Intravenous Ribavirin for Parainfluenza and Respiratory Syncytial Virus in an Infant Receiving Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

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BACKGROUND Viral bronchiolitis remains a significant cause of hospitalization as well as morbidity and mortality during the first year of life, with treatment options beyond supportive care being limited. In cases of severe illness, ribavirin may offer therapeutic benefit.

OBJECTIVE We report the use of intravenous (IV) ribavirin in an infant requiring concomitant venovenous extracorporeal membrane oxygenation (VV-ECMO) and continuous venovenous hemofiltration (CVVH) for respiratory syncytial virus (RSV) and parainfluenza virus (PIV) coinfection.

PATIENTS AND METHODS A 5-week-old male former 33-week preterm infant was admitted with respiratory failure and subsequently tested positive for RSV and PIV-type 1 infection. Progressive clinical deterioration subsequently required the initiation of both VV-ECMO and CVVH. Although the patient received combined VV-ECMO and CVVH, IV ribavirin was administered, and serial plasma and ultrafiltrate samples were obtained for pharmacokinetic analyses after the first dose (collection period 1) and again after an estimated 5 half-lives (collection period 2).

RESULTS Pharmacokinetics for collection period 1 demonstrated a calculated C_{max} of 11.99 mg/L, an AUC_{0-24} of 43.32 mg·hr/L, k_e 0.26 hr⁻¹, $t_{1/2}$ 2.69 hr, Vd 10.04 L (2.92 L/kg, using patient's dosing weight 3.43 kg), CL_T 43.47 mL/min, and CL_{CVVH} 6.75 mL/min. Pharmacokinetics for collection period 2 demonstrated a calculated C_{max} of 10.31 mg/L, AUC_{0-6} of 52.55 mg·hr/L, k_e 0.06 hr⁻¹, $t_{1/2}$ 10.69 hr, Vd 17.5 L (5.1 L/kg), and CL_T 17.44 mL/min. The sieving coefficient during collection period 1 was 1.17 (range, 1.07–1.37). The percent decline between prefilter and postfilter oxygenator was 19.1%.

CONCLUSION Our patient demonstrated therapeutic concentrations of ribavirin, despite drug removal via CVVH and the ECMO oxygenator. Standard ribavirin dosing used and resultant concentrations achieved were associated with viral clearance and clinical improvement.

ABBREVIATIONS AUC, area under the curve; CL_{CVVH} , clearance via continuous venovenous hemofiltration; CL_T , total clearance; C_{max} , maximum concentration; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; eIND, emergency investigational new drug application; ETT, endotracheal tube; HD, hospital day; IV, intravenous; k_e , elimination rate constant; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RVPP, respiratory virus panel PCR; $t_{1/2}$, half-life; Vd, volume of distribution; VV-ECMO, venovenous extracorporeal membrane oxygenation

KEYWORDS extracorporeal membrane oxygenation; paramyxoviridae infections; prematurity; renal dialysis; respiratory syncytial virus; ribavirin

J Pediatr Pharmacol Ther 2018;23(4):337–342

DOI: 10.5863/1551-6776-23.4.337

Introduction

Viral lower respiratory tract infection (LRTI) is the leading cause of hospitalization for infants.¹ Respiratory syncytial virus (RSV) remains the most common cause of a viral LRTI, but coinfection with other respiratory viruses is common.² High viral load and bacterial coin-

fection lead to greater disease severity,^{2–4} requiring escalation in care, including mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Bronchodilators, steroids, and nebulized hypertonic saline lack evidence to support their routine use for the treatment of bronchiolitis.⁵ For life-threatening infections, therapies like ribavirin, palivizumab, and

Figure 1. Response of RSV and PIV viral load to IV ribavirin as reported by PCR cycle time by hospital day and treatment modality. Cycle time indicates the number of PCR cycles needed to detect the virus (less number mean high viral load and vice versa).

CRRT, continuous renal replacement therapy; ETT, endotracheal tube sample; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; PIV, parainfluenza virus; RSV, respiratory syncytial virus; VV-ECMO, venovenous extracorporeal membrane oxygenation.

● RSV ETT; ▲ PIV ETT

intravenous (IV) immunoglobulin may provide benefit, but their associated cost and inherent toxicity limit their use, particularly in the absence of consistently demonstrated benefit or higher level of evidence to support their use.⁶

Ribavirin is a broad-spectrum antiviral medication and the only approved antiviral treatment for RSV infection in the United States. Ribavirin has a molecular weight of 244.2 Da and is not bound to plasma proteins.⁷ The log p value of ribavirin is -1.85 , indicating that this molecule is hydrophilic.⁸ The minimum inhibitory concentration and median effective dose of ribavirin for the treatment of RSV are <1 mg/L and 2 to 8 mg/L, respectively,^{9,10} whereas *in vitro* data suggest ribavirin concentrations of 200 to 1000 mg/L produce a 50% cytotoxic effect.¹¹ Approved administration routes are enteral, IV, and aerosol, but use of each of these routes carries limitations. The enteral route lacks a readily available appropriate pediatric dosage form, aerosolized ribavirin requires isolation and may be limited if the patient is mechanically ventilated, and IV ribavirin is only available through a US Food and Drug–approved emergency investigational new drug application (eIND), but it has demonstrated efficacy in immunocompromised patients with adenoviral infections.^{12,13}

We report our experience using IV ribavirin therapy to treat RSV and PIV LRTI in an infant requiring VV-ECMO and continuous venovenous hemofiltration (CVVH).

To address the lack of published experience using IV ribavirin with concomitant VV-ECMO and CVVH, serial ribavirin plasma and ultrafiltrate samples were measured to determine drug removal and to ensure effective plasma concentrations. Serial lower respiratory tract and nasopharyngeal samples were analyzed by qualitative viral polymerase chain reaction (PCR) to determine clinical response to therapy.

Patient Case Report

A 5-week-old male infant, born at 33 weeks' gestational age and weighing 3.43 kg, was admitted to the pediatric intensive care unit with respiratory failure, requiring immediate mechanical ventilation. Blood, urine, endotracheal tube aspirate and cerebrospinal fluid were sent for culture, and respiratory samples were sent for viral respiratory polymerase chain reaction (PCR) assay. The patient was started on empiric cefepime, amikacin, and vancomycin. Chest radiograph showed lung hyperinflation and bronchial wall thickening consistent with viral bronchiolitis. Nasopharyngeal and endotracheal tube (ETT) respiratory virus panel PCR (RVPP) were positive for RSV and PIV type 1, and ETT cultures were positive for *Haemophilus influenzae*. Antibiotics were changed to ampicillin/sulbactam and eventually amoxicillin/clavulanate for a planned total treatment course of 7 days. On hospital day (HD) 7, the patient's cardiorespiratory status deteriorated,

and VV-ECMO was initiated. Antibiotic therapy was rebroadened to cefepime, amikacin, and vancomycin. Intravenous immunoglobulin (0.5 g/kg on HD 10) and palivizumab (15 mg/kg IV daily $\times$ 3 doses on HDs 11–13) were administered; however, high RSV and PIV viral loads persisted from respiratory samples. The RSV and PIV cycle times from nasopharyngeal and ETT RVPP were noted to decrease, indicating increased viral loads (Figure 1).¹⁴ Subsequent bacterial and fungal cultures showed no growth. On HD 18, he developed acute kidney injury, requiring initiation of CVVH. Given his worsening clinical condition, ribavirin therapy was considered; yet, airway pressure release ventilation precluded the use of nebulized ribavirin. Therefore, IV ribavirin was obtained via eIND approval. Intravenous ribavirin was started on HD 18 with a loading dose of 33 mg/kg, followed by 16 mg/kg per dose every 6 hr for 16 doses, then 8 mg/kg every 8 hr for 9 doses for a total of 7 days (HDs 18–25).

During IV ribavirin treatment, the patient had no laboratory evidence to suggest worsening hemolytic anemia, as evaluated through plasma-free hemoglobin and haptoglobin, or significant increases in liver transaminases. He did develop elevated uric acid concentrations (maximum value, 11.6 mg/dL) 2 days after IV ribavirin therapy was completed. The patient's cycle times from his RVPP samples gradually increased, suggesting decreased viral loads, after starting IV ribavirin. The ECMO and CVVH were ultimately discontinued on HDs 23 and 28, respectively (Figure 1). At the time of this report, the patient has made a complete recovery, including a full renal recovery.

Methods

The ECMO circuit was assembled using a Maquet Quadrox-iD Pediatric (Rastatt, Germany) oxygenator and heparin-bonded biocompatible tubing (Medtronic, Minneapolis, MN). Sterile Norsmosol-R (Hospira Inc, Lake Forest, IL) filled circuits were primed for patient use using heparinized reconstituted whole blood (315 mL). To manage CVVH, a Terumo CAPiox Hemoconcentrator HC05S (Ann Arbor, MI) was incorporated into the ECMO circuit (priming volume, 35 mL). A shunt line delivered afferent blood from the postoxygenerator outlet to the hemofilter, with efferent return to the ECMO circuit at the prepump venous limb. PrismaSate BGK 4/2.5 (Baxter, Round Lake, IL) was used for the prefilter replacement fluid.

Intravenous ribavirin was administered during 30 minutes via a central venous catheter directly to the patient. Serial blood samples were collected and plasma harvested, along with CVVH ultrafiltrate samples, after the loading dose (33 mg/kg, 113 mg total) from the predialysis filter port at time 0 (prior to the start of infusion), then 30, 60, 120, 240, and 300 minutes after the start of infusion (collection period 1). During the dosing of 16 mg/kg per dose (55 mg) IV every 6 hr, a plasma trough

sample was obtained at the predialysis filter just prior to the 10th ribavirin dose (collection period 2, representing the passage of 5 elimination half-lives). We were unable to truly know prior to sample collection what our patient's half-life would be, given the use of ECMO and CVVH. McJunkin et al¹⁵ reported a case series of pediatric patients (ages 3–14 years) given IV ribavirin that had a calculated half-life of 10.8 hr, which we used as the basis for our half-life estimate. The 1-hour postinfusion blood samples were obtained from predialysis and postdialysis hemofilter and pre-ECMO and post-ECMO oxygenator. The hemofilter line was clamped just prior to obtaining the prefilter as well as preoxygenator and postoxygenerator samples. The hemofilter line was then unclamped, and the postfilter sample was obtained. Samples from collection period 1 were designed to help characterize the pharmacokinetics of IV ribavirin after the first dose, as well as to attempt to describe how much drug was being removed in the ultrafiltrate. Samples from collection period 2 were designed to further characterize the contributions of the ECMO circuit setup.

During collection period 1, the ECMO pump flow was 75.8 mL/min/kg, replacement fluid flow was 300 mL/hr with PrismaSate BGK 4/2.5, and residual urine output was 0.91 mL/kg/hr. During collection period 2, ECMO pump flow was 90.4 mL/min/kg, replacement fluid flow was at 350 mL/hr with PrismaSate BK22/4/0 with 10mEq/L of sodium bicarbonate, and residual urine output had decreased to 0.09 mL/kg/hr.

Blood samples were collected in heparinized tubes, whole blood was centrifuged, and plasma was collected and immediately stored at -70°C . Samples were couriered while frozen and packaged in dry ice to Mayo Medical Laboratories (Rochester, MN) and analyzed by liquid chromatography–tandem mass spectrometry.¹⁶ Linear regression analyses of log ribavirin plasma concentrations versus time were used to determine the elimination rate constant (k_e) and half-life ($t_{1/2}$), using T-60 and T-240 values. The area under the curve (AUC) was calculated using the linear trapezoidal method for collection period 1. Consequently, to determine the full AUC from the loading dose, we used the extrapolated peak plasma concentration and decayed ribavirin plasma concentration for 24 hr using the calculated k_e . Total clearance (CL_T) was calculated by dividing the dose by the AUC_{0-24} . The apparent volume of distribution (V_d) was calculated by dividing the CL_T by the k_e , then normalizing to the patient's weight. Pharmacokinetic calculations during collection period 2 used the prefilter plasma samples collected at time points T-60 and T-360. The sieving coefficient was determined by dividing the ribavirin ultrafiltrate concentration by the prefilter plasma concentration for each time interval, then averaging these results. The CVVH clearance (CL_{CVVH}) was calculated by multiplying the product of the ultrafiltration rate, sieving coefficient, and blood

Table. Plasma and Ultrafiltrate Ribavirin Concentrations

Time, min	Plasma Sample Type	Ribavirin, mg/L	Sample Type	Ribavirin, mg/L	Sieving Coefficient
Collection period 1					
0*	Prefilter	<0.5			
30	Prefilter	13.1			
60	Prefilter	6.84	Ultrafiltrate	8.08	1.18
120	Prefilter	4.97	Ultrafiltrate	5.34	1.07
240	Prefilter	3.15	Ultrafiltrate	4.33	1.37
300	Prefilter	3.25	Ultrafiltrate	3.64	1.12
Collection period 2					
0*	Prefilter	7.04			
60	Prefilter	9.92			
60	Postfilter	10.44			
60	Preoxygenator	12.76			
60	Postoxygenator	10.32			
360	Prefilter	7.24			

* Prior to the start of infusion.

flow rate, and dividing that by the sum of the blood flow rate and predilution replacement fluid rate.

Results

Administered treatments and RSV and PIV PCR cycle time results are shown in Figure 1. The patient continued to have measurable ETT RSV and PIV viral loads prior to IV ribavirin administration, although plasma RSV and PIV PCR results remained negative throughout the patient's clinical course. Observed plasma and ultrafiltrate ribavirin concentrations are shown in the Table. The plasma ribavirin concentrations during collection period 1 are shown in Figure 2 and demonstrated a calculated maximum concentration (C_{max}) of 11.99 mg/L, AUC_{0-24} of 43.33 mg·hr/L, k_e of 0.26 hr⁻¹, $t_{1/2}$ of 2.68 hr, Vd of 10.04 L (2.92 L/kg, using the patient's dosing weight 3.43 kg), CL_T of 43.47 mL/min (2.61 L/hr), and CL_{CVH} of 6.75 mL/min. Pharmacokinetics for collection period 2 (after 5 presumed half-lives) demonstrated a calculated C_{max} of 10.31 mg/L, a calculated minimum concentration of 7.22 mg/L, an AUC_{0-6} of 52.55 mg·hr/L, a k_e of 0.06 hr⁻¹, $t_{1/2}$ 10.7 hr, Vd 17.5 L (5.1 L/kg), and CL_T 17.44 mL/min. The sieving coefficient average for each time point during collection period 1 was 1.17 (range, 1.07–1.37). A 19.1% decline in ribavirin concentrations was measured between prefilter and postfilter oxygenator samples.

Discussion

Our ribavirin dosing resulted in plasma ribavirin concentrations that ranged between 7.22 and 10.31 mg/L during maintenance dosing (16 mg/kg/dose IV every 6 hr), which is sufficient to prevent RSV replication^{10,12} and

is well below the concentrations known to produce cytotoxic effects.¹¹ Aebi et al¹⁷ described detectable plasma steady-state concentrations ranging from 8.47 to 4.81 mg/L using IV ribavirin 5 mg/kg per dose IV every 6 hr to treat disseminated adenovirus in a neonate receiving ECMO and hemofiltration. Additionally, we measured a 19% decrease between preoxygenator and postoxygenator plasma values, a finding not previously reported. Drug loss within an ECMO circuit has been previously attributed to the tubing,¹⁸ as well as correlated to the log p or lipophilicity of the medication.¹⁹ Medications that are more lipophilic and have a higher positive log p value are more likely to have drug sequestration within the ECMO circuit. A study by Wildschut et al¹⁹ found that a log p value of -1.85, like ribavirin, should be associated with approximately 30% drug loss, but they did not specify which component(s) may be responsible for the loss. It is unclear, however, if these comparisons would continue to be true, given the likely differences within our current ECMO setup and the setups used within these prior studies.

The calculated sieving coefficient 1.17 is unusual, because the sieving coefficient should not exceed 1. Aebi et al¹⁷ did describe an average sieving coefficient of 0.85 in their report; however, individual calculations ranged from 0.67 to 1.04. A sieving coefficient that approaches 1 indicates free passage across the dialysis membrane, and ribavirin's small molecular size and absent protein binding would support this phenomenon. It is possible that our sampling included drug that was cleared through the ultrafiltrate earlier in the dosing cycle when plasma concentrations were higher, resulting in falsely elevated ultrafiltrate concentrations

Figure 2. Measured and extrapolated plasma ribavirin versus time profile for collection period 1. Time points hours 0 through 6 are observed. Time points hours 8 through 24 are extrapolated.

when compared to the corresponding plasma sample. Additionally, we compared our ultrafiltrate concentration to a prehemofilter plasma concentration and did not include any simultaneous posthemofilter plasma concentrations in this calculation, making the sieving coefficient calculation less robust; however, our individual calculations have less variability than those previously reported.¹⁷

We calculated an apparent Vd of 10.04 L (2.92 L/kg) during collection period 1 and 17.5 L (5.1 L/kg) during collection period 2. These values are quite different from each other and may be accounted for by the reduced intrinsic elimination as the patient's urine output decreased from 0.91 mL/kg/hr during collection period 1 to 0.09 mL/kg/hr during collection period 2. Our results are somewhat lower than a prior pharmacokinetics study that calculated a Vd of 8.2 L/kg in 17 adult men,⁷ but they are perhaps more consistent with the Vd 4.64 L/kg calculated from 9 children,¹⁵ although both of the prior studies lacked patients who were on ECMO, on CVVH, or had renal impairment. In the most comparable report done by Aebi et al,¹⁷ describing IV ribavirin in a neonate receiving ECMO and hemofiltration, the calculated Vd was much smaller at 1.37 L/kg. Ribavirin is known to accumulate in erythrocytes,⁷ and these authors attributed their relatively low Vd to loss of the erythrocyte compartment due to intravascular hemolysis, but they do not¹⁷ comment on what degree of hemolysis is present during their report. Our patient had no laboratory evidence of significant hemolysis, and this may account for the calculated Vd that is larger than for this similar patient. The relatively large Vd would make drug removal by renal replacement therapies more difficult and would appear to be a minor

route of drug clearance. The CL_{CVVH} of 6.75 mL/min only accounts for approximately 15% of the CL_T of ribavirin despite free passage across the dialysis membrane.

Our data have several limitations. First, this is a single-patient case report, and the results that we have obtained may be difficult to extrapolate to other centers or to other patients with different ECMO and renal replacement therapy components. Second, ECMO circuitry has evolved, and much of the historical data that we were able to find as a comparison may be less applicable to our current setup and patient case. For example, the most recent case reported of ribavirin sampling during ECMO was published in 1997,¹⁷ highlighting the fact that this information is needed with modern equipment. Third, we recognize that patients who are this critically ill may never truly achieve a pharmacokinetic steady state; therefore, our sampling may better reflect the patient's specific physiologic time point and not a true steady state. Likewise, obtaining an accurate patient weight can be a challenge while on ECMO, and large fluctuations in a patient's weight and fluid status may influence pharmacokinetics, in particular Vd. Additionally, we did not obtain any samples directly from the patient and have assumed that the samples obtained via the ECMO circuit would be reflective of plasma concentrations achieved within the patient's circulating blood. Finally, the respiratory samples taken from the patient report viral loads as a qualitative and not a quantitative result, and therefore we do not have any direct measurement of viral clearance, although we were able to use cycle times to provide an estimate of the viral load.

In conclusion, clinical improvement and reduction in viral load after IV ribavirin therapy were noted in our patient while receiving simultaneous VV-ECMO and CVVH

for concomitant PIV and RSV LRTI. Standard dosing as approved by the eIND was shown to maintain plasma ribavirin concentrations that are known to inhibit RSV and PIV replication. Hyperuricemia is a known adverse event following ribavirin administration, and we elected to measure uric acid plasma concentrations daily given the unknown nature of drug disposition in our patient. We did note an elevated uric acid concentration 2 days after the completion of IV ribavirin therapy, which was treated with a single dose of rasburicase. This may have been attributable to the ribavirin; however, no toxicity requiring drug modification or discontinuation was observed during the time period of drug administration. Additional studies are needed to confirm these first-of-their-kind results.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Acknowledgment The authors would like to acknowledge W. Joshua Frazier, MD, and Ashley Hodge MBA, CCP, FPP, for their review and contributions to this manuscript.

Accepted January 15, 2018

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