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Pharmacokinetics and Pharmacodynamics of Imipenem and Meropenem in Critically Ill Patients Treated With Continuous Venovenous Hemodialysis

David Afshartous, PhD^{*}, Seth R. Bauer, PharmD[§], Michael J. Connor, MD[^], Olufemi A. Aduroja, M.D.[§], Milen Amde, MD[§], Charbel Salem, MD[§], Joseph J. Groszek^{*}, and William H. Fissell, MD^{*}

William H. Fissell: william.fissell@vanderbilt.edu

^{*}Vanderbilt University, Nashville, Tennessee

[^]Emory University, Atlanta, Georgia

[§]Cleveland Clinic, Cleveland, Ohio

To the Editor

Imipenem and meropenem are widely used in the treatment of Gram-negative infections in critically ill patients, and dosage adjustments are recommended in the setting of reduced kidney function or continuous renal replacement therapy (CRRT) [1]. After recent prospective randomized clinical trials failed to show a survival benefit of intensive CRRT, we hypothesized that extracorporeal clearance of antibiotics might lead to antibiotic underdosing and inadequate treatment of infection [2, 3, 4]. Prior reports of imipenem and meropenem pharmacokinetics (PK) and pharmacodynamics (PD) rarely describe continuous venovenous hemodialysis (CVVHD), and there are no reports regarding meropenem in North American patients receiving CRRT, who may differ from their European counterparts (see first table of Item S1). Here we report PK and PD measurements from 26 patients at The Cleveland Clinic receiving CVVHD and imipenem (n=16) or meropenem (n=10) between February 1, 2009 and July 1, 2012.

Patients or their surrogates provided informed consent prior to study procedures. Demographic and clinical data were recorded on case report forms. Paired blood and CRRT effluent samples were drawn prior to an antibiotic dose, 30 minutes after the 30 minute infusion, and immediately before the following dose. Free imipenem and meropenem concentrations in blood and dialysate were measured by high-performance liquid

Correspondence to: William H. Fissell, william.fissell@vanderbilt.edu.

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Supplementary Material

Item S1: Detailed methods and supplementary results.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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chromatography and fitted to a single-compartment PK model using nonlinear mixed-effects models. Extracorporeal clearance of carbapenems was calculated from effluent flow rates and drug concentrations. Typical PD parameters for in vivo studies of time-dependent antibiotics such as beta-lactams include time in excess of minimum inhibitory concentration (MIC) or some multiple thereof. We selected time in excess of 8 µg/ml, or 4×MIC, as our PD metric for carbapenems active against *Pseudomonas* and *Enterobacteriaceae* [5, 6] (detailed methods in Item S1).

Patients were predominantly male (20/26) and weighed more (92 ± 21 kg) than those in other studies (Table 1; Item S1). Intensive care unit mortality rate was very high (61.5%). CRRT dose was 23.4 ± 7.4 ml/kg/h. Nonlinear mixed-effects PK modelling yielded a fixed-effect estimate for volume of distribution of 29.6 (95% CI, 26.3-33.1) L and for clearance of 5.34 (95% CI, 4.32-6.00) L/h. The corresponding random-effects standard deviation estimates were 6.8 (95% CI, 4.3-10.3) L and 2.4 (95% CI, 1.2-3.0) L/h. Extracorporeal carbapenem clearance was 32.4 ± 9.8 ml/min, only slightly lower than the dialysate flow rate (39.6 ± 9.9 ml/min). Looking at patient-level covariates (age, sex, current weight, admit weight, weight change, albumin), there was a significant effect of current weight on volume of distribution, with a 1-kg increase in current weight corresponding to a 0.17 L increase in volume of distribution on average ($p=0.02$). A significant effect was also observed for drug type: the meropenem group was 6.2 L lower on average (volumes of distribution for imipenem and meropenem of 33.1 and 26.9 L, respectively; $p=0.01$).

There was no evidence of an effect of any patient-level level covariate on clearance. However, drug type did exhibit a significant effect on clearance: the meropenem group was 4.2 L/h lower on average (clearance of 7.2 and 3.0 L/h for imipenem and meropenem, respectively; $p < 0.001$). Although adding drug type to the model reduced the random-effects variation in clearance from 2.4 to 0.6 L/h, the Likelihood Ratio test to assess whether the random-effect for clearance could be removed indicated that it could not be removed ($p = 0.01$).

The nonlinear mixed-effects model was used to estimate the fractional amount of the dosing interval above 4×MIC. As shown in the boxplot in Figure 1, approximately 8/26 patients failed to attain the PD criterion of fractional time plasma concentration exceeded 8 µg/ml being greater than 40%.

The key findings of this study are that a significant number of subjects failed to attain the PD target, and interindividual variability in PK is statistically and clinically significant. This raises concern regarding about one-size-fits-all dosing for critically ill subjects receiving CRRT. The “Green Book” recommends reducing the dose of imipenem or meropenem by two thirds and increasing the dosing interval in patients receiving CRRT [1]. Our study’s small sample size does not provide an adequate basis for improving on that recommendation, but given the generous volumes of distribution we observed, clinicians treating life-threatening infections might choose to administer a loading dose prior to adopting the recommended dose reduction. Further research is urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Distribution of fractional time plasma concentration exceeded 8 $\mu\text{g}/\text{mL}$ ($4\times\text{MIC}$ for susceptible bacteria). Drug exposure as estimated by this metric varied widely between individuals.

Table 1

Descriptive statistics of patients.

Variable	Value
Age (y)	64 [49-70]; 58 ± 18
M:F	6 (23%):20 (77%)
Admission Weight (kg)	96 [76-106]; 92 ± 21
Albumin (g/dL)	2.45 [2.02-2.90]; 2.48 ± 0.57
Total Bilirubin (mg/dL)	1.95 [0.93-6.33]; 6.18 ± 9.13
Dialysate Flow Rate (ml/h)	2500 [2125-2688]; 2387 ± 598
CRRT Carbapenem Clearance (ml/min)	34.7 [24.2-40.2]; 32.4 ± 9.8
Intensive Care Unit Survival	38.5%

N=26, data available for all. Data are presented as median [interquartile range]; mean ± standard deviation.