

Individual Meropenem Clearance in Infants on ECMO and CVVHDF is Difficult to Predict

A Case Report and Review of the Literature

Ali Jabareen, PharmD,*† Laila Nassar, PharmD,‡§ Marina Karasik, MSc,§ Edna Efrati, PhD,§
Amir Hadash, MD,¶ Imad Kassis, MD,‡¶|| and Daniel Kurnik, MD,†‡

Objectives: Meropenem is a broad-spectrum carbapenem antibiotic with mostly renal excretion. Conflicting data are available regarding meropenem pharmacokinetics in critically ill neonates on concomitant continuous renal replacement therapy (CRRT) and/or extracorporeal membrane oxygenation (ECMO). Our objectives were to assess meropenem clearance in a neonate on CRRT and ECMO, compare it to previously published data and assess whether dose recommendations can be generalized in this population.

Case description: A 2.5 kg male infant with a large diaphragmatic hernia was delivered by cesarean section at week 35 and immediately mechanically ventilated due to shock and respiratory insufficiency. He underwent surgical correction of the hernia, but developed recurrent sepsis, multiorgan failure and pulmonary hypertension. He remained mechanically ventilated and required ECMO and continuous veno-venous hemodiafiltration. He was started on meropenem 40 mg/kg/dose, every 8 hs for Enterobacter cloacae bacteremia and sepsis, but due to lack of clinical and microbiologic response despite in vitro susceptibility, he was started on a continuous meropenem infusion of 240 mg/kg/d, based on dose recommendations in a similar case. We measured steady state meropenem plasma concentrations on 2 occasions, during ECMO and continuous veno-venous hemodiafiltration (CVVHDF) and then on CVVHDF only.

Results: Meropenem serum concentrations were 90 and 64 mg/L on the first and second occasion (therapeutic target concentration, 10 mg/L) corresponding to a clearance of 1.9 and 2.6 mL/kg/min. This clearance estimate was substantially lower than that reported in toddlers on CRRT and ECMO in some studies.

Conclusion: In neonates and infants, meropenem clearance is difficult to predict because of dynamic ontogenetic changes in renal function. This problem is further aggravated in acutely ill infants with decreased renal function, renal replacement therapy and/or ECMO. Therefore, Target Concentration Intervention based on meropenem plasma concentrations is indispensable to ensure therapeutic exposure in this population.

Key Words: Meropenem, CRRT, ECMO, Clearance, Infants

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From the *Pharmacy Services, Rambam Health Care Campus, Haifa, Israel;

†Clinical Pharmacology Unit, Section of Clinical Pharmacology and Toxicology, Rambam Health Care Campus, Haifa, Israel; ‡Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel; §Toxicology and Pharmacology Laboratory, Section of Clinical Pharmacology and Toxicology, Rambam Health Care Campus, Haifa, Israel; ¶Pediatric Intensive Care Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel; and ||Pediatric Infectious Diseases Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel.

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Address for correspondence: Ali Jabareen, Pharm.D., Clinical Pharmacology and Pharmacy Services, Rambam Health Care Campus, HaAliya HaShniya St 8, Haifa 3109601, Israel. E-mail: Al_jabareen@rmc.gov.il

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Meropenem is a broad-spectrum carbapenem antibiotic often used in the pediatric intensive care unit (PICU). Patients in the PICU often represent with complicated comorbidities, requiring at times additional support such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO). Such modalities may greatly affect the pharmacokinetics (PKs) of medications, but only limited data are available regarding the PK of meropenem in critically ill neonates and the effect of concomitant ECMO and CRRT.

Meropenem is a small molecule (molecular weight, 383.5 g/mol). Its disposition is characterized by a small volume of distribution (VD) of about 0.2 L/kg in critically ill patients with sepsis¹ and about 0.4 L/kg in infants,² low protein binding (<2%) and mostly renal elimination (about 70% are recovered in the urine as unchanged drug within 12 h after dosing).^{1,3} Although nonrenal clearance can increase in patients with renal insufficiency, dose reductions are still required in patients with reduced renal function. On the other hand, meropenem is also readily removed by various modes of dialysis, further complicating dosing in patients with kidney injury who progress to dialysis.³ In acutely ill adult patients, continuous replacement therapies [continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration (CVVHDF)] contribute about half of the total meropenem clearance, and nonrenal clearance appears to be increased.⁴ Thus, only moderate dose reductions are recommended in such patients, depending on residual renal function, dialyzer flow rates and the target concentrations. Similarly, in acutely ill children on CRRT, meropenem dose rates of 20 mg/kg/dose, every 8 h or 60 mg/kg/d as continuous infusion have been recommended to achieve target exposure, similar to dose regimens in children with normal renal function.⁵

ECMO can alter the PK of medications by serving functionally as an additional compartment. Medication can be adsorbed to the ECMO circuit (sequestration) and then later released.⁶ Thus, ECMO may affect both the volume of distribution and clearance of medications, and this may depend on drug properties (such as molecular weight and lipophilicity) and on the properties and settings of the specific ECMO apparatus.^{7,8} In a number of case reports, the effect of ECMO on meropenem PKs was inconsistent, showing both increases and decreases in clearance and/or VD.^{8–11} Recent population PK studies did not show a significant difference of meropenem PK parameters in children on ECMO compared with those without ECMO, but subgroups of children on ECMO were small.^{5,12} Importantly, meropenem is unstable at 37°C, and exterior circulation of blood during ECMO has been suspected to contribute to higher clearance due to inadvertent drug degradation.¹³

In this case report, our objectives were to assess meropenem clearance in a neonate on CRRT and ECMO, compare it to previously published data, and assess whether dose recommendations can be generalized in this population.

CASE DESCRIPTION

A 2.5kg male infant with a large diaphragmatic hernia diagnosed during the prenatal screening was delivered by cesarean section at week 35 and mechanically ventilated immediately after birth due to respiratory insufficiency and shock. He underwent surgical correction of the hernia 16 days after birth. In the first week postoperative week, his respiratory state improved, but his subsequent course was complicated by recurrent sepsis, multiorgan failure and pulmonary hypertension. He remained mechanically ventilated, and on day 29 after birth he was put on CVVHDF (PRISMAFLEX M60 Set with AN69 dialysis filters) due to kidney injury during an episode of *Enterobacter cloacae* bacteremia and septic shock. The dialysis parameters were determined daily by the attending nephrologist according to clinical needs (ranges: blood flow 20–50mL/min, replacement prefilter 70–100mL/h, dialysate flow 20–100mL/h, replacement post filter 20–100mL/h, removal 40–70mL/h). 3 days later, he was connected to ECMO due to pulmonary hypertension and multiorgan failure [Majet Rotaflow Venoarterial ECMO with polyvinyl chloride tubing (diameter 1/4 inch; blood flow 150–200mL/kg/min)]. His antimicrobial treatment with piperacillin/tazobactam and vancomycin was changed to amikacin, vancomycin and meropenem (40mg/kg/dose, every 8h). All antibiotic solutions were prepared by the PICU's nursing staff. Due to lack of clinical and microbiologic response (persistence of fever and *Enterobacter cloacae* bacteremia), we suspected relative resistance of the bacterium to meropenem [minimal inhibitory concentration (MIC) of >2mg/L] and/or a high meropenem clearance in an infant on combined CVVHDF and ECMO, and his meropenem regimen was switched to a continuous infusion at a dose rate of 240mg/kg/d, as recommended in a previous case report.⁹ Under this regimen, the fever subsided and repeat blood cultures were negative. Blood samples were taken on 2 occasions for the determination of meropenem plasma concentrations, but analyzed in the same batch. Subsequently, the meropenem MIC for the isolated *Enterobacter cloacae* was determined to be 0.25mg/L. The infant subsequently developed candidemia, and antifungal treatment with anidulafungin was added. Despite full treatment, his multiorgan failure worsened, and a decision to gradually withdraw intensive care and continue palliative care was made. ECMO was discontinued, and the child died 7 days later.

METHODS

Blood Sampling

Arterial blood samples were drawn at steady state during the meropenem continuous infusion (10mg/kg/h) on 2 occasions, on day 2 of the infusion (while on ECMO and concomitant CVVHDF: blood flow 20mL/min, dialysate flow 20mL/h, removal 40mL/h, replacement prefilter 100mL/h, replacement postfilter 20mL/h) and on day 7 (2 days after discontinuing ECMO, on CVVHDF only: blood flow 40mL/min, dialysate flow 50mL/h, removal 45mL/h, replacement prefilter 100mL/h, replacement postfilter 100mL/h).

Determination of Meropenem Serum Concentrations

Meropenem plasma concentrations were determined by high performance liquid chromatograph separation module equipped with a PU-2089 Plus pump, an AS-2057 Plus autosampler and a UV detector.¹⁴ The steady state target concentration was 10mg/L (acceptable range, 8–12mg/L).¹⁵

Pharmacokinetic Analyses

We used the following equations to calculate patient-specific PK parameters:¹⁶

$$\text{AUC}_{(24h-\text{ss})} [\text{mg} * \text{min/L}] = C_{\text{ss}} [\text{mg/L}] * 1440 \text{ min} \quad (1)$$

$$CL [\text{L}/\text{min}] = \frac{\text{Daily Dose} [\text{mg}]}{\text{AUC}(24h - \text{ss}) [\text{mg} * \text{min/L}]} \quad (2)$$

where $\text{AUC}_{(24h-\text{ss})}$ is the area under the concentration-over-time curve during 24h, CL is the meropenem clearance, and C_{ss} is the concentration at steady state.

RESULTS

Meropenem serum concentrations were 90mg/L on the first occasion, and 64mg/L on the second occasion. Using the above formulas, we calculated a meropenem clearance of 4.6mL/min and 6.5mL/min (corresponding to 1.9 and 2.6mL/min/kg) on the 2 occasions. In view of the supratherapeutic exposure, the low MIC, and the fact that the new sepsis was attributed to candidemia, the infectious disease consultants recommended to discontinue meropenem.

DISCUSSION

In this infant on CVVHDF and ECMO, because of lack of clinical and microbiologic response during standard meropenem dosing, we increased the meropenem dose rate according to the recommendations in a previous similar case.⁹ However, this regimen produced excessive meropenem plasma steady-state concentrations, since the clearance in our infant was in fact lower than that described in some other children on CRRT and ECMO. Moreover, the clearance was 37% higher on the second occasion, when ECMO had been discontinued, but this increased clearance may have been accounted for by increased blood and dialysate flows set for the CVVHDF.

Knowledge about meropenem clearance in critically ill children is accumulating during the last years. Meropenem clearance is mostly renal and therefore strongly affected by renal function. Thus, meropenem clearance is expected to greatly increase during the first months of life, in parallel to the maturation of renal function of the newborn. According to the manufacturer, in healthy neonates, in term newborns, meropenem clearance increases from 2.3 to 3.4mL/min/kg within the first weeks of life and further increases in toddlers.¹⁷ A population PK model based on data from 50 Japanese children with normal renal function (mean age, 3.1 ± 3.2 years; mean creatinine clearance, 90 ± 34mL/min) estimated a mean meropenem clearance of 7.1 ± 0.3mL/min/kg.¹⁸ Similarly, in a recent study of 57 PICU patients with severe infections and largely normal renal function (mean age, 3.0 years; mean body weight, 15.8kg; mean creatinine clearance, 163 ± 49mL/min/1.73 m²), the median meropenem clearance was 7.2mL/min/kg (range, 2.0–12.0mL/min/kg).¹⁹ A similar mean clearance (7.0 ± 2.5mL/min/kg) was estimated for 9 children in a pediatric intensive care unit 1–9 years of age (mean, 3.1 years) with normal renal function (creatinine clearance = 157 ± 35mL/min/1.73 m²).²⁰

Fewer studies and case reports have assessed meropenem clearance in children on ECMO with or without CRRT, with variable results (Table 1). A recent population PK model based on 40 children 16.8 (1.4–187) months of age, including 11 patients on CRRT and 8 patients on ECMO (2 of whom were on both CRRT and ECMO), estimated that a patient on CRRT would have 90% of the meropenem clearance of a patient with a creatinine clearance of 100mL/min/1.73 m². ECMO did not significantly affect PK parameters.⁵ Using this model, we calculated for our infant a predicted meropenem clearance of 8.4mL/min, somewhat higher than the values calculated from the measured concentrations on the 2 occasions (4.6mL/min and 6.5mL/min).

TABLE 1. Cohort Studies and Case Reports/Case Series of Meropenem Clearance Estimates in Infants and Toddlers With and Without Continuous Renal Replacement Therapy and/or Extracorporeal Membrane Oxygenation

| Patient Population | Age | Clearance (mL/kg/min) |
|---|--|--|
| Healthy neonates ¹⁷ | Neonates | 2.3–3.4 |
| 57 PICU patients with severe infection ¹⁹ | Median 1.4 y, range 0.1–14.4 y | Median 7.2 range 2.0–12.0 |
| 9 PICU patients on CRRT (4 on ECMO) ²⁰ | Median 4 y, range 0.1–18 y | 1.5 |
| PK model based on 40 patients (11 CRRT, 8 ECMO, 2 on both CRRT and ECMO) ⁵ | Median 16.8 months (range, 1.4–187 months) | 1.6 for eGFR of 100 mL/min/1.73 m ² for CRRT; 1.5 |
| 27 children with sepsis receiving meropenem and with ECMO or CRRT ¹² | 2.00 (1.13–6.88) y for CRRT group 2.50 (0.50–5.25) y For ECMO group mean 3.1 y range 1–9 y | 21 (5.6–31.5) for CRRT group 13.3 (6.8–23.2) for ECMO group |
| 9 PICU patients ²² | | 7.0 ± 2.5 |
| Single infant on ECMO ¹¹ | 8 months | 4.2–4.9 (3 occasions) |
| 2 infants on ECMO ¹⁰ | 6 months | 1.8 |
| Single infant on ECMO + CRRT ⁹ | 1 month | 7.9 |
| Single toddler on ECMO + CRRT ²³ | 19 months | 2.2 |
| Current case on ECMO + CRRT on CRRT | 1.5 months | 1.9 2.6 |

CRRT indicates continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; PICU, pediatric intensive care unit; PK, pharmacokinetic; y, years.

Another recently published population PK model, based on 9 children (median age, 4.9 years; IQR, 0.7–13.8 years) on CRRT (4 of whom additionally on ECMO) receiving meropenem, reported an empiric Bayesian estimate mean plasma clearance of 1.5 ± 0.5 mL/min/kg, with a wide range of 0.7–2.6 mL/min/kg.²⁰ The fractional clearance accounted for by CRRT was $81\% \pm 33\%$. ECMO or type of CRRT (CCVHD or CVVHDF) did not significantly affect clearance, although the sample size may have been too small to rule out such an association.

Other studies reported significantly higher clearance estimates during meropenem. A recent study in 27 children receiving meropenem included 6 patients on CRRT. In this subgroup, the median clearance (assessed by noncompartmental analysis) was 262 mL/min (IQR, 35–655 mL).¹² Standardization to body weight using the median weight of 12.5 kg would yield a clearance of 21.0 mL/min/kg (IQR, 2.8–55 mL/Kg/min) in the CRRT subgroup, a much higher value than that estimated in the previously described studies. It is not clear whether methodologic differences (population PK analysis with Bayesian parameter estimate versus noncompartmental analysis) contributed to these differences. Notably, in a case report of a 1-month-old infant on ECMO and CRRT, the authors calculated a meropenem clearance of 7.9 mL/kg/min during a continuous infusion of 240 mg/kg/d.⁹ It was based on this report that we increased the meropenem dose rate in our case. However, in our infant clearance was significantly lower (1.9–2.6 mL/kg/min), more similar to the range estimated in some of the recent population PK models.²⁰

When meropenem is administered as a continuous infusion, constant steady-state plasma concentrations are achieved, allowing the calculation of plasma clearance without the use of complex modeling. Furthermore, for a given daily dose, the administration via continuous infusion achieves higher steady-state concentrations than the trough concentrations achieved with divided doses. This is particularly important in view of meropenem's "time-dependent" pharmacodynamic profile, where the proportion of time in the dosing cycle during which meropenem plasma concentrations remain above a certain minimal concentration predicts its efficacy. However, a continuous meropenem infusion requires a separate, dedicated intravenous access, and the infusion needs to be prepared afresh every 6–8 h due to the instability of the solution at room temperature.²¹ Moreover, even when steady-state conditions appear to have been met during prolonged continuous infusion, a single

sample, although convenient, may not always reliably represent true steady-state concentrations, and repeat sampling may improve the accuracy of the estimate of true steady-state plasma concentrations and, thus, clearance.

The wide between-patient variability in meropenem clearance estimates among infants and toddlers reflects the dynamic ontogenetic changes in renal function on the one hand, but in patients on CRRT also differences in dialysis parameters (eg, dialysis membrane, setting of blood flow and dialysis rate). Other factors potentially contributing to the widely varying estimates of meropenem clearance include differences in the analytical assays for the determination of meropenem concentrations, in the methodology of PK analyses (compartmental versus noncompartmental), in the dosing regimen (3 times daily dosing vs. continuous infusion), and in potential differences between arterial versus venous sampling. Furthermore, in patients on ECMO, plasma concentrations of meropenem can be acutely reduced after exchanging the circuit tubing, possibly due to adsorption to the new ECMO circuit, requiring additional bolus doses to maintain therapeutic plasma concentrations.¹⁰ Thus, infants on CRRT and ECMO may also exhibit considerable within-patient variability in meropenem PK parameters. Accordingly, in view of the high between- and within-patient variability in this population, individualized dose adjustment based on the determination of meropenem plasma concentrations and the bacterial MIC is necessary to ensure achievement of target exposure.

CONCLUSIONS

In neonates and infants, meropenem clearance is difficult to predict because of dynamic ontogenetic changes in renal function. This problem is further aggravated in acutely ill infants with decreased renal function, renal replacement therapy and/or ECMO which further increase between-patient and within-patient PK variability. Therefore, in this population, dose recommendations cannot be generalized, and target concentration intervention based on meropenem plasma concentrations and the bacterial MIC is necessary to ensure achievement of target exposure.

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