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In Practice

Medication Dosing in Critically Ill Patients With Acute Kidney Injury Treated With Renal Replacement Therapy

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Critically ill patients with acute kidney injury may be treated with a variety of renal replacement therapies (RRTs). Each of these RRTs has profound yet differing effects on drug dosing. Although the doses of some drugs can be titrated to an immediately observable pharmacodynamic effect, the effects of many drugs, such as antibiotics for example, are not immediately apparent. Attainment of desired pharmacodynamic response is a complex interplay between patient, RRT, and pharmacokinetic factors. In the case of antibiotics, microorganism-specific factors also must be considered. Rational and effective drug dosing in this clinical setting cannot occur until all these issues are addressed by the clinician. Failure to account for the pharmacokinetic influences of critical illness, kidney disease, and choice of intermittent hemodialysis or prolonged intermittent or continuous RRT can contribute to the high mortality rates seen in these patients. Pharmacotherapy considerations for each of these therapies are addressed in this article by applying them to a patient case.
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INDEX WORDS: Pharmacokinetics; pharmacodynamics; renal replacement therapy; antibiotics; infection; critical illness.

CASE PRESENTATION

A 60-year-old man weighing 80 kg presents to the emergency department from an assisted living facility with altered mental status. He is febrile with a heart rate of 115 beats/min, respiratory rate of 23 respirations/min, blood pressure of 90/60 mm Hg, white blood cell count of 14.5 $\times 10^3/\mu$L, serum creatinine level of 1.8 mg/dL (estimated glomerular filtration rate, 41 mL/min/1.73 m^2 using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation), and blood urea nitrogen level of 75 mg/dL, which are increased from his baseline serum creatinine level of 1.1 mg/dL (estimated glomerular filtration rate, 73 mL/min/1.73 m^2) and baseline serum urea nitrogen level of 25 mg/dL, respectively. While in the emergency department, his respiratory function deteriorated, requiring intubation. He was admitted to the medical intensive care unit (ICU) for probable urosepsis. During the past 24 hours, the patient's vital signs have not improved much. He has a positive fluid balance and his white blood cell count continues to increase. Culture results are still pending, but based on his medical history, it is likely that at least one antibiotic-resistant organism is present. The ICU and infectious disease teams are deciding among the following antibiotics: daptomycin, vancomycin, gentamicin, piperacillin/tazobactam, and meropenem. A final decision on the antibiotic combination to begin has not been made yet. The ICU team consults nephrology to discuss starting renal replacement therapy (RRT) due to his decreased kidney function.

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INTRODUCTION

Every year, 2.1 million Americans are admitted to an ICU directly from the emergency department.[1] In many of these patients, decreased kidney function will be present and while in the ICU, patients often receive nephrotoxins.[2] Treatment with RRT is necessary in 70% of patients in the ICU who develop acute kidney injury (AKI).[3] The RRT modality instituted depends on clinical factors, physician preference, RRT resource availability, and staff capabilities. Treatment of decreased kidney function differs from that of other organ dysfunction in that far less standardization exists in practice. For example, a patient in respiratory distress likely would receive similar intubation and ventilation regardless of institution, practitioner, or geographic location.[4,5] In contrast, that same critically ill patient with AKI might receive a wide variety of RRTs. Recent published RRT consensus guidelines do not suggest one form of RRT as better than another except for very specific indications.[6] Consequently, several forms of RRT are used clinically with little standardization among them. The lack of RRT standardization has limited our ability to provide optimal pharmacotherapy in this setting because each RRT requires substantially different drug dosing, and the specifics of that drug dosing are dependent on the interplay between drug, patient, and RRT factors. The lack of uniformity in RRT prescription leads to a lack of uniformity in drug dosing in these patients, which can be problematic. We know that improper antibiotic selection results in worsened ICU patient outcomes.[7] Similarly, poorly dosed appropriate drugs that do not meet pharmacokinetic and pharmacodynamic goals also result in worsened patient outcomes[8-10] and likely

increase the possibility of selecting for resistant organisms.[11,12] The use of RRTs with varying drug clearances compounds the possibility of inadequate drug dosing of the antibiotics deemed appropriate. All these factors likely contribute to sepsis/infection being the leading cause of death in this patient population.[3,13]

PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS

Pharmacokinetic parameter alterations in ICU patients with AKI affect the ability of clinicians to attain pharmacodynamic targets. Patients experience multiple physiologic changes simultaneously while in the ICU, and almost every pharmacokinetic change seen in critically ill patients results in reduced ability to attain particular serum concentration goals (eg, high enough peak concentrations or areas under the curve). When deciding how to dose medications in critically ill patients, clinicians should take into account all potential changes and adjust accordingly (Table 1). Serum concentration goals are extrapolated from in vitro studies evaluating pharmacodynamic measures such as antimicrobial kill curves and in vivo trials evaluating patient outcomes.[14,15] Many studies have shown improved patient outcomes when antibiotic-specific pharmacodynamic goals are met.[16-18]

Antibiotics can be thought to exhibit 1 of 2 different pharmacodynamic profiles; concentration- or time-dependent antimicrobial activity. The bacterial killing of time-dependent antibiotics depends on the time the serum concentration is higher than the organism's minimum inhibitory concentration (MIC). Attaining serum concentrations higher than this threshold does not seem to enhance antimicrobial effect. The efficacy of time-dependent antibiotics is enhanced when serum concentration is maintained at 2-4 times the MIC for at least 40% of the dosing interval,[19] although some studies have found best results when time above MIC is 100% of the dosing interval.[20] Increasing the frequency of the dosing interval, increasing the dose, or using extended/continuous antibiotic infusions have been strategies used to ensure that goal serum concentrations (2-4 times higher than MIC) are reached.[19,21,22] In contrast, concentration-dependent antibiotics are dependent on reaching high antibiotic serum concentrations. Area under the concentration time curve to MIC ratio and peak concentration to MIC ratio are used to measure whether pharmacodynamic targets are being met. Antibiotic concentrations targeted are typically 10 or more times the bacteria's MIC. The pervasive use of once-daily aminoglycosides in patients with normal kidney function has grown from our knowledge of the concentration-dependent pharmacodynamics of the aminoglycosides.

For many drugs used in the ICU, ensurance of meeting pharmacodynamic goals can be achieved through patient assessment. Inotrope and vasopressor effects can be monitored using blood pressure and heart rate,[23] sedation scores can be measured using a scale such as the Glasgow Coma Scale,[24] and when therapeutic goals are not being met, drug doses can be titrated immediately to desired effect. Immediate feed-

Table 1. Physiologic Changes in the ICU Alter the Ease of Pharmacodynamic Attainment

Physiologic Change in the ICU	Effect on Pharmacokinetic Properties	Ease of Pharmacodynamic Attainment	Clinician Response to Dosing[a]
Fluid overload	Increased volume of distribution	More difficult	Give a larger loading dose
Increased capillary permeability	Increased volume of distribution	More difficult	Give a larger loading dose
Hypoalbuminemia	Increased drug availability to exert pharmacologic effect or increased drug elimination	Less or more difficult, respectively	Potential dosage adjustment for highly protein-bound drugs
Augmented renal clearance	Increased drug elimination	More difficult	More frequent dosing interval
AKI	Decreased drug elimination	Less difficult	Adjust doses on drugs eliminated by the kidney
AKI requiring RRT	Increased drug elimination	More difficult	Dose adjust as RRT modality chosen
Preserved nonrenal clearance in AKI	Preserved drug elimination in face of AKI in selected drugs	More difficult	More frequent dosing interval
Increased cardiac output	Increased drug elimination	More difficult	
Impaired GI motility/reduced GI blood flow	Decreased oral drug absorption	More difficult	Avoid oral medications

Abbreviations: AKI, acute kidney injury; GI, gastrointestinal; ICU, intensive care unit; RRT, renal replacement therapy.

[a]In all cases listed in the table, therapeutic drug monitoring should be used when possible, except in the case of impaired GI motility/reduced GI blood flow.