pre-specified target therapeutic range (1.5–4.0 mg/L) over the dosing interval; target attainment for 90% of patients was considered clinically relevant.

Results

A total of 120 plasma ribavirin concentrations from 24 lung transplant recipients ($n = 11$ at St Vincent's Hospital, $n = 13$ at University Medical Centre Groningen) and 188 concentration–time data points extracted from previously reported data for 6 healthy normal volunteers²⁵ were included in the population pharmacokinetic analysis. No data points were excluded from the dataset. A summary of patient characteristics is presented in Table 1.

Population pharmacokinetic model

A three-compartment model with first-order elimination from the central compartment was found to describe ribavirin concentration–time data most adequately. The model incorporated population parameter variability for CL, V_c, CL_{d1}, CL_{d2}, K_a and F, and proportional residual unexplained variability. The final population pharmacokinetic model is illustrated in Figure 1 and population parameter estimates of the final pharmacokinetic model are presented in Table 2. A summary of model development is presented in Table S1 and the final model control stream is included in Appendix S1.

Introduction of covariates into the structural model identified an effect of CL_{CR} (calculated using the Cockcroft–Gault equation) and patient type (i.e. lung transplant recipient or healthy normal volunteer) on CL (Figure S1).

Based on model diagnostics, the model was found to characterize well the ribavirin concentration–time data, and comparison of observed data and median and 90% prediction intervals of simulated data demonstrated close prediction over the time course of the study (Figure S2). Full details of the model performance are available as [Supplementary data](#) at JAC Online.

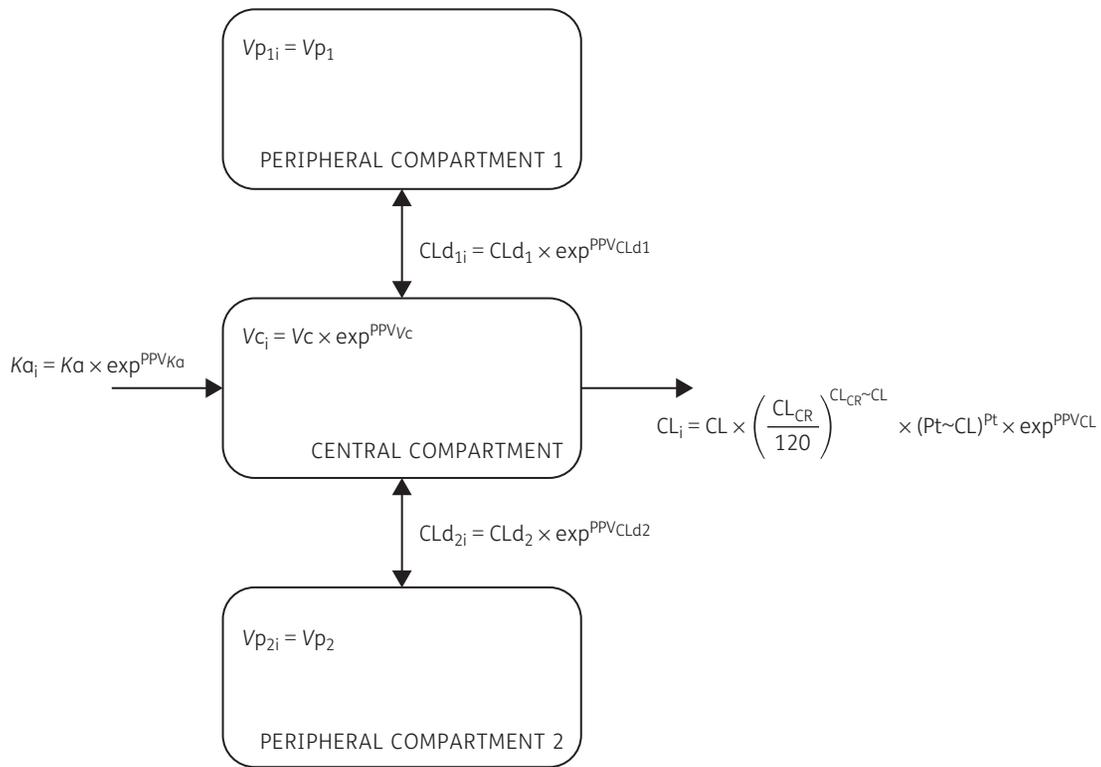


Figure 1. Schematic of the final ribavirin population pharmacokinetic model. $CL_{CR} \sim CL$, effect of CL_{CR} on CL ; $Pt \sim CL$, patient type, where 0 = healthy control and 1 = lung transplant recipient; $Pt \sim CL$, effect of patient type on CL ; PPV , population parameter variability.

Table 2. Final ribavirin population pharmacokinetic model parameter estimates

Parameter	Final model: estimate (RSE, %)	Shrinkage	Eta bar P
Fixed effects			
CL (L/h)	17.5 (27.0)		
Vc (L)	52.2 (18.6)		
Vp1 (L)	152 (38.8)		
Vp2 (L)	1140 (21.8)		
CLd1 (L/h)	40.7 (22.0)		
CLd2 (L/h)	39.8 (17.5)		
Ka (h ⁻¹)	0.318 (19.8)		
F (%)	0.512 (12.1)		
$CL_{CR} \sim CL$	0.574 (64.6)		
$Pt \sim CL$	0.586 (33.8)		
Random effects			
PPV CL (CV, %)	34.9	39.5	0.759
PPV Vc (CV, %)	34.1	51.5	0.803
PPV CLd1 (CV, %)	34.6	49.9	0.787
PPV CLd2 (CV, %)	49.4	26.3	0.842
PPV Ka (CV, %)	19.7	64.3	0.946
PPV F (CV, %)	44.8	13.8	0.938
Residual variability			
proportional (CV)	25.7	9.9	

$CL_{CR} \sim CL$, effect of CL_{CR} on CL ; $Pt \sim CL$, effect of patient type on CL ; PPV , population parameter variability; RSE, relative standard error; CV, coefficient of variation.

Examination of current and alternative dosing regimens

A representative patient population of 10000 lung transplant recipients with distributions of CL_{CR} and associated body weights consistent with that seen within the patient cohort was constructed and concentration–time profiles were simulated using the developed population pharmacokinetic model to examine the ability of the current and alternative dosing regimens to achieve target concentrations over a 14 day treatment course. It should be noted that, for oral dosing regimens, doses administered were rounded to the nearest 200 mg (i.e. tablet size).

Both of the standard dosing regimens used within the study centres (11 mg/kg q8h orally or intravenously + 10 mg/kg q12h orally) performed well in achieving the predicted target concentrations within the first 24 h of starting; however, plasma ribavirin concentrations continued to accumulate over the course of the treatment period such that >90% of patients were predicted to have concentrations well above the upper limit of the defined therapeutic range on day 14. Similar results were seen for the standard intravenous-only regimen (11 mg/kg q8h intravenously + 10 mg/kg q12h orally).¹³ For the median patient, these terminal concentrations were predicted to be 2- to 3-fold higher than the target concentrations (Figure 2). Similar results were observed when stratified by renal function, indicating that the observed drug accumulation was not primarily due to altered CL_{CR} in a specific patient subgroup (data not presented).

Alternative dosing regimens were examined to determine doses predicted to result in concentrations within the therapeutic range throughout the treatment course. An oral dosing regimen of

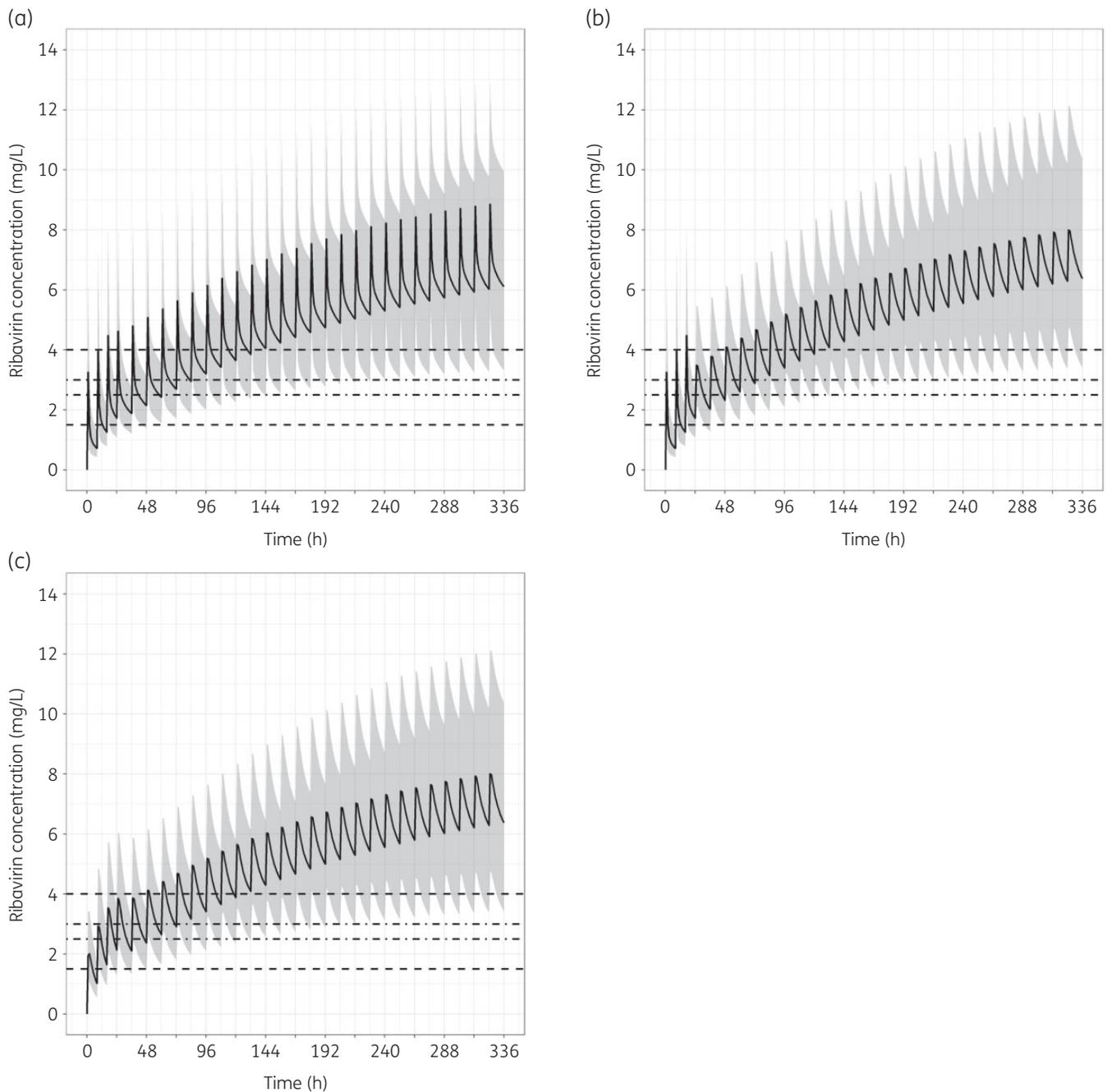


Figure 2. Plasma ribavirin concentration–time profile after administration of the standard ribavirin dosing regimens. Data are presented as median (solid line) and 90% prediction intervals (shaded). Target (2.5–3.0 mg/L, dot dashed line) and acceptable (1.5–4.0 mg/L, dashed line) therapeutic range denoted for reference. (a) 11 mg/kg q8h intravenously for the first 24 h, followed by a maintenance dose of 10 mg/kg q12h intravenously. (b) 11 mg/kg q8h intravenously for the first 24 h, followed by a maintenance dose of 10 mg/kg q12h orally. (c) 11 mg/kg q8h orally for the first 24 h, followed by a maintenance dose of 10 mg/kg q12h orally.

11 mg/kg q8h orally + 4 mg/kg q12h orally was found to result in plasma ribavirin concentrations for the median patient in the desired 2.5–3 mg/L range and >90% of patients achieving concentrations >1.5 mg/L at the end of the 14 day treatment period. However, despite the loading dose achieving therapeutic targets at the end of day 1, plasma concentrations declined on day 2 and

then progressively increased by the end of the nominal treatment period (Figure 3a). Consistent results were seen across the spectrum of renal functions (data not presented). Similar results were seen for a dosing regimen of 11 mg/kg q8h orally + 8 mg/kg q24h orally (Figure 3b). On the other hand, a regimen of 8 mg/kg q6h orally for 48 h followed by 8 mg/kg q24h orally for the remainder of

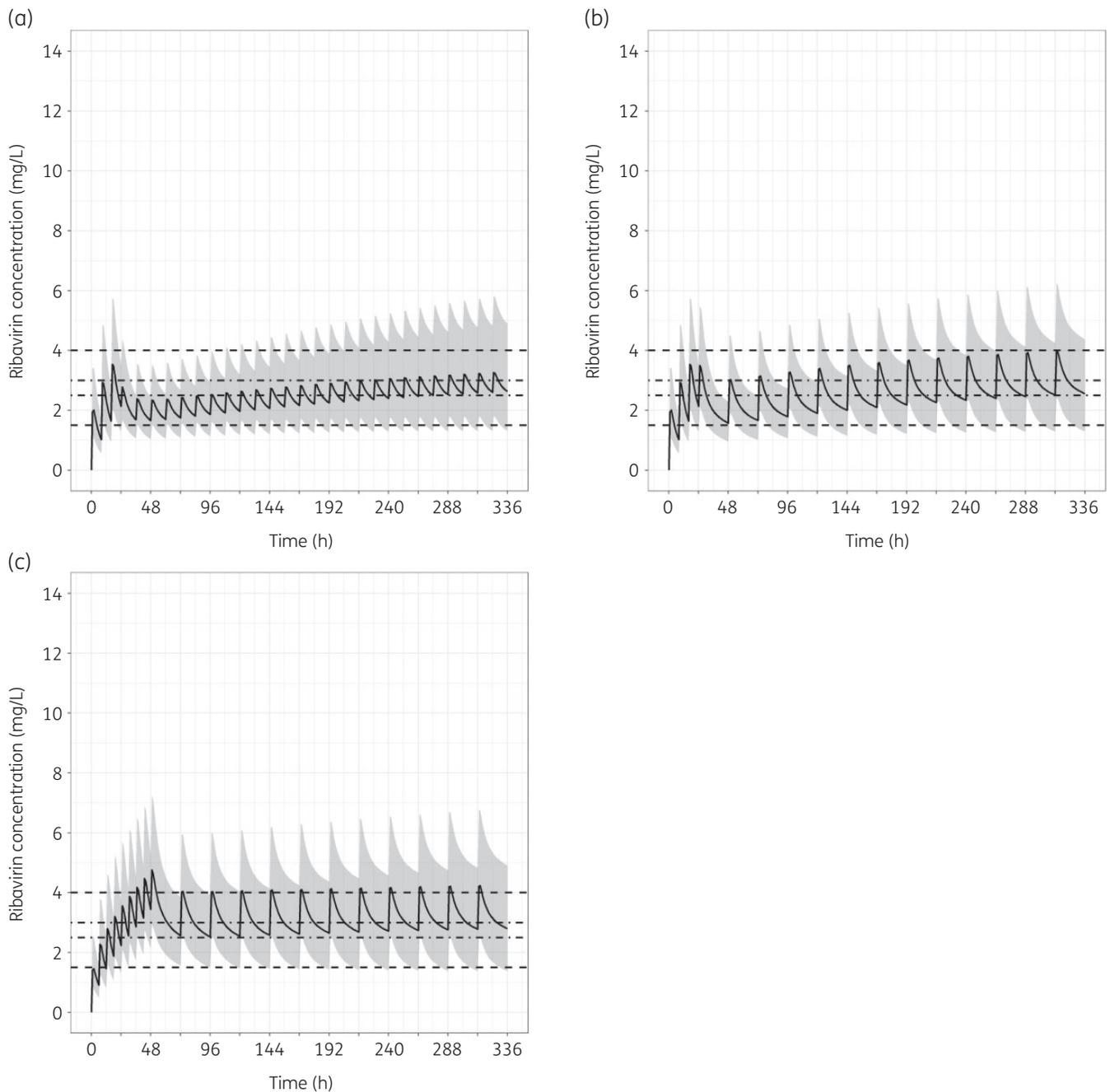


Figure 3. Plasma ribavirin concentration–time profile after administration of the alternative ribavirin dosing regimens. Data are presented as median (solid line) and 90% prediction intervals (shaded). Target (2.5–3.0 mg/L, dot dashed line) and acceptable (1.5–4.0 mg/L, dashed line) therapeutic range denoted for reference. (a) 11 mg/kg q8h orally for the first 24 h, followed by a maintenance dose of 4 mg/kg q12h orally. (b) 11 mg/kg q8h orally for the first 24 h, followed by a maintenance dose of 8 mg/kg q24h orally. (c) 8 mg/kg q6h orally for the first 48 h, followed by a maintenance dose of 8 mg/kg q24h orally.

the treatment period was predicted to result in >90% of patients exhibiting concentrations within the defined target range throughout the entire treatment course (Figure 3c). Slight drug accumulation was seen for patients with severe renal impairment (<30 mL/min, data not presented); however, concentrations were predicted to remain below those seen for the dosing regimens currently used in clinical practice.

Discussion

Despite the use of ribavirin for the treatment of paramyxovirus infections, little is known in regard to the ability of current dosing regimens to meet effective target concentrations. This is particularly relevant for the lung transplant population, for which sub-therapeutic treatment is likely to result in significant morbidity

and reduced median survival, and supra-therapeutic doses have been associated with haemolytic anaemia, renal impairment and other side effects.^{16,18,23,24} Evidence-based dosing regimens are therefore critical for the optimal treatment of these patients. This study undertook a population pharmacokinetic approach to determine the pharmacokinetic properties of ribavirin and the factors contributing to variability in this patient group. This then allowed the examination of current and alternative dosing regimens and their ability to meet predefined therapeutic targets.

The population pharmacokinetic analysis confirmed that ribavirin is characterized by three-compartment pharmacokinetics, with first-order elimination, consistent with a compartmental analysis previously reported²⁵ and with the known pharmacokinetic properties of ribavirin that have been previously described.^{14,16,18,19,27} The model found CL to be influenced by CL_{CR} (with a 10% reduction in CL_{CR} associated with a 6% reduction in systemic CL), which is not surprising given that renal CL accounts for approximately one-third of total CL.²⁵ Patient type also influenced CL, with lung transplant recipients exhibiting a 41% reduction in systemic CL compared with healthy controls.

Simulations of current intravenous and/or oral ribavirin dosing regimens indicate that, whilst administration of the standard loading doses results in plasma concentrations within the target therapeutic range early in the treatment course, concentrations continue to accumulate throughout the 14 day treatment period such that later concentrations are substantially higher than the defined upper limit of 4.0 mg/L (Figure 2). Previous studies indicated that ribavirin concentrations >3.5 mg/L are associated with severe side effects, even after only a few days of treatment, and thus it is feasible that these regimens may be associated with increased risk of side effects.^{15,23,24} On the other hand, alternative dosing regimens that target effective concentrations at the end of the treatment period are predicted to result in sub-therapeutic concentrations during the first days of treatment (Figure 3), thereby potentially placing patients at risk of ineffective treatment. Utilizing the developed pharmacokinetic model and known characteristics of ribavirin, this study has been able to propose a dosing regimen, consisting of 8 mg/kg q6h orally for the first 48 h followed by a maintenance dose of 8 mg/kg q24h orally, that is predicted to result in early attainment of therapeutic concentrations and continued maintenance at these levels throughout the treatment course (Figure 3). Arguably, this indicates that therapeutic levels can be achieved with a 45% reduction in total dose administered; the combination of oral administration and dose reduction has potential for substantial cost savings. Notably, whilst this regimen includes higher loading doses, the predicted exposure remains below that observed later in the treatment period for the current regimens and therefore is considered to pose no additional risk of toxicity.

Whilst this study provides valuable information on the pharmacokinetics of ribavirin in the lung transplant population, the majority of patients within this study were recruited as outpatients and no severe inflammatory states were seen. Thus, the impact of this more complex clinical situation on ribavirin pharmacokinetics cannot be determined from this analysis. Furthermore, due to limited data and/or lack of information for some patients, the influence of factors such as underlying disease (including cystic fibrosis), time since transplantation and the immunosuppressive scheme could not be determined. Preliminary examination of the data

indicated no discernible trends; however, full exploration with a larger dataset would be required for definitive conclusions to be made.

Importantly, it should be noted that current evidence for the proposed therapeutic target concentrations utilized within this study is limited and requires additional work. Longitudinal research examining the concentration–adverse effect relationship would be desirable in order to provide more evidence of the upper limit of ribavirin concentrations that can be tolerated for short-term therapy and how this relates to what is currently considered ‘safe’. Nonetheless, the developed population pharmacokinetic model provides an effective tool for anticipating ribavirin exposure in a population with unique antimicrobial needs and providing an evidence basis for effective treatment protocols once target therapeutic concentrations are formally established. This study provides a valuable first step in determining optimal ribavirin treatment regimens for paramyxovirus infections in the lung transplant population.

Acknowledgements

We wish to acknowledge the valuable contribution of Professor Ric Day and Associate Professor Ross Norris of St Vincent’s Hospital, Sydney, as well as Dr Nisha Menon and Dr Cara Platts for their practical assistance.

Funding

This work was supported by internal funding and the National Health and Medical Research Council (APP1054746 to S. E. R.).

Transparency declarations

None to declare.

Supplementary data

Supplementary data, including Table S1, Appendix S1 and Figures S1 and S2, are available at JAC Online.

References

- 1 Gross AE, Bryson ML. Oral ribavirin for the treatment of noninfluenza respiratory viral infections. *Ann Pharmacother* 2015; **49**: 1125–35.
- 2 Park SY, Baek S, Lee SO *et al*. Efficacy of oral ribavirin in hematologic disease patients with paramyxovirus infection: analytic strategy using propensity scores. *Antimicrob Agents Chemother* 2013; **57**: 983–9.
- 3 Shah JN, Chelamly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood* 2011; **117**: 2755–63.
- 4 Wright M, Piedimonte G. Respiratory syncytial virus prevention and therapy: past, present, and future. *Pediatr Pulmonol* 2011; **46**: 324–47.
- 5 Fuehner T, Dierich M, Duesberg C *et al*. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. *Antivir Ther* 2011; **16**: 733–40.
- 6 Hirsch HH, Martino R, Ward KN *et al*. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis* 2013; **56**: 258–66.

- 7 Niggli F, Huber LC, Benden C et al. Human metapneumovirus in lung transplant recipients: characteristics and outcomes. *Infect Dis (Lond)* 2016; **48**: 852–6.
- 8 Allyn PR, Duffy EL, Humphries RM et al. Graft loss and CLAD-onset is hastened by viral pneumonia after lung transplantation. *Transplantation* 2016; **100**: 2424–31.
- 9 Gottlieb J, Schulz TF, Welte T et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. *Transplantation* 2009; **87**: 1530–7.
- 10 Beaird OE, Freifeld A, Ison MG et al. Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the midwestern respiratory virus collaborative. *Transpl Infect Dis* 2016; **18**: 210–5.
- 11 Li L, Avery R, Budev M et al. Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation. *J Heart Lung Transplant* 2012; **31**: 839–44.
- 12 Burrows FS, Carlos LM, Benzimra M et al. Oral ribavirin for respiratory syncytial virus infection after lung transplantation: efficacy and cost-efficiency. *J Heart Lung Transplant* 2015; **34**: 958–62.
- 13 Glanville AR, Scott AI, Morton JM et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. *J Heart Lung Transplant* 2005; **24**: 2114–9.
- 14 Glue P. The clinical pharmacology of ribavirin. *Semin Liver Dis* 1999; **19** Suppl 1: 17–24.
- 15 Arase Y, Ikeda K, Tsubota A et al. Significance of serum ribavirin concentration in combination therapy of interferon and ribavirin for chronic hepatitis C. *Intervirology* 2005; **48**: 138–44.
- 16 Morello J, Rodriguez-Novoa S, Jimenez-Nacher I et al. Usefulness of monitoring ribavirin plasma concentrations to improve treatment response in patients with chronic hepatitis C. *J Antimicrob Chemother* 2008; **62**: 1174–80.
- 17 Stanke-Labesque F, Loustaud-Ratti V, Babany G et al. Ribavirin therapeutic drug monitoring: why, when and how? *Fundam Clin Pharmacol* 2010; **24**: 401–6.
- 18 Wade A, Sasadeusz J. Ribavirin and viramidine. In: ML Grayson, ed. *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic and Antiviral Drugs*. London, UK: ASM Press, 2010; 2923–58.
- 19 Wade JR, Snoeck E, Duff F et al. Pharmacokinetics of ribavirin in patients with hepatitis C virus. *Br J Clin Pharmacol* 2006; **62**: 710–4.
- 20 Wyde PR, Chetty SN, Jewell AM et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin *in vitro*. *Antiviral Res* 2003; **60**: 51–9.
- 21 Brochet E, Castelain S, Duverlie G et al. Ribavirin monitoring in chronic hepatitis C therapy: anaemia versus efficacy. *Antivir Ther* 2010; **15**: 687–95.
- 22 D'Avolio A, Ciancio A, Siccardi M et al. Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associated anemia in patients receiving standard anti-HCV treatment. *Ther Drug Monit* 2012; **34**: 165–70.
- 23 Maeda Y, Kiribayashi Y, Moriya T et al. Dosage adjustment of ribavirin based on renal function in Japanese patients with chronic hepatitis C. *Ther Drug Monit* 2004; **26**: 9–15.
- 24 Saito H, Tada S, Ebinuma H et al. Role of erythrocytes as a reservoir for ribavirin and relationship with adverse reactions in the early phase of interferon combination therapy for chronic hepatitis C virus infections. *J Clin Microbiol* 2006; **44**: 3562–8.
- 25 Preston SL, Drusano GL, Glue P et al. Pharmacokinetics and absolute bioavailability of ribavirin in healthy volunteers as determined by stable-isotope methodology. *Antimicrob Agents Chemother* 1999; **43**: 2451–6.
- 26 Van Der Lijke H, Alffenaar JW, Kok WT et al. Determination of ribavirin in human serum using liquid chromatography tandem mass spectrometry. *Talanta* 2012; **88**: 385–90.
- 27 Glue P, Schenker S, Gupta S et al. The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *Br J Clin Pharmacol* 2000; **49**: 417–21.