Antibiotic Dosing in Continuous Renal Replacement Therapy

Alexander R. Shaw and Bruce A. Mueller

Appropriate antibiotic dosing is critical to improve outcomes in critically ill patients with sepsis. The addition of continuous renal replacement therapy makes achieving appropriate antibiotic dosing more difficult. The lack of continuous renal replacement therapy standardization results in treatment variability between patients and may influence whether appropriate antibiotic exposure is achieved. The aim of this study was to determine if continuous renal replacement therapy effluent flow rate impacts attaining appropriate antibiotic concentrations when conventional continuous renal replacement therapy antibiotic doses were used. This study used Monte Carlo simulations to evaluate the effect of effluent flow rate variance on pharmacodynamic target attainment for cefepime, ceftazidime, levofloxacin, meropenem, piperacillin, and tazobactam. Published demographic and pharmacokinetic parameters for each antibiotic were used to develop a pharmacokinetic model. Monte Carlo simulations of 5000 patients were evaluated for each antibiotic dosing regimen at the extremes of Kidney Disease: Improving Global Outcomes guidelines recommended effluent flow rates (20 and 35 mL/kg/h). The probability of target attainment was calculated using antibiotic-specific pharmacodynamic targets assessed over the first 72 hours of therapy. Most conventional published antibiotic dosing recommendations, except for levofloxacin, reach acceptable probability of target attainment rates when effluent rates of 20 or 35 mL/kg/h are used.

Key Words: Antibiotics, Acute kidney injury, Renal replacement therapy, Pharmacokinetics, Pharmacodynamics

Martinez and colleagues[1] suggested that antibiotic dose matters when treating patients with sepsis. Essentially, these authors make the case that it is the exposure achieved from the first antibiotic dose that is relevant for determining the therapeutic outcome of an infection. Administration of the correct antibiotic[2] administered as quickly as possible[3] at a dose that achieves therapeutic concentrations at the site of infection[1] is most important act that a clinician can perform for patients with sepsis. This act is so simple, and any clinician can tell you that this should be their primary purpose. However, the evidence suggests that we do a poor job of accomplishing this single feat. Empirical selection of antibiotic is not always correct,[4] antibiotic doses are often administered late,[5,6] and we often do not attain therapeutic antibiotic exposure in the critically ill.[7]

Death as a result of infection remains the most common form of death in critically ill patients receiving continuous renal replacement therapy (CRRT),[8] suggesting we do even worse at accomplishing the feat of right drug, right dose, as fast as possible when CRRT is running. Bagshaw and colleagues found that the most common reason for starting CRRT was sepsis,[9] so successfully achieving therapeutic antibiotic dosing is especially important in these patients. Unfortunately, the physiological make up of patients requiring CRRT and the CRRT treatment itself works against a clinician's ability to meet this primary goal. The evidence suggests that in patients receiving CRRT, we often do not achieve therapeutic levels.[10,11] Some of the reasons that we do not meet our targets are pharmacokinetic in nature (fluid overload, unrecognized residual kidney function, CRRT transmembrane drug clearance, drug-membrane binding, vasoactive agents that inhibit antibiotic deliver to infection site, and so forth). Antibiotic pharmacodynamic issues (antibiotic-resistant organism prevalence in the intensive care unit [ICU], large inoculum effect in septic patients) also explain part of our failure to adequately treat infection in these patients.

Although Martinez and colleagues suggested that dose matters for a good patient outcome,[1] we began to wonder whether any CRRT factors matter in determining outcome in infected patients receiving CRRT. At one time, CRRT modality (convective vs diffusive) was postulated to matter[12,13] but the consensus now is that CRRT modality likely does not influence patient infectious outcomes.[14]

Effluent flow is one CRRT factor that varies substantially between institutions and often within a given institution. Even with stated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines effluent rate recommendations,[14] we find that in practice, effluent flows vary substantially in every part of the world.[15-17] Effluent flow rate is used as a surrogate marker for CRRT intensity, although it is an imperfect measure of delivered dose of therapy.[14,18,19] For example, solute saturation (SA)/sieving coefficients decline with time with hemodiafilters, meaning that a given effluent rate will give more solute clearance on day 1 than it will on day 3 if all else is held the same.[20] CRRT often gets interrupted, resulting in less delivered solute removal, which results in a difference between the prescribed and delivered CRRT dose.[21]

Most large clinical trials of CRRT intensity have revealed that patient outcomes are not different when comparing effluent rates within KDIGO guideline range (20-35 mL/kg/h),[15,18,22] consequently the consensus of the critical care nephrology community is that CRRT intensity within this

From the Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Bruce A. Mueller, Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, 428 Church Street, Ann Arbor, MI 48109-1065. E-mail: muellerb@umich.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2017.05.004

effluent range does not matter.[14,23] However, some have continued to hold the opinion that CRRT intensity does matter, but the major trials were not designed to examine this question appropriately.[24-26] One critique has been that the major studies comparing higher CRRT effluent rates to lower CRRT rates used identical antibiotic doses in both cohorts.[27] Consequently if the same antibiotic dose is used, there will be less antibiotic exposure in the high intensity CRRT group than the low intensity CRRT group because of differences in CRRT drug clearance. Is it possible that if these dose intensity studies ensured equivalent antibiotic exposure in high and low intensity CRRT treatment groups that it would have resulted in a better patient outcome in the high CRRT intensity (high effluent flow) group? It is unlikely such a trial will ever be conducted to conclusively address this question. Thus, the question remains, does effluent flow matter in terms of attaining "the right drug, right dose, as fast as possible?" Effluent flow rate definitely is an important determinant of CRRT drug clearance for many drugs because transmembrane clearance is determined by effluent flow multiplied by a sieving/saturation coefficient that describes how well the antibiotic crosses the dialyzer membrane.

Although a clinical trial comparing outcomes of different effluent rates while controlling for antibiotic serum concentrations may never be conducted, there is another way to test this hypothesis. Monte Carlo simulations (MCSs) have been used to determine whether antibiotic pharmacodynamic targets are likely to be achieved using varying doses in virtual patients.[28-30] More recently, publications have used MCSs to determine appropriate antibiotic dosing in patients receiving hybrid hemodialysis[31,32] intermittent hemodialysis,[33] and CRRT.[34] We sought to determine whether effluent flow matters in attaining appropriate antibiotic concentrations when conventional CRRT antibiotic doses were used. To do this, we applied MCS to investigate antibiotic dosing in CRRT against 2 different CRRT effluent rates, not to determine optimal dosing (which is likely to vary from individual to individual), but rather to finally address the question; Does effluent flow matter in a large population of virtual, critically ill patients?

CLINICAL SUMMARY

- Critically ill patients receiving continuous renal replacement therapy (CRRT) commonly perish because of infection, and evidence suggests that critically ill patients receiving CRRT may have suboptimal antibiotic concentrations.
- The wide variability of CRRT effluent rates may affect the antibiotic exposure between patients, which may affect patient outcomes.
- This study evaluated pharmacodynamic attainment rates of antibiotics using effluent flow rates at the extremes of the Kidney Disease: Improving Global Outcomes guidelines.
- Most conventional published cefepime, ceftazidime, meropenem, piperacillin, and tazobactam dosing recommendations reach acceptable probability of target attainment rates when effluent rates of 20 or 35 mL/kg/h are used; conventional levofloxacin dosing does not reach acceptable rates at any effluent rate.

METHODS

Pharmacokinetic Model Development

The MCS model integrated relevant input parameters to construct a virtual patient population. Body weight was derived from a large renal replacement therapy study[8] and pharmacokinetic data were gathered from published cefepime,[35-41] ceftazidime,[42-48] levofloxacin,[49-52] meropenem,[53-59] piperacillin,[10,60-65] and tazobactam[10,60,61] studies in critically ill patients receiving renal replacement therapy. Antibiotics in this study were chosen based on whether (1) known pharmacokinetic data in CRRT exists, (2) pharmacodynamic target data associated with patient outcomes have been identified, and (3) routine therapeutic drug monitoring are unavailable at most hospitals.

Limits were obtained from the range extremes of the published studies and were set for all relevant input parameters (Table 1). Correlation between body weight and volume of distribution or nonrenal clearance was derived for each antibiotic and integrated into the models to better approximate realistic pharmacokinetic parameters. A continuous venovenous hemodialysis (CVVHD) treatment with varying effluent rates (the low and high end of the KDIGO recommendations[14]; 20 or 35 mL/kg/min) for 24 hours each day over the initial 72 hours was modeled. For each model, the first dose of the antibiotic was administered at the start of the CRRT on day 1. Blood flow rate (Q_b) was fixed at 200 mL/min. Blood flow has a large influence on solute clearance in intermittent hemodialysis (because blood flow $<$ dialysate flow), it only has a small influence on drug clearance in CRRT (blood flow $\gg$ effluent rate), and thus it was not varied in this model. CRRT drug clearance was calculated by the following formula: CL_{HD} (L/h) = SA $\times$ Q_d, where CL_{HD} is the transmembrane clearance during hemodialysis, SA is the drug's saturation coefficient, and Q_d is the dialysate flow rate.

A one-compartment, multiple dose pharmacokinetic model was developed to evaluate the effect of drug removal by CRRT on the plasma concentration-time profile of cefepime, ceftazidime, levofloxacin, meropenem, and piperacillin/tazobactam. Following the methodology from a previously published study,[31] MCSs (Crystal Ball Classroom Edition, Oracle) were used to generate virtual cohorts of 5000 patients with individual 72-hour total plasma drug concentration profiles for each dosing regimen. To better approximate the diverse patient population of patients receiving CRRT, variability within each cohort was produced using the mean and standard deviation of the input parameters used in the model (V_d, CL_{NR}, weight, SA). Body weight had a lower limit set to 40 kg because of the assumption that the study patients were adults. Dosing regimens were gathered from publicly available literature including drug information websites,[66] drug dosing calculators,[67,68]