Seminars in Dialysis

We Underdose Antibiotics in Patients on CRRT

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ABSTRACT

Appropriate antibiotic dosing in critically ill, infected, patients receiving continuous renal replacement therapy (CRRT) is crucial to improve patient outcomes. Severe sepsis and septic shock result in changes in pharmacokinetic parameters, including increased volume of distribution, hypoalbuminemia, and changes in renal and nonrenal clearances. The lack of CRRT standardization, nonrecognition of how CRRT variability affects antibiotic removal, fear of antibiotic toxicity, and limited drug dosing resources all contribute to suboptimal antibiotic therapy. Even when antibiotic CRRT pharmacokinetic studies are available, they are often based on old CRRT methodologies that do not exist in contemporary CRRT practice, resulting in unhelpful/inaccurate dosing recommendations. Application of these older doses in Monte Carlo simulation studies reveals that many of the recommended dosing regimens will never attain pharmacodynamic targets. In this review, using cefepime as an example, we illustrate whether clinicians are likely to achieve pharmacokinetic/pharmacodynamic targets when the recommended dosing regimens are prescribed in this patient population. We encourage clinicians to aggressively dose antibiotics with large loading dose and higher maintenance doses to reach the targets.

Continuous renal replacement therapy (CRRT) has been used for acute kidney injury (AKI) management in hemodynamically unstable critically ill patients. CRRT prescriptions differ in the type of modalities, hemofilters, and effluent flow rates, all of which may profoundly affect antibiotic dosing. The wide variety of clinically used CRRT settings results in a subsequent lack of uniformity in antibiotic dosing (1). Although KDIGO guidelines (2) recommend an effluent rate of 20–25 ml/kg/hour for CRRT in AKI treatment, ICU physicians most commonly prescribe initial effluent flow rates that are even higher (25–35 ml/kg/hour) (3). Even if the delivered CRRT dose is less than prescribed, "standard" antibiotic dosing conducted at KDIGO-effluent rates is often nontherapeutic (4) and the use of even higher effluent rates would require even higher daily antibiotic doses. The septic patient receiving CRRT desperately needs antibiotics dosed to therapeutic levels, but many barriers exist to ever achieving this goal (5). As a result, we frequently underdose antibiotics in patients on CRRT.

Severe sepsis and septic shock are among the two most common reasons for CRRT initiation. Proper antibiotic dosing is crucial to minimize the morbidity and mortality associated with sepsis (6). Patients with sepsis or septic shock often present with a variety of physiologic abnormalities that often preclude effective antibiotic dosing. Inflammatory mediators released during the immune response result in increased capillary permeability leading to fluid accumulation and hypoalbuminemia (7). Sepsis also results in acute kidney and liver injury, however, a patient with AKI may still have well-preserved nonrenal (hepatic) drug clearance (5). These physiologic changes alter the pharmacokinetic parameters that must be considered for proper antibiotic dosing.

The most important pharmacokinetic factors to consider in patients receiving CRRT are a drug's volume of distribution, protein binding and metabolism. Fluid accumulation due to medication, nutrition, and blood product administration, fluid resuscitation and increased capillary permeability causes an increase in the volume of distribution of water soluble drugs. Through dilution, a reduction in antibiotic concentration in the plasma and at the site of infection will be seen. The extent of fluid overload is most prominent during the initial stages of severe sepsis but declines during the course of treatment due to the normalization of the physiologic changes and from fluid removal by CRRT (7). Hypoalbuminemia has been reported in 40–50% of critical care patients (8) and can have a large effect on the amount of free (unbound) drug that has pharmacologic activity. However, the increase in free drug allows for more drug to be distributed into the interstitial space and more free drug that

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