The use of antimicrobials in septic patients with acute kidney injury

O uso de antimicrobianos em pacientes sépticos com lesão renal aguda

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ABSTRACT

Sepsis is the most common cause of death in critically ill patients and it may be associated with multiorgan failure, including acute kidney injury (AKI). This situation can require acute renal support and increase mortality. Therefore, it is essential to administrate antimicrobials in dosis to achieve adequate serum levels, preventing overdosis and drug toxicity or underdosing and risk for resistance to antibiotics and higher mortality. To date, there aren't validated guidelines on antibiotic dosis adjustment in septic patients with AKI and the recommendations are extrapolated from studies conducted in non-critical patients with chronic kidney disease in end stage receiving chronic renal replacement therapy. This study aimed to review and discuss the complexity of that issue, considering the several factors related to the drugs removal: critically ill patient characteristics, antimicrobial properties and dialysis method.

Keywords: acute kidney injury; intensive care units; anti-bacterial agents.

RESUMO

A sepse é a principal causa de óbito em pacientes críticos e pode cursar com falência de vários órgãos, entre eles os rins, requerendo, com frequência, suporte renal agudo e elevando a mortalidade. Assim, torna-se imprescindível a administração de antimicrobianos em dose que garanta nível sérico adequado para evitar superdosagem e toxicidade medicamentosa ou ainda subdosagem e risco de resistência microbiana, ambas as situações contribuindo para maior mortalidade. Até o momento, não há diretrizes validadas para auxiliar no ajuste de dose de antibióticos nos pacientes sépticos com lesão renal aguda em suporte renal, sendo as recomendações extrapoladas de estudos realizados em pacientes não críticos e com doença renal em estádio final recebendo terapia renal substitutiva crônica. Esse estudo teve como objetivo revisar e discutir a complexidade desse assunto, levando em consideração os vários fatores relacionados à remoção de drogas: características do paciente crítico, propriedades dos antimicrobianos e método dialítico utilizado.

Palavras-chave: lesão renal aguda; unidades de terapia intensiva; antibacterianos.

INTRODUCTION

Among patients in intensive care units, the main cause of death is sepsis, with mortality rates ranging between 30 and 60%.[1,2] Sepsis can occur with failure of several organs, including the kidneys, with a 70% mortality in those cases.[3]

Sepsis is the main etiology of acute kidney injury (AKI) in critically ill patients, and half of these patients require acute renal support.[2,4,5] Thus, measures that reduce mortality and costs are paramount. Among the actions with the greatest impact, we stress the early administration of antimicrobials.[6]

In septic patients, there are distribution volume and clearance variations, which may affect antimicrobial concentration. In those under acute kidney support (AKS), there is also clearance by dialyzing membranes, resulting in a risk of subtherapeutic dose and, consequently, antibiotic resistance.[6,7]. Therefore, the use of adequate doses of antimicrobials is key to avoiding the emergence of bacterial resistance, infection by opportunistic germs, as well as mortality reduction.[6]

To date, there are no validated guidelines to assist in the dose adjustment of

antibiotics in septic patients in AKS, and the recommendations are extrapolated from studies performed in non-critical patients with end-stage renal disease receiving chronic renal replacement therapy.[4,8] Thus, the purpose of this review is to discuss the complexity of this issue, taking into account the various factors related to drug clearance: critical patient characteristics, antimicrobial properties and dialytic method used.

PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIMICROBIALS IN CRITICAL PATIENTS

The parameter used to measure the microbiological activity of antimicrobials is the minimum inhibitory concentration (MIC), an *in vitro* measure of the antimicrobial effectiveness on the pathogen.

Pharmacokinetics and pharmacodynamics are tools that determine how much and how often the drug should be administered.[9] Pharmacokinetics describe drug absorption, distribution, metabolism and clearance, while pharmacodynamics describe the impact of serum concentration and response to the drug.[6,9]

Thus, the pharmacodynamics of an agent can be time dependent (T > MIC), related to the time of exposure to a specific MIC, such as beta-lactams, concentration dependent (Cmax/MIC), for aminoglycosides; concentration/time dependent (AUC/MIC), for the glycopeptides, as shown in Figure 1.

Several mechanisms influence antimicrobial pharmacokinetics in critical patients[10,11] (Figure 2). Absorption of a drug via the oral route may be impaired[7] by gastric dysmotility, adherence to the loops, interaction with nutritional components, gastric pH altered by the concomitant use of proton pump inhibitors,[12] as well as in the subcutaneous route of administration , absorption may be decreased due to reduced skin circulation secondary to the redistribution of blood flow and aggravated by edema.[7] Considering these effects on absorption, preference is given to the intravenous administration of antimicrobials in critically ill patients.

The distribution of antimicrobial agents also undergoes profound changes in critically-ill patients: the production of endotoxins by a microorganism during a septic shock can lead to the release of several inflammatory mediators that affect the vascular endothelium and culminate in poor blood flow distribution, increased capillary permeability, acid changes and endothelial injury.

Figure 1. Pharmacodynamics of an antimicrobial agent in relation to its concentration versus time. T > MIC: time (T) that the drug concentration remains above the minimum inhibitory concentration (MIC); C max/MIC: maximum concentration rate (C max) by MIC; AUC/MIC: rate of the area under the curve (AUC) of the concentration versus the time above the MIC. Adapted from Roberts and Lipman.[6]
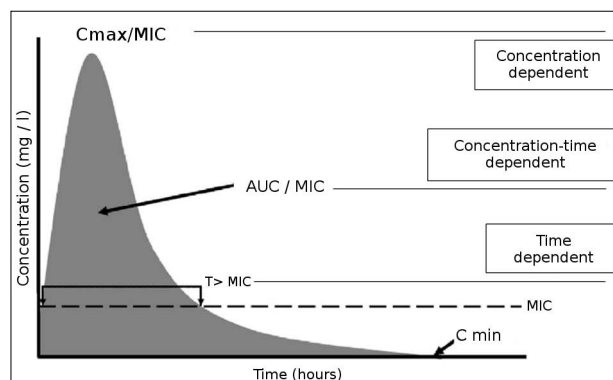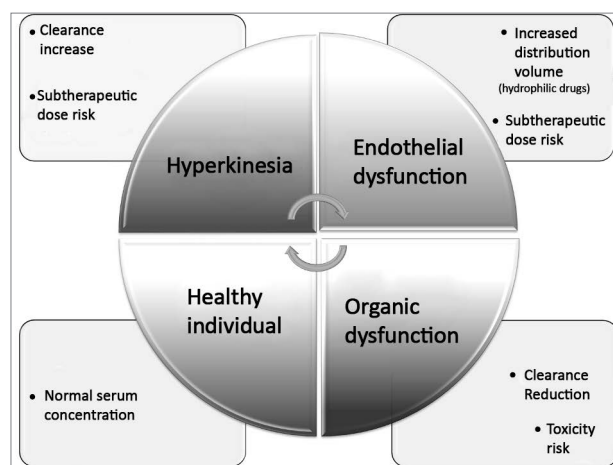

Figure 2. Influence of the patient's clinical status on antimicrobial pharmacokinetics. Adapted from Roberts and Lipman.[6]

Thus, there is extravasation of fluid from the intravascular space to the interstitium, increasing the volume of hydrophilic drug delivery and decreasing its serum concentration, which occurs with beta-lactams, aminoglycosides, glycopeptides, linezolid and colistin. This distribution volume can also be increased in the presence of mechanical ventilation, hypoalbuminemia and extracorporeal circuits.[6,7,13]

Drug clearance also occurs in septic patients: in the absence of organic dysfunction, there is an increase in renal perfusion and creatinine clearance, leading to an increase in the clearance of hydrophilic drugs,[6] as well as optimization of other routes of metabolization and clearance (biliary and transintestinal),[7] causing a reduction in the serum concentration of some antimicrobials.[6]

With the deterioration of the patient's state of health, there is myocardial depression and decreased perfusion, leading to a decrease in antimicrobial

clearance (either due to renal or hepatic dysfunction), an increase in the half-life and the potential toxicity of the high serum concentration of the drug and/or a buildup of its metabolites.[6]

The liver metabolism of antimicrobials may be affected in AKI, although this is not fully elucidated, probably due to changes in hepatic blood flow and reduction in the cytochrome P450 and CYP 3A[7] enzyme activity.

Regarding renal function adjustments, the regimen is based on distribution volume and systemic clearance[13]. Indirect methods to estimate the glomerular filtration rate are not so precise, despite the ease of monitoring.[10,13] Among the currently available calculations to estimate creatinine clearance are the Cockroft-Gault or the Modified Diet in Renal Diseases (MDRD), and the Chronic Kidney Disease EPI (CKD EPI) equations, all of which are validated in patients with stable renal function, which does not occur in the context of AKI.[10]

An alternative method is to measure clearance directly in 24-hour urine collection or in 2, 4 or 8-hour samples using the formula: Urinary creatinine concentration x urinary volume x serum time/creatinine, the result being expressed in mL/min, this method is not practical and it is limited in anuric patients.

Therapeutic drug monitoring can measure serum antimicrobial concentration, and its clearance can be calculated to improve the accuracy of subsequent dosing adjustments.[13] Bioanalytical methods include immunoassays, such as fluorescence polarization (FPIA), multiplied by enzyme (EMIT) and enzyme-linked immunosorbent assay (ELISA), all of which are methods that use the reaction of an antibody to its antigen. However, metabolites of drugs with similar structure may also be recognized by the antibody, resulting in falsely elevated concentration.

High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC/MS) are more specific methods that can separate and quantify drugs based on their molecular polarities and interactions with the stationary phase of a column, but these bear high cost and require highly skilled professionals, which makes it difficult to use them in medical practice.[16]

THE INFLUENCE OF ACUTE KIDNEY SUPPORT (AKS)

An important factor for drug clearance is the dialysis technique, based mainly on two types of transport: diffusion or convection, both efficient in the removal of low molecular weight solutes; but the most effective convective therapy in the clearance of high molecular weight substances.

The selection of the dialyzing membrane also alters clearance, since the high flow ones, with greater permeability to medium-size molecules, have a higher capacity to remove high molecular weight drugs than low-flow membranes.[7,17]

This difference was demonstrated in a small prospective cohort (n = 9) performed in the Czech Republic, comparing vancomycin clearance in critically ill patients with AKI patients dialyzed with high versus low-flow membranes. The median percentage of vancomycin clearance in low flow membrane dialyses was 17%, while that for high flow membranes was 31%. The study concluded that, despite these differences between membranes, monitoring serum vancomycin levels and dose administration after each dialysis is required, since these patients had sub-therapeutic levels of antibiotics.[18]

Another characteristic of the dialyzer membrane under discussion is its adsorption rate. Hydrophobic synthetic membranes have high adsorption, while cellulose acetate membranes have lower adsorption.[19] The clinical importance of this property in relation to serum antimicrobial level interference is still lacking, but some evidence suggests an early saturation of this process.[20]

The options for AKS in critically ill patients are peritoneal dialysis (PD) and hemodialysis (HD), which can be classified as intermittent (IHD), prolonged (PHD) and continuous (CHD)[21-23] hemodialysis (Table 1).

PD is an option for a selected group of patients, and recent studies suggest that, when indicated, it should be performed continuously, with large volumes of dialysate and through a flexible catheter and cycler, with survival results are similar to those from patients treated with IHD.[24] In PD the dialyzer membrane is the peritoneum and little is known about the clearance of drugs in high volume therapies.

IHD is characterized by high blood and dialysate fluxes, a 4 to 5 hours duration and an affordable cost.[25] IHD is indicated in patients with AKI who are hemodynamically stable, and it can be done on alternate days or daily, according to the patient's clinical and laboratorial conditions.[26]

CHD is defined as a long and continuous 24-hour treatment that uses dialysate and blood flows lower than the conventional ones.[27,28] It is an efficient

TABLE 1	TYPES OF DIALYSIS AND ITS MAIN CHARACTERISTICS			
	CHD	PHD	IHD	PD
Clearance of uremic toxins	Convection/Diffusion	Diffusion	Diffusion	Diffusion
Membranes	High flow	High flow/Low flow	High flow/Low flow	Peritoneum
Dialysate flow	Low (1000-1500 ml/h)	Low (200-300 ml/min)	High (500 ml/min)	High dialysate volume
Blood flow	Low (100-150 ml/min)	Low (100-200 ml/min)	High (300-400 ml/min)	50-100 ml/min (Blood flow in the peritoneum)
Ultrafiltration and solute clearance	Continuous (24 hours)	Intermittent (6-18 hours)	Intermittent (3-5 hours)	Continuous (24 hours)
Anticoagulation	Continuous	Intermittent	Intermittent	Unnecessary
Hemodynamic stability	Excellent	Good	Bad	Excellent
Use of standard dialysis machine	No	Yes	Yes	Yes
Costs	High	Low	Low	Low

CHD: continuous hemodialysis; PHD: prolonged hemodialysis, IHD: intermittent hemodialysis; PD: peritoneum dialysis.

method because it provides adequate metabolic and volume control without impairing the patient's hemodynamic stability.

An intermediate method that provides hemodynamic stability and adequate metabolic control of the patient with a shorter duration than CHD is prolonged hemodialysis (PHD), lasting between 6 and 18 hours, with lower blood flows and less dialysate than what is conventionally used.[28,29]

IHD and PHD can be performed with capillaries of low or high flow and efficiency, that is, with greater or lesser capacity for medium-size molecules removal, according to their ultrafiltration coefficients and performance (Kuf and KoA, respectively), and with variable blood flow and treatment duration. CHD is performed by means of hemofilters, that is, capillaries with great capacity to remove larger molecules using low blood flows.[30]

Regarding the different AKS modalities, there are few antibiotic clearance studies in PD and HD, and the studies in IHD and CHD do not always involve critical patients. Thus, there are many questions regarding drug regimen corrections for critically ill patients in different dialytic modalities.

In clinical practice, one of the most commonly used guidelines is The Sanford Guide to Antimicrobial Therapy,[31] which considers the IHD and CHD modalities, and there are recommendations that the dose of antimicrobials for PHD be estimated according to

that of CHD. However, Mushatt et al.[32] recommend that for antibiotics given every 24 hours, a supplementary dose should be considered immediately after PHD or, alternatively, a daily dose be prescribed after PHD. For those given every 12 hours, keep one dose after the PHD and another after 12h. Another suggestion is that drugs such as vancomycin and gentamicin, which can have their serum levels measured, are measured immediately after PHD to determine the need for supplemental dose after dialysis.[32]

Table 2 shows the pharmacodynamic (PD) and pharmacokinetic (PK) particulars of the major antimicrobials used in intensive care. Although the recommended doses have been extrapolated from studies not performed with the critically ill population with AKI and under AKS, they are used in clinical practice.

CONCLUSION

The topics discussed in this review show that critical patients have several changes in the pharmacokinetics and pharmacodynamics of antimicrobials, culminating in variations in their serum concentrations. Thus, there is an increased risk of overdose and drug toxicity, as well as subtherapeutic dosage and risk of bacterial resistance, infection by opportunistic germs and higher mortality.

Moreover, antimicrobial clearance by the different modalities of AKS in critical patients is a complex issue, since, besides being dependent on the

TABLE 2   ANTIMICROBIAL AGENTS USED IN INTENSIVE CARE AND THEIR MAIN CHARACTERISTICS (BASED ON THE SANFORD GUIDE TO ANTIMICROBIAL THERAPY)[31]

	Vancomycin	Meropenem	Cefepime	Piperacillin/ Tazobactam	Fluconazole	Micafungin
PD	AUC/MIC	T > MIC	T > MIC	T > MIC	AUC/MIC	AUC/MIC
Molecular weight	1485	384.46	571.5	539.5 322.3	306.99	1292.26
Distribution volume* (L/Kg)	0.7	0.23-0.35	0.3	0.24-0.4	0.7 - 0.8	0.39
% linked to proteins*	10-55	2	20	16-48	10	> 99
Clearance	Renal	Renal	Renal	Renal	Renal	Hepatic/Renal
Dose in normal kidney function	15-20 mg/kg every 8-12h	1 g every 8h	1-2 g every 8-12h	3,375 g every 6h	100-400 mg every 24h	100-150 mg every 24h
Dose in CHD	500 mg every 24-48h	500mg every 24h	2 g every 24h	2,25g every 6h	200-400 mg every 24h	Without correction
Dose in PHD**	Without information	Without information	Without information	Without information	Without information	Without correction
Dose in IHD***	15 mg/kg after HD	500 mg every 24h	1g every 24h (+ extra 1 g after HD	2,25 g every 12h (+ extra 0,75g after HD)	100-400 mg every 24h - after HD	Without correction
Dose in PD****	7,5 mg/kg every 2-3 days	500 mg every 24h	1-2 g every 48h	2,25 g every 6h	50-200 mg every 24h	Without correction

PD = pharmacodynamics; AUC = area under the curve; MIC = minimum inhibitory concentration; T = time; CHD = continuous hemodialysis; PHD = prolonged hemodialysis, IHD = intermittent hemodialysis; PD = peritoneal dialysis

*In healthy individuals **The same doses used in CHD are suggested for being used ***Considering the next IHD in 1 day ****Dose in COPD (continuous outpatient peritoneal dialysis).

dialyzing membrane characteristics (surface area and pore size) and drug specificities (water solubility, molecular weight, extension of binding to proteins), it also depends on the blood flow used, treatment duration and the type of transport used, diffusion and/or convection.

There are no validated guidelines to aid in dose adjustment of antibiotics in septic patients in AKS, with recommendations being, so far, extrapolated from studies in non-critical patients and with end-stage renal disease receiving chronic renal replacement therapy. Thus, due to the importance of maintaining the therapeutic level of antimicrobials, more studies on this complex topic are necessary to reduce microbial resistance and mortality.

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