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Molecular Adsorbent Recirculating System Therapy with Continuous Renal Replacement Therapy Enhanced Clearance of Piperacillin in a Pediatric Patient and Led to Failure to Attain Pharmacodynamic Targets

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Abstract

Molecular Adsorbent Recirculating System (MARS), an extracorporeal support device used in patients with liver failure, specifically removes albumin-bound molecules, including antibiotics. Case reports in adult patients showed that MARS enhances the clearance of piperacillin. However, for those patients, pharmacodynamic targets were achieved when piperacillin/tazobactam was administered as extended infusions over 3–4 hours. In contrast, piperacillin/tazobactam is typically given as short intermittent infusions in children. No reports describe the effect of MARS on piperacillin pharmacokinetics or pharmacodynamic target attainment in pediatric patients with liver failure. In this case report, we describe the effects of MARS on piperacillin clearance and target attainment in a child with liver failure. We found that MARS, in conjunction with continuous renal replacement therapy (CRRT), enhanced the clearance of piperacillin, when compared to CRRT alone (6.4–7.4 L/hr vs. 3.0 L/hr). Pharmacodynamic targets were not attained during MARS/CRRT cycles with free piperacillin concentrations being above 64 µg/mL for less than 50% of dosing intervals, the goal target. We performed simulation analysis to identify a dosing regimen to optimize target attainment. For this patient, doses three times what she received

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over 3-hour extended infusions and an additional dose within 5 hours of cycle initiation, would have led to target attainment throughout MARS/CRRT cycles.

Keywords

Piperacillin; Molecular Adsorbent Recirculating System; Pharmacokinetics; Pharmacodynamics

Introduction

Molecular Adsorbent Recirculating System (MARS) is an extracorporeal liver support system used in adult and pediatric patients with liver failure, who are often awaiting liver transplant.^{1,2} MARS combines continuous renal replacement therapy (CRRT) with albumin filtration, removing both small hydrophilic molecules and albumin-bound molecules. While MARS efficiently removes excess water and albumin-bound toxins, such as bilirubin,² it may inadvertently increase the clearance of protein-bound drugs, which can cause inadequately low drug concentrations.

Piperacillin/tazobactam is a broad spectrum β -lactam antibiotic beta-lactamase inhibitor combination often used in the treatment of abdominal infections and sepsis, and is reported to be 30% protein bound.³ Maintaining appropriate antibiotic concentrations for beta-lactams is vital for bactericidal activity. Previous case reports in adults have shown enhanced clearance of piperacillin, the active antimicrobial portion of the drug combination, in patients undergoing MARS therapy, with up to 50% of the drug being removed by the system.^{4,5} Attaining a pharmacodynamic (PD) target where free piperacillin concentrations remain above four times the minimum inhibitory concentration for at least 50% of the dosing interval (50% $fT > 4 \times \text{MIC}$) is suggested for bacterial clearance and prevention of bacterial resistance against piperacillin in critically ill patients.^{6,7} In the described adult cases, PD targets were attained when extended infusions over 3–4 hours of piperacillin/tazobactam were administered.^{4,5} However, piperacillin/tazobactam is routinely administered as intermittent infusions (30 minutes) in children, and thus concentrations may not achieve the PD targets. Clinical care providers may pre-emptively increase the number of doses during MARS therapy based on the assumption of increased clearance of the antibiotic, but there are no studies describing the pharmacokinetics (PK) or PD of piperacillin in children during MARS.

In this case report, we describe the piperacillin PK and PD target attainment in a child with liver failure who received MARS/CRRT therapy and intermittent dosing of piperacillin/tazobactam. We also report findings of a PK/PD simulation analysis with proposed dosing regimens to improve the attainment of PD targets throughout MARS therapy.

Case Report

The patient described in this report was enrolled in a prospective observational study of β -lactam antibiotics in critically ill patients that was approved by the Institutional Review Board (IRB). Although IRB approval was obtained, potentially identifiable patient information has been withheld. The patient is a 13 year-old 42-kg female with history of

renal dysfunction and hepatic fibrosis leading to end-stage liver failure who was admitted for sepsis. Her hospital course was complicated by ascites, bacteremia, and portal hypertension. She recovered from her initial bacteremia. However, one day prior to pediatric intensive care unit (PICU) admission, the patient was started on vancomycin and piperacillin/tazobactam for suspected sepsis, with piperacillin/tazobactam dosed at 48 mg/kg (piperacillin component is 89% of dose) over 30 minutes every 8 hours (Figure 1, time zero). This initial lower dosing regimen was administered due to her poor renal function (creatinine clearance of 25 mL/min/1.73m²), as recommended by the clinical pharmacist. Laboratory studies demonstrated blood urea nitrogen-serum creatinine ratio of 72, alanine aminotransferase (ALT) of < 7 unit/L, aspartate aminotransferase (AST) of 18 unit/L, prothrombin time of 13.4 seconds, INR of 1.33, activated partial thromboplastin time of 51.7 seconds, total bilirubin of 2.1 mg/dL, direct bilirubin of 1.3 mg/dL, albumin of 4.4 g/dL fibrinogen of 277 mg/dL, white blood cell count of 15.1 K/ μ L, hemoglobin of 8.5 g/dL and platelet count of 108 K/ μ L.

Due to worsening hepatic encephalopathy and fluid overload, she was transferred to the PICU for MARS/CRRT initiation. She was continued on the initial dosing regimen of 48 mg/kg piperacillin/tazobactam over 30 minutes every 8 hours. After 3 doses of piperacillin/tazobactam, she received her first cycle of MARS/CRRT (blood flow rate and MARS/albumin flow rate: both at 170 mL/min, pre-blood flow replacement rate: 150 mL/hr, dialysate rate: 150 mL/hr, 5.3-hour duration), during which she received one dose of 48 mg/kg of piperacillin/tazobactam over 30 minutes (Figure 1A). She received another 48 mg/kg piperacillin/tazobactam dose over 30 minutes between MARS/CRRT cycles. During the 2nd MARS/CRRT cycle (blood flow rate and MARS/albumin flow rate: both at 150 mL/min, pre-blood flow replacement rate: 150 mL/hr, dialysate rate: 150 mL/hr, duration of 6.0 hours), the clinical pharmacist recommended she receive one dose of 38 mg/kg piperacillin/tazobactam over 30 minutes. Due to concerns for low piperacillin concentrations during a longer MARS/CRRT cycle, this 38 mg/kg dose was administered as a bridge between the initial 48 mg/kg dosing regimen and the adult dosing regimen (3375 mg piperacillin/tazobactam every 6 hours) that would be initiated after completion of MARS therapy. After completion of the 2nd cycle, her piperacillin/tazobactam dosing regimen was increased to 80 mg/kg (standard adult 3375 mg dose) over 30 minutes every 6 hours while on CRRT alone (Figure 1A). The first 80 mg/kg dose was given only 3 hours after the previous dose. Vancomycin levels were followed in real-time and provided an estimate of renal function. Based on the low estimate, it was assumed that the patient had low piperacillin concentrations, which were not measured in real-time, and thus the adult dosing regimen was chosen. Prior to her next MARS/CRRT cycle, her antibiotic regimen was broadened to meropenem and piperacillin/tazobactam was discontinued due to concerns for persistent neurologic symptoms. She was continued on MARS/CRRT while on meropenem until she received a liver transplant three days later.

Methods

The patient was enrolled into a larger study of β -lactam antibiotics in critically ill pediatric patients. In the parent study, an opportunistic sampling approach is used in which residual blood from clinical samples obtained from patients administered one of four β -lactam

antibiotics (cefepime, ceftriaxone, meropenem and piperacillin/tazobactam) are scavenged throughout their PICU admission as described previously.⁸ Residual blood was stored at 4°C for up to 4 days (median: 3 days) before processing. Stability of piperacillin at this temperature and for 3–4 days has been demonstrated previously⁹ and reproduced by our own group (data not shown). Blood was centrifuged (2060 x g, 10–20°C, 10 min) and the supernatant was stored at –80°C until free concentrations were measured.

Piperacillin concentrations were measured using a validated high performance liquid chromatography (HPLC) assay. Sample preparation for *free* β -lactam concentrations in plasma was based on the user guide (Merck Millipore)¹⁰. After centrifugation, a 100 μ L aliquot of filtrate was distributed to an autosampler vial. To this vial, 100 μ L internal standard was added. After mixing, a 10 μ L aliquot of the sample was injected into the HPLC system.

Piperacillin measurement was performed using a linear gradient HPLC with UV detection. The mobile phase was 3% acetonitrile in 50 mM potassium phosphate buffer (pH 4.6). Column temperature was set at 30°C and the flow rate set at 1 mL/min. Linear gradient was carried out from 3% acetonitrile at time 0 and increased to 48% acetonitrile in 10 min. The column was re-equilibrated at 3% acetonitrile for 5 minutes prior to each injection. UV detection of piperacillin and ferulic acid (used as internal standard) were performed at 210 nm and 320 nm, respectively. The lower limit of quantitation of piperacillin was 0.5 μ g/mL. The upper limit of quantitation was 400 μ g/mL. Assay data examined for analytical methods met all criteria recommended by FDA for bioanalytical method validation including accuracy, precision, selectivity, sensitivity, reproducibility, and stability, as previously performed for other medications.¹¹

PK modeling of the concentration vs. time profile during MARS therapy was performed with MWPharm++ (Mediware, Prague, Czech Republic), which can account for variable doses over time, time on and off MARS and/or CRRT, sampling times and drug concentrations.¹² Using a previously published population PK model of piperacillin in critically ill pediatric patients with adjustment of the parameters to reflect free piperacillin concentrations by assuming 30% protein binding,^{3,13} the measured free piperacillin concentrations from the patient were analyzed using Bayesian estimation, and a concentration vs. time profile was generated. Piperacillin clearance prior to MARS or CRRT, during MARS/CRRT cycles, between MARS/CRRT cycles, and during CRRT only were estimated, as well as the percentage of time free piperacillin concentrations were above four times the MIC for each dosing interval (% $fT > 4 \times \text{MIC}$). The volume of distribution and inter-compartment clearance were not estimated and fixed to the population mean value for free piperacillin ($V_1 = 7.7\text{L}$, $V_2 = 6.8\text{L}$, $Q = 8.9\text{ L/hr}$ in a 42-kg patient)¹³ in this analysis due to the limited sparse sampling points. Since the patient did not have any positive cultures and was treated as culture-negative sepsis, the Clinical & Laboratory Standards Institute piperacillin breakpoint for *Pseudomonas aeruginosa* (16 μ g/mL) was used for MIC.¹⁴ Simulations were performed to identify dosing regimens that would allow for optimal PD target attainment.

Results

Through opportunistic sampling, we obtained residual blood from nine clinical samples when the patient was not on any extracorporeal support, three samples while she was on CRRT only, one sample immediately after the completion of the first MARS/CRRT cycle and one sample during the second MARS/CRRT cycle (Figure 1B). The patient's estimated free piperacillin concentrations vs. time profile was derived based on observed free piperacillin concentrations and a population PK model of piperacillin¹³ using Bayesian estimation (Figure 1B). Clearance and % $fT > 4x$ MIC for each dosing interval were estimated during the various phases of care for the patient (Table 1). Prior to the first MARS/CRRT cycle, the clearance was estimated to be 2.1 L/hr. Piperacillin concentrations remained above 4x MIC for 54–92% of the piperacillin/tazobactam dosing intervals, achieving the defined PD target (50% $fT > 4x$ MIC). During the 1st MARS/CRRT cycle, the clearance was estimated to have increased to 6.4 L/hr and the % $fT > 4x$ MIC was only 21%, well below the 50% target. Between the two cycles, clearance decreased to 2.0 L/hr and the % $fT > 4x$ MIC was 62%, above the PD target. During the 2nd MARS/CRRT cycle, the estimated clearance increased to 7.4 L/hr, higher than during the 1st cycle, and the % $fT > 4x$ MIC was only 37%. Although the dose given during the 2nd cycle was decreased, the % $fT > 4x$ MIC was higher than in the 1st cycle since the post-MARS/CRRT piperacillin/tazobactam dose was only 3 hours after the previous dose. While on CRRT alone, the clearance of piperacillin was 3.0 L/hr and the % $fT > 4x$ MIC approached 100%.

Simulation with MWPharm++ was performed to determine dosing regimens that would achieve free concentrations above 4x MIC for nearly 100% of the dosing intervals, the most stringent PD target, during both MARS/CRRT cycles. The recommended dosing regimen for this patient is dependent on the timing between the initiation of MARS/CRRT and the most recent dose, as well as the length of the MARS/CRRT cycle (Figure 2). For this patient, the 1st MARS/CRRT cycle started more than 5 hours after the previous piperacillin/tazobactam dose, therefore a 3-fold higher dose (144 mg/kg of piperacillin/tazobactam) initiated at the beginning of MARS/CRRT and infused over 3 hours would have been recommended. An additional 48 mg/kg piperacillin/tazobactam dose given over 30 minutes five hours after the initiation of MARS/CRRT would have prevented free concentrations from falling below 4x MIC (Figure 3). Since the 2nd MARS/CRRT cycle started within 5 hours of the previous dose, a 3-fold higher dose (114 mg/kg) administered over 3 hours could have been given at any time within the first hour of MARS/CRRT initiation. As long as the 80 mg/kg every 6 hours dosing regimen was initiated immediately after the conclusion of the 2nd MARS/CRRT cycle, free piperacillin concentrations would not have been below 4x MIC for a significant period of time.

Discussion

We demonstrate that MARS, beyond CRRT alone, increases clearance of piperacillin, and substantially contributes to the failure to attain the PD target in a child on MARS/CRRT. This finding is not unexpected given that piperacillin is 30% protein bound³ and MARS removes protein-bound toxins and medications. Consistent with the adult case reports,^{4,5} we show that MARS enhances clearance of piperacillin above that of CRRT alone. This finding

is not surprising given that the patient is an adolescent and whose weight would warrant adult dosing. However, unlike in the adult case reports, the observed free concentrations did not remain above 4x MIC (64 µg/mL) for the entire dosing intervals during MARS/CRRT or for even 50% of the dosing intervals (50% $fT > 4x$ MIC), the recommended pharmacodynamic target. This discrepancy is likely due to both the use of intermittent dosing over 30-min infusions in our patient as compared to the extended infusions of 3–4 hours often used in adults, and the initial lower doses administered to the patient due to her poor baseline renal function. Had the patient grown bacteria with an MIC lower than 16 µg/mL, her dosing regimen may have been sufficient to meet the PD target as we used the CLSI piperacillin breakpoint for *Pseudomonas aeruginosa*.

Based on the hypothesis that MARS will increase the clearance of piperacillin, clinical care providers at our institution often recommend increasing the frequency of piperacillin/tazobactam doses to attain PD targets. However, since therapeutic drug monitoring of β -lactam antibiotics is not routinely done for pediatric patients, it is unknown if empiric changes in doses achieve targets as expected. Renal dysfunction makes dosing recommendations more complex since it is particularly difficult to manage decreased piperacillin clearance when not on extracorporeal dialysis mechanisms and increased clearance when on MARS and/or CRRT. For this patient, a lower piperacillin/tazobactam dose prescribed due to low baseline renal clearance was sufficient when not on MARS and/or CRRT. However, this lower initial dose was not sufficient to attain the PD target during the first MARS/CRRT cycle, even though the increased clearance while on MARS/CRRT (6.4 L/hr) did not reach an average clearance of a child of her weight (13.0 L/hr for free piperacillin) based on population PK studies in critically ill children.¹³

Between MARS/CRRT cycles, her estimated clearance of piperacillin was approximately the same as the estimated piperacillin clearance prior to any MARS/CRRT therapy (2 L/hr vs. 2.1 L/hr). During the time between cycles, there may have been a “rebound” effect in which piperacillin from the peripheral compartment returns to the central compartment (i.e. blood), stabilizing concentrations, as well as hemodynamic changes that might affect clearance as described previously in other drugs.^{15,16} We noted an increase in piperacillin clearance during the 2nd MARS/CRRT cycle (7.4 L/hr) despite lower blood flow and MARS pump/albumin flow rates when compared to the 1st MARS/CRRT cycle (6.4 L/hr). This finding may be due to the timing of sampling, with the clearance of the 1st MARS/CRRT cycle estimated from an observed concentration immediately after completion of the cycle, and the clearance of the 2nd MARS/CRRT cycle estimated from a sample obtained during the cycle. In the latter case, the estimated clearance is driven towards the population mean of the previously published model (13 L/hr in a 42 kg critically ill patient), due to the lack of observed concentrations at elimination phase. We chose to fix the volume of distribution and inter-compartmental clearance to the population mean values due to our limited number of samples and recognize that it is a limitation in our clearance estimations.

We performed simulations for this patient to determine what dosing regimens are required to maintain concentrations above 4xMIC throughout most of the dosing interval while on MARS/CRRT. The stringent PD target would have been achieved if a higher dose was administered over three hours (at the beginning of each MARS/CRRT cycle) and redosed 5

hours later. Validation of the proposed dosing algorithm in patients on MARS/CRRT is necessary, as the algorithm was developed based on this specific patient and may not apply to other critically ill pediatric patients. Our findings provide rationale to conduct a future prospective study to characterize piperacillin PK during MARS/CRRT. Model informed precision dosing, in which previously published population PK models and measured concentrations from patients are used to determine individualized dosing with Bayesian estimation in real time, may be needed to ensure appropriate target attainment throughout therapy.

Conclusion

To our knowledge, this is the first report on the PK and PD of piperacillin in a pediatric patient on MARS/CRRT therapy. We demonstrate that MARS enhanced piperacillin clearance and led to failure to achieve PD targets during MARS/CRRT cycles. Simulation analysis suggests that higher doses administered as extended infusions would allow for PD target attainment, but further validation is needed. More important, our findings provide evidence that antibiotic concentrations should be measured during MARS/CRRT therapy to ensure target attainment, and that model-informed precision dosing may be warranted.

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References

1. Kapoor D Molecular adsorbent recirculating system: albumin dialysis-based extracorporeal liver assist device. *J Gastroenterol Hepatol.* 2002;17 Suppl 3:S280–286. [PubMed: 12472950]
2. Schaefer B, Schmitt CP. The role of molecular adsorbent recirculating system dialysis for extracorporeal liver support in children. *Pediatr Nephrol.* 2013;28(9):1763–1769. [PubMed: 23179193]
3. Pfizer. Zosyn (Piperacillin and Tazobactam for Injection, USP) package insert. Philadelphia, PA, 2012.
4. Ruggero MA, Argento AC, Heavner MS, Topal JE. Molecular Adsorbent Recirculating System (MARS((R))) removal of piperacillin/tazobactam in a patient with acetaminophen-induced acute liver failure. *Transpl Infect Dis.* 2013;15(2):214–218. [PubMed: 23279615]
5. Personett HA, Larson SL, Frazee EN, Nyberg SL, El-Zoghby ZM. Extracorporeal Elimination of Piperacillin/Tazobactam during Molecular Adsorbent Recirculating System Therapy. *Pharmacotherapy.* 2015;35(8):e136–139. [PubMed: 26289310]
6. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med.* 2009;37(3):840–851; quiz 859. [PubMed: 19237886]
7. Taccone FS, Laterre PF, Dugernier T, et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care.* 2010;14(4):R126. [PubMed: 20594297]
8. Girdwood ST, Kaplan J, Vinks AA. Methodologic Progress Note: Opportunistic Sampling for Pharmacology Studies in Hospitalized Children. *J Hosp Med* 2020; 15(2): E1–E3.

9. Mortensen JS, Jensen BP, Zhang M, Doogue M. Preanalytical Stability of Piperacillin, Tazobactam, Meropenem, and Ceftazidime in Plasma and Whole Blood Using Liquid Chromatography-Tandem Mass Spectrometry. *Ther Drug Monit.* 2019;41(4):538–543. [PubMed: 31306394]
10. MilliporeSigma. Centrifree Ultrafiltration Device with Ultracel PL membrane. https://www.emdmillipore.com/US/en/product/Centrifree-Ultrafiltration-Device-with-Ultracel-PL-membrane,MM_NF-4104?ReferrerURL=https%3A%2F%2Fwww.google.com%2F&bd=1 Accessed July 23, 2020.
11. Food and Drug Administration. Bioanalytical Method Validation: Guidance for Industry. U.S. Department of Health and Human Services FDA, Center for Drug Evaluation and Research, Center for Veterinary Medicine, ed. Silver Spring, MD, 2018.
12. Proost JH, Meijer DK. MW/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. *Comput Biol Med.* 1992;22(3):155–163. [PubMed: 1617949]
13. De Cock P, van Dijkman SC, de Jaeger A, et al. Dose optimization of piperacillin/tazobactam in critically ill children. *J Antimicrob Chemother.* 2017;72(7):2002–2011. [PubMed: 28387840]
14. CLSI, ed Performance Standards for Antimicrobial Disk Susceptibility Tests. CLSI standard M02. 13th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
15. Bohler J, Reetze-Bonorden P, Keller E, Kramer A, Schollmeyer PJ. Rebound of plasma vancomycin levels after haemodialysis with highly permeable membranes. *Eur J Clin Pharmacol.* 1992;42(6):635–639. [PubMed: 1623904]
16. Sowinski KM, Magner SJ, Lucksiri A, Scott MK, Hamburger RJ, Mueller BA. Influence of hemodialysis on gentamicin pharmacokinetics, removal during hemodialysis, and recommended dosing. *Clin J Am Soc Nephrol.* 2008;3(2):355–361. [PubMed: 18235142]

A **B**

Figure 1: (A) Timeline of piperacillin/tazobactam doses with respect to MARS/CRRT and CRRT cycles. (B) Fitted free piperacillin concentration vs. time profile for the patient based on observed free piperacillin concentrations and a previous population PK model of piperacillin in critically ill children.¹³

Blue circles and arrows represent time of administration of piperacillin/tazobactam, of which 89% is the piperacillin component. Red circles represent observed free piperacillin concentrations measured from residual blood obtained by opportunistic sampling. Red line represents the fitted concentration curve. The dotted black line represents 4x MIC, for which the piperacillin CLSI breakpoint for *Pseudomonas aeruginosa* was used. TZP: piperacillin/tazobactam; MARS: Molecular Adsorbent Recirculating System; CRRT: Continuous Renal Replacement Therapy; MIC: Minimum Inhibitory Concentration

Dosing at Initiation of MARS/CRRT

Redosing During MARS/CRRT

Figure 2: Algorithm with recommendations for piperacillin/tazobactam dosing for the patient on MARS/CRRT to maintain concentrations above 4x MIC throughout most of the entire dosing intervals.

Upper panel shows dosing recommendations at the initiation of MARS/CRRT cycle and bottom panel shows recommends re-dosing recommendations during MARS/CRRT cycles. MARS: Molecular Adsorbent Recirculating System; CRRT: Continuous Renal Replacement Therapy; MIC: Minimum Inhibitory Concentration

Figure 3: Simulated concentration curve if patient received doses as recommended in algorithm.

To achieve the stringent pharmacodynamic target of maintaining concentrations above 4x MIC throughout most of the MARS/CRRT cycles, the patient should have received three times the dose over a three-hour infusion at the initiation of the first MARS/CRRT cycle, and within an hour of the initiation of the second MARS/CRRT cycle. During the first cycle, an additional normal dose over 30 minutes would have been recommended five hours after the initiation of the cycle. Blue arrows represent time of administration of the recommended piperacillin/tazobactam doses. Red line shows the simulated concentration curve if doses as recommended in the algorithm were given. For comparison, the gray line is the concentration curve based on observed concentrations (gray circles) and the actual dosing regimen the patient received. The dotted black line represents 4x MIC, for which the piperacillin CLSI breakpoint for *Pseudomonas aeruginosa* was used. MARS: Molecular Adsorbent Recirculating System; CRRT: Continuous Renal Replacement Therapy; MIC: Minimum Inhibitory Concentration

Table 1:
Estimated clearance and percentage of time free concentrations remained over 4x MIC (64 µg/mL) during each dosing interval.

Concentrations should be above 4x MIC for at least 50% of the dosing interval. The percentages reported in this table are specific to this patient and to the timing of doses and MARS/CRRT she received. L: liters; hr: hour; kg: kilograms; µg: micrograms; mL: milliliter

	Before MARS/ CRRT	1 st MARS/ CRRT Cycle	Between MARS/CRRT Cycles	2 nd MARS/ CRRT Cycle	CRRT Only
Clearance (L/hr;L/hr/kg [*])	2.1/0.13	6.4/0.39	2.0/0.12	7.4/0.45	3.0/0.18
Percentage of dosing interval above 64 µg/mL	Dose 1: 54% Dose 2: 92% Dose 3: 72%	21%	62%	37%	Dose 1: 96% Dose 2: 100% Dose 3: 100%

^{*} The L/hr/kg clearance was calculated using allometric scaling ($L/hr/kg = L/hr * (1/42)^{0.75}$)