CRITICAL CARE

COMMENTARY

Appropriate antibiotic dosing in severe sepsis and acute renal failure: factors to consider

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See related research by Seyler *et al.*, http://ccforum.com/content/15/3/R137

Abstract

Severe sepsis and septic shock cause considerable morbidity and mortality. Early appropriate empiric broad-spectrum antibiotics and advanced resuscitation therapy are the cornerstones of treatment for these conditions. In prescribing an antibiotic regimen in septic patients with acute renal failure treated with continuous renal replacement therapy, several factors should be considered: pharmacokinetics, weight, residual renal function, hepatic function, mode of renal replacement therapy (membrane and surface area, sieving coefficient, effluent and dialysate rate, and blood flow rate), severity of illness, microorganism, minimum inhibitory concentration, and others. Studies that determine the serum antibiotic concentrations are very useful in establishing the correct dosage in critical patients.

Inappropriate antimicrobial therapy refers not only to an unsuitable drug choice in terms of spectrum of activity but also to an inadequate dosing regimen. With this in mind, Seyler and colleagues [1] conducted a prospective study in order to determine whether recommended β-lactam regimens ensure appropriate phamacokinetic/ pharmacodynamic exposure against *Pseudomonas aeruginosa* in septic patients treated with continuous renal replacement therapy (CRRT).

Severe sepsis and septic shock cause significant morbidity and mortality. Early appropriate empiric broad-spectrum antibiotics and advanced resuscitation therapy are the cornerstones of treatment for these conditions [2]. Acute kidney injury requiring renal replacement therapy occurs in 5% to 6% of critical patients. These

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patients use significant resources and up to 60% die from their injuries [3]. Optimized antibiotic dosing may help reduce this burden; however, data to guide dosing in patients with severe sepsis/septic shock and multiple organ dysfunction under CRRT are scant. Antibiotic dosing in these conditions is complicated, and incorrect dosage may result in drug toxicity or treatment failure and resistance.

Antibacterial pharmacokinetics are affected by CRRT and may be altered by acute renal failure and critical illness [4]. Recommendations for patients who have chronic renal failure and who are undergoing intermittent hemodialysis are not appropriate for the critically ill, because of differences in the mode of renal replacement therapy and in pharmacokinetics [5]. The optimal dose of antibiotics is usually based on theoretical considerations derived from data from non-critical patients (healthy individuals or those with chronic renal failure with dosage adjustment based on creatinine clearance) [6]. Many studies that focus on calculating the dosing regimen in critical patients fail to consider basic pharmacokinetic parameters like volume of distribution (Vd), protein binding, weight, residual renal function, hepatic function, mode of CRRT, membrane and surface area, sieving coefficient, effluent and dialysate rate, blood flow rate, and severity of illness. Various dose adjustment equations have been proposed for critical patients requiring CRRT. These assume either that measurement of antibiotic concentrations is widely available or that the sieving coefficient can be accurately estimated from data on protein binding obtained from non-critical patients. Only unbound antibiotic is pharmacologically active, but serum protein levels in critical patients vary considerably, so the proportion of unbound drug is unpredictable [7,8].

CRRT is sometimes initiated early in septic patients without unduly impaired renal function to facilitate water balance control. In these circumstances, the creatinine clearance can be substantially maintained [9,10]. If we add the clearance of the extracorporeal circuit, the dose must be adjusted to avoid underdosage. Critical patients can have hepatic dysfunction but hepatic

drug clearance may actually increase in patients with acute renal failure, so hepatic function should also be considered [11].

The modality and dosage of CRRT in critical patients vary widely both between and within studies. Likewise, a patient may undergo different modalities, blood and ultrafiltration flows may vary, and the prescribed dose could differ from the current dose. Changes in CRRT modality, blood flow, ultrafiltration rate, or location of fluid replacement require dose adjustments, and interrupting CRRT because of multiple filter clotting or for surgical or image procedures may affect plasma drug removal. Adsorption of antibiotics on the filter may also result in drug elimination. The clinical importance of β-lactam adsorption is unknown. Moreover, recent modifications to CRRT, including high-volume hemofiltration, high-adsorption hemofiltration, high-cutoff membranes, and hybrid systems like coupled plasma filtration absorbance, increase β-lactam elimination [12].

β-lactams have low molecular weights, low Vd (0.3 to 0.4 L/kg), and relatively low protein binding (10% to 68%). Nearly all are excreted primarily unchanged via glomerular filtration. Thus, hemofiltration removes β-lactams, so CRRT requires dosage adjustments. β-lactams have time-dependent bactericidal activity and a slow continuous bactericidal effect. Their effectiveness depends on how long the serum concentration exceeds a threshold (four to five times the minimum inhibitory concentration (MIC)). Depending on the target organism and the choice of β-lactams, the serum concentration should exceed the threshold during 40% to 100% of the dosing interval. This is particularly important for life-threatening pathogens potentially resistant to multiple antibiotics as intermittent dosing may allow drug concentrations to fall below the MIC [13]. Continuous or extended infusion could maximize the pharmacodynamics of β-lactams [14]. Finally, tissue concentrations differ from plasma concentrations and vary among antibiotics [15].

Given the number of variables to consider for antibiotic prescription in critical patients undergoing CRRT and the deleterious impact of underdosage, data from real patients are important. Studies should focus on infections with high intensive care unit incidence caused by germs with high multi-antibiotic resistance, as in the article by Seyler and colleagues [1]. By determining serum concentrations of β-lactam antibiotics in patients with sepsis and renal failure under CRRT, these authors confirmed that antibiotic dosage is often insufficient in this setting. These findings are clinically relevant: the authors recommend not reducing the dose of β-lactams during the first 48 hours and monitoring pharmacokinetics thereafter. More studies like this are needed to evaluate the appropriate dosage of other antibiotics in patients with acute renal failure and severe sepsis.

Abbreviations

CRRT, continuous renal replacement therapy; MIC, minimum inhibitory concentration; Vd, volume of distribution.

Competing interests

The authors declare that they have no competing interests.

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