Original Manuscript

Perfusion

Oxygenator impact on peramivir in extra-corporeal membrane oxygenation circuits

Perfusion
2022, Vol. 0(0) 1–6

DOI: 10.1177/02676591211060975
journals.sagepub.com/home/prf
SAGE

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Abstract

Introduction: This study aims to determine the oxygenator impact on alterations of peramivir (PRV) in a contemporary neonatal/pediatric (1/4-inch) and adolescent/adult (3/8-inch) extra-corporeal membrane oxygenation (ECMO) circuit including the Quadrox-i® oxygenator.

Methods: 1/4-inch and 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 one-time dose of PRV was administered into the circuits and serial pre- and post-oxygenator concentrations were obtained at 5-min and 1-, 2-, 3-, 4-, 5-, 6-, 8-, 12-, and 24-h time points. PRV 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-in. circuit with an oxygenator, there was < 15% PRV loss, and for the 1/4-in. circuit without an oxygenator, there was < 3% PRV loss during the study period. For the 3/8-in. circuits with an oxygenator, there was < 15% PRV loss, and for the 3/8-in. circuits without an oxygenator, there was < 3% PRV loss during the study period.

Conclusion: There was no significant PRV loss over the 24-h study period in either the 1/4-in. or 3/8-in circuit, regardless of the presence of the oxygenator. The concentrations obtained pre- and post-oxygenator appeared to approximate each other, suggesting there may be no drug loss *via* the oxygenator. This preliminary data suggests PRV dosing may not need to be adjusted for concern of drug loss *via* the oxygenator. Additional single and multiple dose studies are needed to validate these findings.

Keywords

extra-corporeal membrane oxygenation, pharmacokinetics, pharmacodynamic, drug sequestration, peramivir oxygenator, Quadrox

Introduction

Influenza is a highly infectious, acute respiratory illness that causes significant morbidity and mortality in children and adults in the United States and globally.[1,2] Annually, influenza affects 5–20% of the population, resulting in 25–50 million cases, 225,000 hospitalizations, and 36,000 deaths in the United States alone.[2,3] Globally, the World Health Organization (WHO) estimates 20% of the population is infected with influenza each year, causing up to one billion infections, three-to-five-million cases of severe disease, and up to 300,000–500,000 deaths.[2,4] Additionally, severe acute respiratory failure has a high mortality despite advances in intensive care management.[5,6] Extra-corporeal membrane oxygenation (ECMO) uses cardiopulmonary bypass technology to support gas exchange in severe acute respiratory failure. ECMO has been used globally since the 2009 novel influenza A (H1N1) pandemic to support patients of all ages with influenza-induced respiratory failure.[5,7]

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In October 2009, the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization for peramivir (PRV) during the H1N1 pandemic.[8,9] Ultimately, in December 2014, PRV was approved by the FDA and is currently indicated for the treatment of acute, uncomplicated influenza in patients ≥ 6 months of age who have been symptomatic for ≤ 2 days.[10] PRV is an intravenous influenza virus neuraminidase (NA) inhibitor that prevents viral growth by selectively inhibiting the NA in human influenza A and B viruses. Despite the lack of an FDA-approved indication, PRV is utilized in severe cases of influenza-induced respiratory failure, including cases requiring ECMO support.[2] To date, no clinical trials have been conducted to assess the pharmacokinetics and pharmacodynamic of PRV in patients receiving ECMO support. Therefore, the purpose of this study was to determine the alterations of PRV 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,[11–14] but in brief, 1/4-inch (n = 2) and 3/8-inch (n = 2), 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 S.R.L., 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. 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, sodium bicarbonate, heparin, and calcium gluconate. 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/minute for the 1/4-inch circuit and 2 L/minute for the 3/8-inch circuit. Utilizing the simulated closed-loop ECMO circuits, levels of PRV were obtained pre- and post-oxygenator at the following time intervals: 0–5 min (right after drug administration) and 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. Additionally, 1/4-inch (n = 2) and 3/8-inch (n = 2), simulated closed-loop ECMO circuits were also prepared without an oxygenator in series, and levels of PRV were obtained from the same two access ports as stated above to obtain two concentrations at the same time intervals to determine the impact of the oxygenator on PRV alterations within the ECMO circuit. The purpose of obtaining two samples at each time point was to assess for re-circulation or re-distribution phenomena over the course of the experiment at a given time point that may occur pre- and/or post-oxygenator and to attempt to determine the degree of oxygenator binding and/or saturation during the experiment. Additionally, a second sample allows for a higher degree of confidence in the concentration results and to determine whether 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, 20 mg of PRV was added to the 1/4-inch circuit and 35 mg of PRV was added to the 3/8-inch circuit, respectively, for an estimated initial target concentration of 50 mg/L of PRV. The 50 mg/L concentration was chosen based on the *in-vivo* peak concentration range for PRV of 38–61 mg/mL 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.[10] Additionally, a 200-mg/20-mL vial of PRV 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 those of the experiment.

Samples for PRV determination were collected in regular red top tubes, 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 min of collection at 3000 rpm for at least 15 min to separate the plasma. Separated plasma was then transferred to a cryovial and stored at −80°C until concentration determination. PRV samples were analyzed by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) (United States Food and Drug Administration guidelines: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic Laboratories (Bensalem, PA). The LC-MS/MS method was accurate and precise at a linearity range of 1–60,000 ng/mL with a correlation coefficient (r) of ≥ 0.99 and an inter-day assay variability that was less than 4% across all control samples and an intra-day assay variability that was less than 10% across all control samples.

PRV data were plotted (concentration vs time) and analyzed. To calculate the percentage of drug recovered from the circuit, the drug concentration remaining at each time point and at 24 h was divided by the total PRV

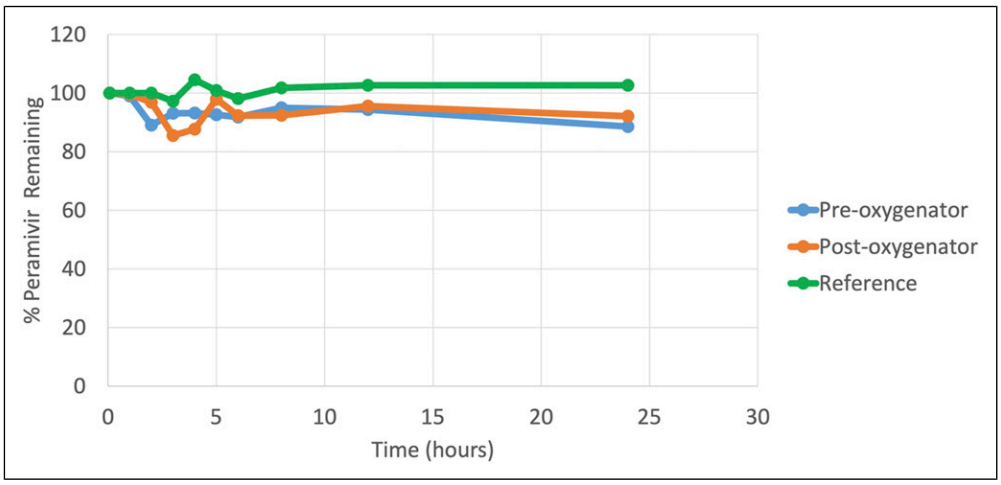

Figure 1. Graph of the mean percent of peramivir remaining of pre-oxygenator, post-oxygenator, and reference concentrations versus time in a 1/4-inch extra-corporeal membrane oxygenation circuit with a Quadrox-i pediatric oxygenator.

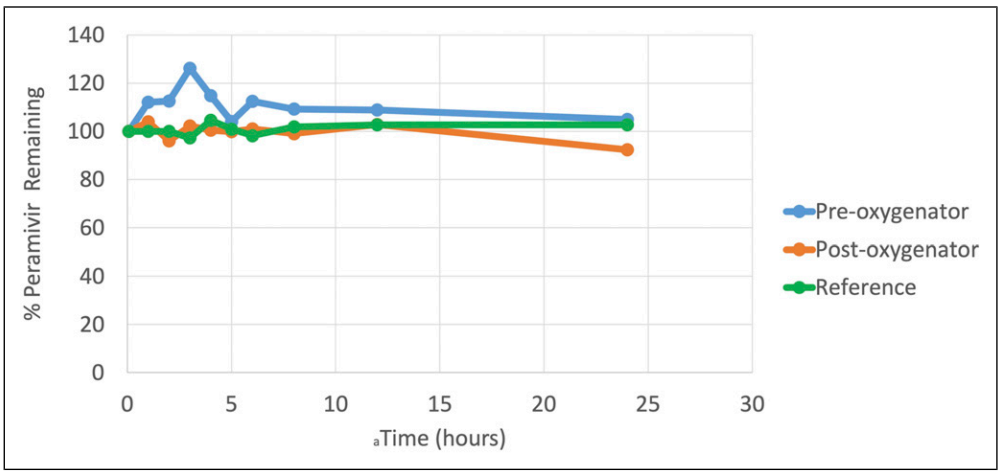

Figure 2. Graph of the mean percent of peramivir remaining of pre-oxygenator, post-oxygenator, and reference concentrations versus time in a 1/4-inch extra-corporeal membrane oxygenation circuit without a Quadrox-i pediatric oxygenator.

concentrations in the circuit, confirmed with the concentration taken immediately after addition of PRV to the circuit. A paired t-test and/or ANOVA testing with a post-hoc Tukey's test were performed to assess differences in drug concentrations and recovery over 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, United States).

Results

The concentration versus time profile for PRV 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 < 10% drug loss during the study period. Similarly, for the 1/4-inch ECMO circuit without oxygenator, there was < 8% drug loss during the study period. The concentration versus time profile for PRV 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 oxygenator, there was < 12% drug loss during the study period for most of the samples tested. For the 24-h post-oxygenator single time point, there was 15% drug loss. For the 3/8-inch ECMO circuit without oxygenator, there was < 5% drug loss during the study period. Overall, there were no statistically significant drug

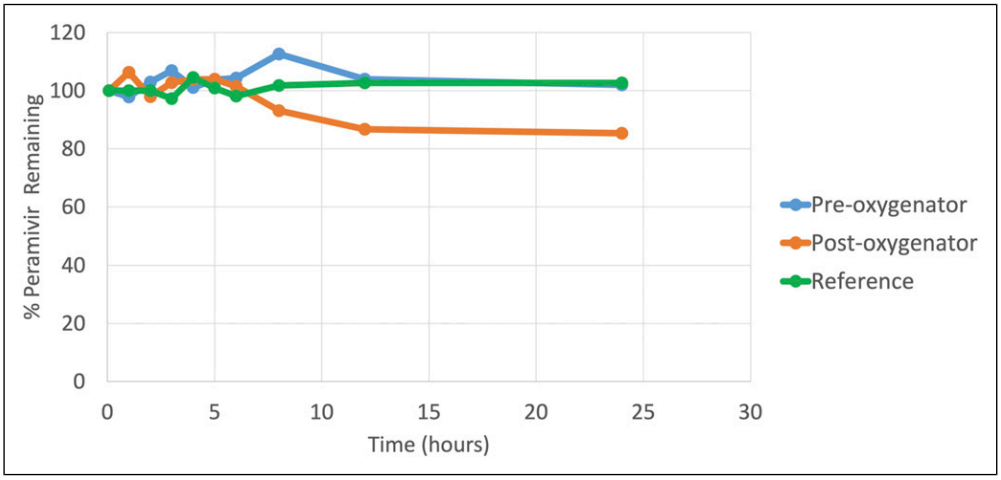

Figure 3. Graph of the mean percent of peramivir remaining of pre-oxygenator, post-oxygenator, and reference concentrations versus time in a 3/8-inch extra-corporeal membrane oxygenation circuit with a Quadrox-i pediatric oxygenator.

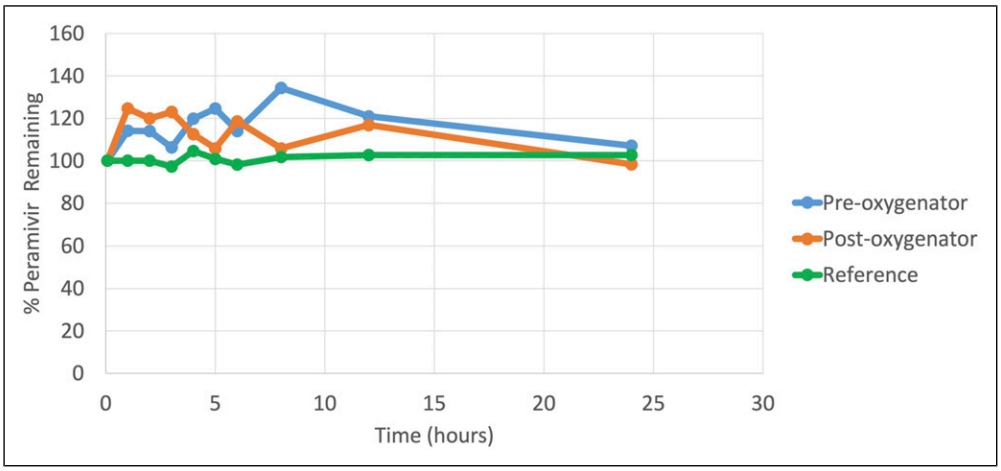

Figure 4. Graph of the mean percent of peramivir remaining of pre-oxygenator, post-oxygenator, and reference concentrations versus time in a 3/8-inch extra-corporeal membrane oxygenation circuit without a Quadrox-i pediatric oxygenator.

losses found within or between circuits for any experiment over the study period.

Discussion

This investigation demonstrated no significant PRV loss over the 24-h study period in closed loop 1/4-inch and 3/8-inch ECMO circuits regardless of the presence of an oxygenator. To our knowledge, there is no robust data regarding the effects of ECMO on PRV. Hernandez[15] and colleagues described the clinical experience of PRV during the 2009 H1N1 pandemic under the emergency investigational new drug (IND) program. Under the IND program, PRV was given to 20 adults and 11 children. Details describing the adults that received PRV while on ECMO were not provided nor were any details describing the PK parameters from any therapeutic drug monitoring (TDM). There was a total of seven pediatric patients that received PRV while on ECMO and only a single report of TDM with PRV. The instance of PRV TDM on ECMO describes a 10-year-old immunosuppressed kidney transplant recipient on ECMO and continuous renal replacement therapy (CRRT).[16] The patient was initially given 2.2 mg/kg every 24 h but required a dose increase to 5.4 mg/kg every 24 h to achieve a target trough concentration > 1.5 mg/mL. Considering standard dosing for a child this age with normal renal function is 10 mg/kg q 24 h, it is unclear why the initial dosage reduction was initiated. While our preliminary data in this report suggests no significant alterations in PRV relating to the ECMO circuitry, dedicated studies of peramivir use with *in-vivo* advanced

forms of life support, including CRRT, will provide valuable information for the care of critically ill adult and pediatric patients, considering PK data for critically ill pediatric patients already exists.[17]

Several factors can affect drug PK with ECMO including the composition and configuration of the circuit, the individual drug, and the clinical status of patient, including organ function.[18] 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 impact the amount of drug sequestration.[19] The octanol/water partition coefficient (logP) provides information regarding the lipophilicity of a particular drug.[20] 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. However, this belief has not been confirmed with polymethylpentene oxygenators. Based on the logP range of −2.1 to −0.27 and protein binding estimate of < 30% for PRV, the expectation would be minimal PRV loss.[10,20] While there was minimal PRV loss based on the logP and protein-binding values, our previous work with ceftaroline (CPT) suggests contemporary circuits may not demonstrate results similar to historical findings. The expected CPT loss in an ECMO circuit would be minimal based on its physiochemical properties with a logP range of −3.7 to −0.79 and a protein-binding estimate of ∼20%. However, our findings demonstrated 76–82.5% CPT loss.[12] The dichotomy between PRV and CPT highlights the need for continued research in this area with contemporary ECMO circuitry.

There are no dosing adjustments recommended in patients with hepatic dysfunction since approximately 90% of PRV is excreted in the urine as unchanged drugs.[10] For patients with an estimated glomerular filtration rate (eGFR) > 50 mL/min, no dosing adjustments are required. Once the eGFR is < 50 mL/min, a dosing adjustment is suggested.[10] Acute kidney injury (AKI) is frequently observed during ECMO therapy which can impact mortality with one adult investigation suggesting a reported 4-fold increase in mortality rate a mortality odds ratio increase of 1.7–3.2 for neonatal and pediatric ECMO patients.[21–24] The guidance provided regarding dosing in renal dysfunction is to reduce the individual mg/kg/dose but to keep the dosing interval the same (i.e., q 24 h).[10] Coupling the physiological changes associated with critical illness, including an increased volume of distribution, with the increased volume of distribution related to ECMO circuitry, we would advise against this strategy. Rather, providing a full therapeutic dose for age, up to 600 mg per dose, and extending the dosing interval to allow for drug elimination would be the preferable dosing strategy to ensure patients obtain therapeutic concentrations with PRV initiation.

As described previously with similar work,[11–14] there are several limitations of this investigation. First, this was an observational study with a small sample size. Second, a crystalloid-primed circuit was not evaluated but this was intentional to simulate the effects of blood within the ECMO circuit as would be seen in clinical practice. Third, a single dose of PRV was given, and the effects of repeated dosing could not be evaluated. Fourth, since a single dose of PRV was given, the effects of circuit age and potential saturation of PRV within the ECMO circuit could not be evaluated. Fifth, patient factors such as renal elimination could not be evaluated. Sixth, for PRV concentration determination, all samples are compared to a reference standard that is freshly prepared the day the study samples are analyzed. As such, since the study sample is being compared to a freshly prepared reference standard, this can allow for concentrations to be "greater" than 100%. As such, since there is no significant loss over the study period; that is why we are concluding the PRV concentrations remained relatively constant. Seventh, 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 re-distribution phenomenon where the drug is sequestered in the bladder or within the oxygenator (un-related to stasis) and subsequently released into the circuit which is why some of the pre-samples are higher than the post samples. This is one of the reasons why two specimens per time point are obtained. Commonly, the presumption of clinicians is the 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 the lack of PRV alterations and can be used to guide future experiments with PRV and other anti-infectives.

Conclusion

This *ex-vivo* investigation demonstrated no significant PRV loss within an ECMO circuit with an oxygenator in series with both sizes of the Quadrox-i oxygenator at 24 h. Further evaluations with multiple dose *in-vitro* and *in-vivo* investigations are needed before specific drug dosing recommendations can be made for clinical application with ECMO.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JJC is a consultant for Atlantic Diagnostic Laboratories and has received grants and/or honoraria from Allergan, Merck, Thermo Fisher Scientific, and Melinta. He also is an advisory board member for DoseMeRx.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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