JPPT | Laboratory-Based Simulation Study

Impact of Extracorporeal Membrane Oxygenation Circuitry on Remdesivir

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OBJECTIVES This study aimed to determine the oxygenator impact on alterations of remdesivir (RDV) in a contemporary neonatal/pediatric (1/4-inch) and adolescent/adult (3/8-inch) extracorporeal membrane oxygenation (ECMO) circuit including the Quadrox-i oxygenator.

METHODS One-quarter–inch and a 3/8-inch, simulated closed-loop ECMO circuits were prepared with a Quadrox-i pediatric and Quadrox-i adult oxygenator and blood primed. Additionally, 1/4-inch and 3/8-inch circuits were also prepared without an oxygenator in series. A 1-time dose of RDV was administered into the circuits and serial preoxygenator and postoxygenator concentrations were obtained at 0 to 5 minutes, and 1-, 2-, 3-, 4-, 5-, 6-, 8-, 12-, and 24-hour time points. The RDV was also maintained in a glass vial and samples were taken from the vial at the same time periods for control purposes to assess for spontaneous drug degradation.

RESULTS For the 1/4-inch circuits with an oxygenator, there was a 35% to 60% RDV loss during the study period. For the 1/4-inch circuits without an oxygenator, there was a 5% to 20% RDV loss during the study period. For the 3/8-inch circuit with and without an oxygenator, there was a 60% to 70% RDV loss during the study period.

CONCLUSIONS There was RDV loss within the circuit during the study period and the RDV loss was more pronounced with the larger 3/8-inch circuit when compared with the 1/4-inch circuit. The impact of the oxygenator on RDV loss appears to be variable and possibly dependent on the size of the circuit and oxygenator. These preliminary data suggest RDV dosing may need to be adjusted for concern of drug loss via the ECMO circuit. Additional single- and multiple-dose studies are needed to validate these findings.

ABBREVIATIONS ECMO, extracorporeal membrane oxygenation; RDV, remdesivir

KEYWORDS drug sequestration; extracorporeal membrane oxygenation; oxygenator; pharmacodynamic; pharmacokinetics; quadrox; remdesivir

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Introduction

Remdesivir (RDV) is a monophosphoramidate nucleoside analog prodrug with antiviral activity against human and zoonotic coronaviruses, including severe acute respiratory syndrome coronavirus 1 and 2, and Middle East Respiratory Syndrome coronavirus.[1–3] Remdesivir received US Food and Drug Administration approval in January 2022 for adults and pediatric patients ages 12 years and older for the treatment of COVID-19 in conjunction with a positive result for severe acute respiratory syndrome coronavirus 2, and subsequently, in April 2022, RDV also gained US Food and Drug Administration approval for pediatric patients ages ≥28 days and weighing ≥3 kg.[3]

According to the World Health Organization COVID-19 dashboard, as of May 23, 2023, there have been more than 750 million confirmed cases of COVID-19, with approximately 6.9 million deaths globally.[4] The pneumonia associated with COVID-19 can lead to respiratory failure with profound hypoxemia requiring endotracheal intubation and mechanical ventilation with rates ranging between 29% and 90%.[5,6] Moreover, estimates of COVID-19–induced myocardial injury have been shown to occur in up to 60% of patients hospitalized and can induce cardiogenic shock unresponsive to medical management.[7,8] Patients who do not respond to optimal conventional mechanical ventilation or pharmacologic intervention may be candidates for management with extracorporeal membrane oxygenation (ECMO).[9]

To date, no clinical trials have been conducted to assess the pharmacokinetics or pharmacodynamics of RDV in patients receiving ECMO support. Therefore, the purpose of this study was to determine the alterations of RDV in a contemporary neonatal/pediatric and adolescent/adult ECMO circuit with and without the Quadrox-i oxygenator in series.

Materials and Methods

Our methodology has been previously published,[10–14] but in brief, 1/4-inch (n = 1) and 3/8-inch (n = 1), simulated closed-loop ECMO circuits were prepared using custom tubing with 1/4-inch diameter and 3/8-inch diameter, made of polyvinylchloride and super Tygon with Cortiva BioActive surface coating (Medtronic Inc, Minneapolis, MN), 3/8-inch diameter circuits used the Sorin RevOlution blood pump with PC coating (Sorin Group Italia SRL, Milan, Italy), and a Quadrox-i Peds and a Quadrox-i Adult membrane oxygenator (Maquet, Wayne, NJ), respectively, with Bioline coating, with a total length of 20 feet for the 1/4-inch circuit and 20 feet for the 3/8-inch circuit. Each coated circuit was crystalloid primed. The 1/4-inch circuit was primed with approximately 400 mL of crystalloid, and the 3/8-inch circuit was primed with approximately 700 mL of crystalloid. After debubbling the circuit, 10 mL of 5% albumin was added to the 1/4-inch circuit and 30 mL of 5% albumin was added to the 3/8-inch circuit. The initial crystalloid/albumin prime was then displaced with packed red blood cells (2 units for the 1/4-inch circuit and 3 units for the 3/8-inch circuit), sodium bicarbonate (30 mEq for 1/4-inch and 45 mEq for 3/8-inch), heparin (200 units for 1/4-inch and 300 units for 3/8-inch), and calcium gluconate (2 g for 1/4-inch and 3 g for 3/8-inch). The closed-loop design was established by connecting the ends of the arterial and venous tubing to a reservoir bag, allowing continuous flow of the priming fluid around the circuit. The flow rates within the circuits remained steady for the duration of the experiment at 1 L/min for the 1/4-inch circuit and 2 L/min for the 3/8-inch circuit. Using the simulated closed-loop ECMO circuits, RDV concentrations were obtained from access ports before and after oxygenator (see Supplemental Figure 1) at the following time intervals: 0 to 5 minutes (right after drug administration), and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours. Likewise, 1/4-inch (n = 1) and 3/8-inch (n = 1), simulated closed-loop ECMO circuits were also prepared without an oxygenator in series, and concentrations of RDV were obtained from the same 2 access ports (labeled preoxygenator and postoxygenator, see Supplemental Figure 2) as stated above to obtain 2 concentrations at the same time intervals to determine the impact of the ECMO circuitry without the oxygenator on RDV alterations within the ECMO circuit. The purpose of obtaining 2 samples at each time point was to assess for recirculation or redistribution phenomena during the course of the experiment at a given time point that may occur before and/or after oxygenator and to attempt to determine the degree of oxygenator binding and/or saturation during the experiment. A second sample allows for a higher degree of confidence in the concentration results and to determine whether a single result may be a spurious finding. Using the estimated circuit volume of 400 mL for the 1/4-inch circuit and 700 mL for the 3/8-inch circuit, 4 mg of RDV was added to the 1/4-inch circuit and 7 mg of RDV was added to the 3/8-inch circuit, respectively, for an estimated initial target concentration of 10 mg/L RDV. The 10 mg/L plasma concentration was chosen based on the *in vivo* peak concentration range for RDV that is obtained clinically with current dosing recommendations in an effort to obtain concentrations within the experimental circuit to compare with the range of *in vivo* clinical values.[3] Also, a 5 mg/mL vial of RDV was maintained for control purposes. The purpose of the reference control vial is to estimate whether there is spontaneous drug degradation at room temperature under the same conditions as the experiment.

Blood samples for RDV determination were collected in regular red top tubes, and a plastic vacutainer containing a clot activator but no anticoagulant, preservatives, or separator material, and subsequently taken to the lab for immediate processing. Upon receipt in the laboratory, samples were centrifuged within 30 minutes of collection at 3000 rpm for at least 15 minutes to separate the plasma. Separated plasma was then transferred to a cryovial and stored at −80°C until concentration determination. Remdesivir samples were analyzed by validated liquid chromatography tandem mass spectrometry (US Food and Drug Administration guidelines: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic Laboratories (Bensalem, PA). The liquid chromatography tandem mass spectrometry method was accurate and precise at a linearity range of 1 to 30 mg/mL with a correlation coefficient (r) of ≥0.99 and an interday assay variability that was less than 4% across all control samples and an intraday assay variability that was less than 10% across all control samples.

Remdesivir data were plotted (plasma concentration versus time) and analyzed. To calculate the percentage of drug recovered from the circuit, the drug concentration remaining at each time point and at 24 hours and performed a paired assessment for differences at each plasma concentration time point. A paired t test and/or analysis of variance testing with a post hoc Tukey test were performed to assess differences in drug concentrations and recovery during the study period in addition to differences between the 1/4-inch and 3/8-inch circuits with and without an oxygenator in series. Statistical significance was defined as a p value <0.05. All analyses were performed using IBM SPSS Version 24 (IBM SPSS Inc, Chicago, IL).

Results

The plasma concentration versus time profile for RDV in the 1/4-inch ECMO circuit with the Quadrox-i Peds oxygenator is presented in Figure 1 and without an oxygenator is presented in Figure 2. For the 1/4-inch ECMO circuit with oxygenator, there was 35% to 60% drug loss during the study period. For the 1/4-inch ECMO circuit with oxygenator, there was

Figure 1. Graph of the mean percent of remdesivir remaining of preoxygenator, postoxygenator, and reference concentrations versus time in a 1/4-inch extracorporeal membrane oxygenation circuit with a Quadrox-i pediatric oxygenator.

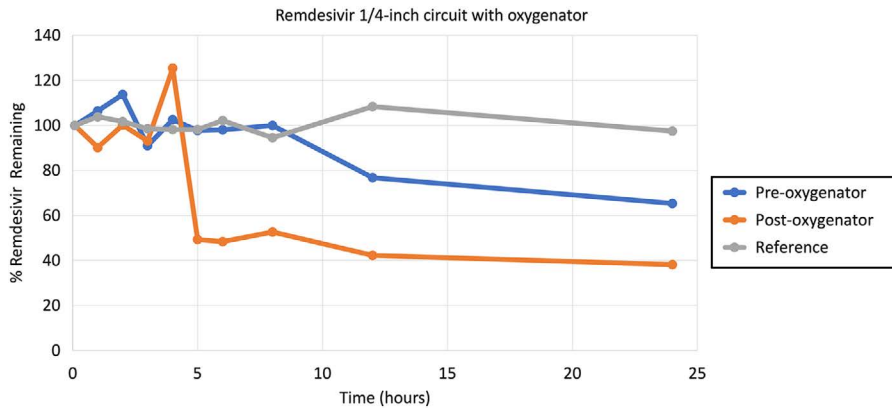
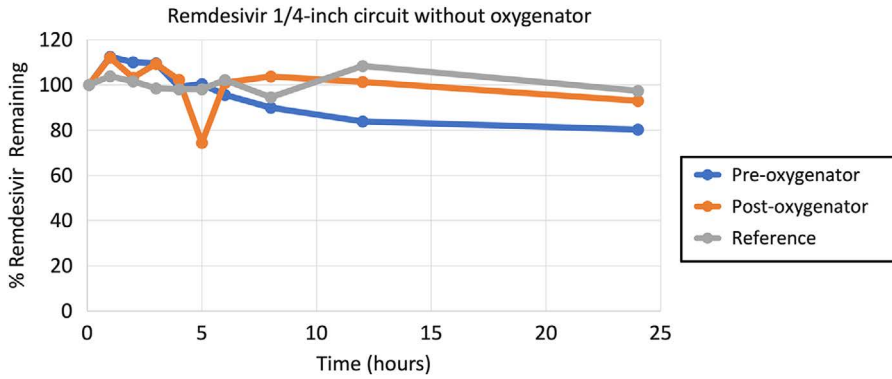


Figure 2. Graph of the mean percent of remdesivir remaining of preoxygenator, postoxygenator, and reference concentrations versus time in a 1/4-inch extracorporeal membrane oxygenation circuit without a Quadrox-i pediatric oxygenator.



a statistically significant difference in drug loss from hour 0 to hour 24, $p < 0.01$. For the 1/4-inch ECMO circuit without oxygenator, there was 5% to 20% drug loss during the study period. For the 1/4-inch ECMO circuit without oxygenator, there was not a statistically significant difference in drug loss from hour 0 to hour 24, $p = 0.67$. For the comparison of drug loss between the 1/4-inch circuit with and without an oxygenator, there was a statistically significant difference, $p < 0.01$. The concentration versus time profile for RDV in the 3/8-inch ECMO circuit with the Quadrox-i adult oxygenator is presented in Figure 3 and without an oxygenator is presented in Figure 4. For the 3/8-inch ECMO circuit with and without oxygenator, there was 60% to 70% drug loss during the study period. For the 3/8-inch ECMO circuit with and without oxygenator, there was a statistically significant difference in drug loss from hour 0 to hour 24, $p < 0.01$. For the comparison of drug loss between the 3/8-inch circuit with and without an oxygenator, there was not a statistically significant difference, $p = 0.73$.

Discussion

This investigation demonstrated RDV loss during the 24-hour study period in closed-loop 1/4-inch and 3/8-inch ECMO circuits regardless of the presence of an oxygenator, and the RDV loss was more pronounced with the larger 3/8-inch ECMO circuits. The amount of RDV loss in the 3/8-inch circuit in this investigation is similar to the results demonstrated by Imburgia and colleagues.[15] Extracorporeal membrane oxygenation has been employed during other pandemics, notably the outbreaks of Middle East Respiratory Syndrome coronavirus in 2012, and Influenza A (H1N1) in 2009.[16–19] Reports from these pandemics indicated ECMO can improve oxygenation and ventilation, as well as reduce mortality in younger infected patients with very severe lung

Figure 3. Graph of the mean percent of remdesivir remaining of preoxygenator, postoxygenator, and reference concentrations versus time in a 3/8-inch extracorporeal membrane oxygenation circuit with a Quadrox-i pediatric oxygenator.

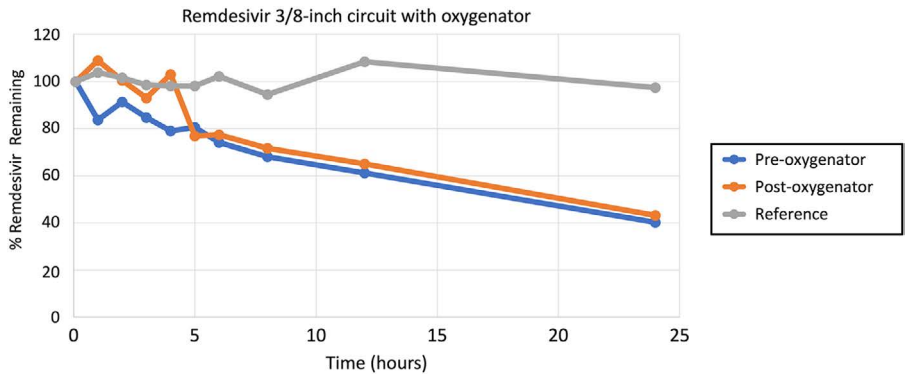
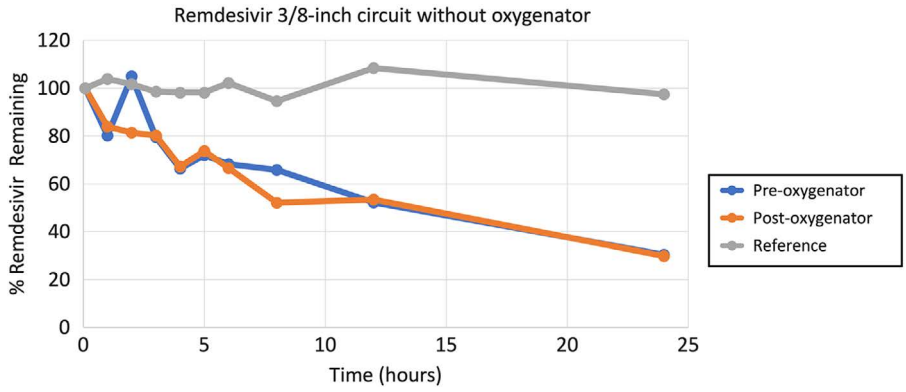


Figure 4. Graph of the mean percent of remdesivir remaining of preoxygenator, postoxygenator, and reference concentrations versus time in a 3/8-inch extracorporeal membrane oxygenation circuit without a Quadrox-i pediatric oxygenator.



dysfunction. A multicenter French study of 83 patients with COVID-19–related acute respiratory distress syndrome managed with ECMO revealed an estimated 60-day mortality of 31%.[20,21] Subsequently, data from the Extracorporeal Life Support Organization Registry reported an estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation of 37.4%. This report included 1035 patients with COVID-19 who received ECMO in 36 countries.[21,22] An additional observational study reported 45% mortality for 1531 patients from 177 centers in Europe and Israel.[21,23] The possibility exists that some of the excess mortality could be due to reduced RDV systemic exposures while receiving ECMO and possibly other extracorporeal therapies.[15] Treatment with RDV for COVID-19 has been associated with reduced mortality, and understanding the effects of the ECMO circuitry on RDV is critical to ensuring patients receive appropriate RDV systemic exposures that have been associated with improved outcomes.[24,25]

Several factors can affect drug pharmacokinetics with ECMO, including the composition and configuration of the circuit, the individual drug, and the clinical status of patient, including organ function.[26] The Quadrox-i oxygenators are composed of a polymethylpentene microporous fiber material and a polyurethane heat exchanger with a large surface area–to-size ratio that may affect the amount of drug sequestration.[27] The octanol/water partition coefficient (logP) provides information regarding the lipophilicity of a particular drug.[28] As lipophilicity increases, the logP value becomes more positive. Historically, as the logP increased (i.e., more positive, higher lipophilicity) the amount of drug sequestration increased. This was thought to occur because of the higher solubility of lipophilic compounds in the organic components of the ECMO circuit.[11–14,29] However, this belief has not been confirmed with polymethylpentene oxygenators. The log P of RDV is 3.2, although the log P of GS-441524 is −1.79.[28] The protein binding of RDV is as high as

87.9%, and drugs with higher protein binding historically were found to have higher losses despite similar lipophilicity.[3]

To our knowledge, there are no robust data regarding the effects of ECMO on RDV. Ide and colleagues[30] reported on a 63-year-old American man who underwent mechanical ventilation and ECMO for severe COVID-19 who received RDV for 10 days.[30] The peak plasma concentrations of RDV and GS-441524 were 3220 and 231 ng/mL, respectively, which the authors noted were lower than previous non-ECMO investigations.[31,32] Furthermore, the authors noted the RDV plasma concentration was not within the quantification limit, although blood samples were obtained 18 hours after administration.

We also reported RDV pharmacokinetic data for 3 critically ill adolescents, 1 of whom was on ECMO during RDV treatment.[33] These 3 patients contributed 74 samples for determination of RDV and the active GS-441524 metabolite. The median age was 16 years (IQR, 15.5–16) with a median weight of 76.4 kg (IQR, 74.9–94.3). Patient 1 received ECMO support for the duration of RDV therapy. Patients 1 and 2 received RDV for 10 days with plasma concentrations obtained daily. Patient 3 received RDV for 5 days with plasma concentrations determined daily. For all patients, mean RDV exposures ranged from 272 to 893 ng/mL and were below the mean exposures reported in the RDV investigators brochure of 2900 to 7800 ng/mL.[3] Patient 1 received ECMO, and RDV exposures did not appear affected by ECMO when compared with patients 2 and 3, who did not receive ECMO. For all patients, the mean GS-441524 exposures ranged from 109 to 258 ng/mL and approximated the mean exposures reported in the RDV investigators brochure, range of 69 to 184 ng/mL. Similarly, the GS-441524 exposure did not appear to be affected by ECMO.

Acute kidney injury is frequently observed during ECMO therapy, which can affect mortality, with 1 adult investigation suggesting a reported 4-fold increase in mortality rate and a mortality odds ratio increase of 1.7 to 3.2 for neonatal and pediatric ECMO patients.[34–37] For patients with an estimated glomerular filtration rate >30 mL/min, no RDV dosing adjustments are required.[3] The package insert does not provide guidance for dosing adjustments when the estimated glomerular filtration rate is <30 mL/min; however, a dosing adjustment may be needed depending whether dialysis is being used. In a pharmacokinetic observation of a single patient receiving intermittent hemodialysis and a 5-day course of RDV, GS-441524 reached high but stable plasma concentrations, with dialysis reducing these plasma drug concentrations by ~50%.[38] We also reported an observational study of 3 patients with end-stage kidney disease receiving hemodialysis who received 5-day courses of RDV. The RDV half-lives were approximately doubled compared with healthy volunteers (~2 hours versus ~1 hour), but concentrations were undetectable by the end of the dosing interval. GS-441524 concentrations were 10-fold higher than the day 5 Cmax in healthy volunteers (1470 versus 142 ng/mL), and hemodialysis reduced concentrations by 45% to 49%.[39] Remdesivir has also been shown to be removed by continuous renal replacement therapy circuitry, with 1 estimate of ~96% removal.[15] Because dialysis is often employed for acute kidney injury in the setting of ECMO, understanding the effects of dialysis on RDV is important. The possibility exists that standard dosing in the setting of dialysis and/or ECMO may not result in the RDV exposures that have been associated with improved outcomes.[24,25]

As described previously with similar work,[10–13] there are several limitations of this investigation. First, this was an observational study with a small sample size. Second, a single dose of RDV was used and the effects of repeated dosing could not be evaluated. Third, because a single dose of RDV was used, the effects of circuit age and potential saturation of RDV within the ECMO circuit could not be evaluated. Fourth, patient factors such as renal elimination could not be evaluated. Fifth, regarding the set flow rate for the experiment, this could have resulted in some stasis within the adult circuit. Additionally, this could have also contributed to the redistribution phenomenon where drug is sequestered in the bladder or within the oxygenator (unrelated to stasis) and subsequently released into the circuit, which is why 2 specimens per time point are obtained. Sixth, the effect of the ECMO circuitry on the active GS-441524 metabolite was not able to be determined from an *in vitro* study. Commonly, the presumption of clinicians is the drug concentration is the same throughout the circuit, but this may not be accurate. Despite these limitations, this investigation provides interesting insight into the effects of ECMO circuitry, specifically the oxygenator, on RDV alterations and can be used to guide future experiments with RDV and other anti-infectives.

Conclusion

This *ex vivo* investigation demonstrated RDV loss within the circuit during the study period, and the RDV loss was more pronounced with the larger 3/8-inch circuit when compared to the 1/4-inch circuit. The impact of the oxygenator on RDV loss appears to be variable and possibly dependent on the size of the circuit and oxygenator. These preliminary data suggest RDV dosing may need to be adjusted for concern of drug loss via the ECMO circuit and plasma drug concentration monitoring should be considered in the setting of ECMO. Further evaluations with multiple-dose *in vitro* and *in vivo* investigations are needed before specific drug dosing recommendations can be made for RDV's clinical application with ECMO.

Article Information

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