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Applying pharmacokinetic/pharmacodynamic principles for optimizing antimicrobial therapy during continuous renal replacement therapy

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Abstract

Continuous renal replacement therapy (CRRT) is progressively supplanting intermittent haemodialysis (IHD) in critically ill patients. Although CRRT indeed offers more appropriate haemodynamic, fluid, and metabolic stability, concern is rising about its impact on concomitant drugs and, in particular, antimicrobial treatment. Antimicrobial dose recommendations have been elaborated to avoid drug accumulation and toxicity in patients undergoing IHD. However, these dosing regimens have resulted in significant underdosing in patients undergoing CRRT, thereby increasing the risk of treatment failure and development of resistance. Applying pharmacokinetic/pharmacodynamic (PK/PD) principles may aid one to obtain more adequate antimicrobial therapy during CRRT. Much progress has been made in recent years resulting in relevant changes in particular antimicrobial therapies.

In this review, we discuss antimicrobials that are frequently used in an intensive care setting. Drugs are divided according to their PK/PD characteristics and, wherever possible, dose recommendations during CRRT are provided. Of course, while therapeutic drug monitoring remains the best way to cope with PK/PD variability within a critically ill CRRT population, its bedside use is actually limited to some specific antibiotics.

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Early and adequate broad-spectrum antimicrobial therapy is crucial in septic patients and, as a milestone, reduces mortality [1]. Pharmacokinetic and pharmacodynamic (PK/PD) characteristics determine the effect of antimicrobials against pathogens and enable one to create dose strategies that allow for the most optimal therapy at the lowest risk of resistance and toxicity. The kidney is a key organ for eliminating drugs from the body. Acute kidney injury (AKI) and renal replacement therapy significantly alter PK/PD characteritics of commonly used drugs, including most antimicrobials. In due course, dose adaptations were developed for intermittent haemodialysis (IHD). However, in critically ill patients, IHD is being progressively supplanted by continuous renal replacement therapy (CRRT). Compared with IHD, CRRT is indeed better haemodynamically tolerated, offers rapid correction of life-threatening metabolic alterations, allows more adequate control of fluid balance, and may even lower the incidence of post-intensive care (IC) need for chronic dialysis. Of note is that antimicrobial PK/PD characteritics during CRRT has been harshly judged because clinicians obstinately stuck to dosing regimens that were similar to those applied in IHD. This attitude proved painfully wrong and resulted in the inadequate treatment of septic CRRT patients [2]. The reduced drug doses recommended for IHD indeed proved to be far too low during CRRT where either "normal", or even increased doses were required to obtain therapeutic efficacy. Moreover, antimicrobial characteristics (e.g. molecular weight, protein binding, hydro- or lipophilicity) and CRRT-related parameters (e.g. membrane sieving coefficient or adsorption capacity) also determine CRRT-related drug elimination [3, 4]. Antibiotic clearance (CL) and volume of distribution (Vd) can be significantly altered in

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critically ill patients because of volume expansion, vasopressor treatment, unexpected changes in renal CL, and the used CRRT modality [5, 6]. Finally, drug elimination also depends on membrane porosity which is due to changes over time [7]. Therapeutic drug monitoring (TDM) of antimicrobials is the method of choice to cope with PK/PD variability within a CRRT population [2]. However, only few antibiotics can actually be routinely "monitored". For the vast majority, we must rely on continuously refined and updated PK/PD-based recommendations [8].

In this review, we will discuss some of the most frequently used antimicrobials in an IC setting. For the sake of clarity, we will divide antimicrobials on a PK/PD basis into respectively time-dependent (i.e. maximally suppressing microorganisms as long as concentrations remain above the minimum inhibitory concentration (MIC), peak-dependent (i.e. maximal suppression at highest possible peak concentration (Cpeak)) and both peak and time-dependent agents.

TIME DEPENDENT ANTIMICROBIALS

BETA-LACTAMS

Continuous infusion (CI) of beta-lactams, maintaining drug concentrations 4 to 5 times higher than the MIC, is the theoretically proposed PK/PD driven approach to obtain complete microbiological eradication [1, 2]. It must be kept in mind that CI has no convincing effect on clinical outcome and probably only benefits specific patient populations where intermittent infusion fails to achieve PK/PD goals (e.g. patients infected with high-MIC organisms, unstable critically ill patients, …) [7]. The physicochemical and pharmacokinetic properties of beta-lactams make them susceptible for significant removal by CRRT. However, few studies have linked PK/PD principles to an effective and safe management of continuous beta-lactam infusion in critically ill patients requiring CRRT.

In a recent PK/PD study, patients undergoing CRRT were given a loading dose of 4.5 g of piperacillin-tazobactam followed by a CI of 500 mg h^{-1}. Piperacillin concentrations during CI were above the target susceptibility breakpoint for the entire dosing interval in all patients [9, 10]. The currently recommended piperacillin-tazobactam approach for CI in CRRT is a bolus loading dose of 4.5 g followed by an infusion of 18 g 24 u [11]. A recent systematic review and meta-analysis suggested that an extended or continuous infusion strategy of piperacillin/tazobactam had a significantly higher clinical cure rate and lower mortality rate in comparison with intermittent therapy [12]. Experience with ceftazidime is equivocal. Administration of 1 to 2 g ceftazidime every 6h resulted in high trough levels increasing the risk of nephrotoxicity during continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF) [13]. In contrast, a 2 g loading dose of ceftazidime followed by a CI of 3 g day^{-1} resulted in serum concentrations more than four times the MIC for all susceptible pathogens in seven critically ill patients undergoing CVVHDF [14].

According to a population PK/PD model of meropenem developed in critically patients undergoing CRRT, Isla *et al.* [15] recommended CI for treatment of pathogens with a MIC ≥ 4. Meropenem is significantly eliminated by high-volume CVVH, necessitating steady-state doses of 1g every 8 h to maintain concentrations active against more resistant organisms [16]. Because the stability of meropenem reconstituted in a solution is influenced by storage temperature [17], it is advised to infuse 2 g meropenem for 8 h, 3 times daily to cover a 24h period.

VANCOMYCIN

In 2009, joint guidelines issued by the American Society of Health System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists determined that the area under the concentration-time curve (AUC)/MIC ratio is the best PK/PD parameter to predict vancomycin effectiveness. A target ratio ≥ 400 mg $h^{-1}L^{-1}$ was put forward to eradicate methicillin-resistant *Staphylococcus aureus* [18]. Although not supported clinically, this target AUC/MIC ratio is attained when increasing vancomycin trough concentrations to 15–20 mg L^{-1} provided that MIC values do not exceed 1.5–2 mg L^{-1}.

Whether vancomycin should be administered in divided doses or as a CI is matter of debate. Intermittent trough-guided vancomycin dosing remains controversial. Neely *et al.* [19] reported that dose adjustment based on trough concentrations resulted in poor achievement of safe and effective plasma concentrations. Moreover, adequate vancomycin AUCs over 24h (AUC24) were often seen when the trough concentration was less than 15 mg L^{-1}. In contrast, Prybylski [20] recently showed that trough-based vancomycin dosing had a high probability of achieving an AUC24 of at least 400 mg $h^{-1}L^{-1}$, yet was associated with more toxicity. High dose (i.e. > 4 g day^{-1}) vancomycin treatment is related to a higher likelihood of nephrotoxicity exacerbated by weight, estimated creatinine Cl, and IC residence [21]. CI of vancomycin is considered to be more practical, cheaper, easier to monitor, and is theoretically associated with less PK/PD variability than intermittent administration [7]. Current CI practice includes a loading dose of 15–20 mg kg^{-1} followed by an infusion of 10–40 mg $kg^{-1}day^{-1}$ based on the patient's renal function and aiming at a steady-state concentration between 20 and 30 mg L^{-1} [22].

Nephrotoxicity is the most observed adverse effect related to vancomycin administration. The incidence of nephrotoxicity during trough-based intermittent vancomycin therapy varies from 5% to 43%. Vancomycin troughs exceeding 15 mg L^{-1} were independently associated with a greater risk of AKI. A recent meta-analysis comparing continuous

and intermittent vancomycin therapy showed comparable clinical efficacy and mortality of both treatment modalities but a significantly lower incidence of nephrotoxicity in patients receiving CI [23].

However, several studies challenge the concept that continuous vancomycin infusion might alleviate the risk of AKI in critically ill patients [24, 25]. When targeting serum levels between 20 and 30 mg L^{-1}, AKI was observed in 30% of patients. The incidence of AKI increased substantially when plasma levels exceeded 30 mg L^{-1}.

CI of vancomycin (35 mg kg^{-1} loading dose followed by 1.5 g (60 mg h^{-1}) daily) in critically ill patients on CVVH achieved target levels of 15 to 25 mg L^{-1} within 24 h faster than intermittent administration whilst consistently keeping vancomycin levels within therapeutic range [26]. Increasing the loading dose to 35 mg kg^{-1} given over a 4 h period allowed more rapid achievement of target drug concentrations in a majority of patients [27].

LINEZOLID

Linezolid has a molecular weight of 337 daltons (Da) which is lower than the cut-off of the "high-flux" and "high cut-off" (HCO) membranes that are often used in IC CRRT protocols. Free drug fraction is approximately 70%, Vd is relatively low [28, 29] and albumin-bound linezolid is removed by HCO membranes [30]. Linezolid thus is highly cleared by CRRT resulting in extreme variability in linezolid PK/PD behaviour across critically ill patients treated with CRRT [29].

Adembri *et al.* [31] compared the PK/PD profile of linezolid administered by intermittent infusion (600 mg 12 h^{-1}) or CI (300 mg loading dose + 900 mg CI on day 1, followed by 1200 mg daily thereafter) in critically ill septic patients. Trough serum levels of linezolid varied widely and remained below susceptibility breakpoints after intermittent administration during the study period. In the CI group, linezolid serum levels were more stable and always above susceptibility breakpoints. CI enabled to achieve significantly more therapeutic AUC/MIC values than intermittent infusion.

In obese critically ill patients affected by pneumonia, CI of linezolid (600 mg loading dose + 1200 mg CI $24h^{-1}$) resulted in significantly higher linezolid plasma concentrations above MIC (range 1–4 mg L^{-1}) as compared with intermittent infusion. Pulmonary penetration was also significantly higher in the CI group [32].

So far, no PK/PD study has compared in intermittent infusion vs. CI of linezolid in CRRT-treated subjects. We advise to administer linezolid during CRRT either as a high intermittent dose (3 × 600 mg day^{-1}) or as a loading dose of 600 mg, followed by a CI of 1200 mg $24h^{-1}$.

FLUCONAZOLE

Although pharmacokinetically classified as a drug with time-dependent activity, fluconazole exhibits concentration-related fungistatic activity over a narrow range of concentrations. Fluconazole concentrations > 4 × MIC also do not produce additional *in vitro* antifungal activity [33]. Of note is that fluconazole activity does not depend on serum concentrations but on concentrations obtained at the infection site. Although tissue fluconazole concentrations (except for bone) were found to be higher than serum concentrations [34], the latter remain mathematically linked to the amount of the drug at the site of infection [24]. While most Candida strains are inhibited at a concentration of 6 mg L^{-1} fluconazole [35], concentrations above 10 mg L^{-1} may be necessary for treating other fungi (e.g. *Cryptococcus neoformans*) [35].

In invasive candidiasis, fluconazole is administered at a loading dose of 800 mg (12 mg kg^{-1}), followed by an average daily dose of 400 mg (6 mg kg^{-1}) [36]. An early PK/PD study reported that fluconazole CL during CVVHDF was almost twofold higher than in patients with normal renal function but surprisingly proposed no dose adaptation [37]. Kishino *et al.* [38] assessed low dose (100 to 200 mg day^{-1}) fluconazole PK/PD in 6 liver transplant patients undergoing CVVHDF. Fluconazole elimination half-life was less than one-third of that of normal volunteers. Increasing the daily fluconazole dose to 800 mg reached target serum levels in all subjects. A comparable PK/PD study in 4 critically ill patients undergoing similar renal replacement therapy evaluated this higher fluconazole dose (400 mg every 12 h or 800 mg every 24 h). Elimination half-life was also markedly lower than in normal volunteers but none of the dose regimens reached effective plasma trough concentrations [37]. Albeit scarcely documented, it is evident that fluconazole is extensively removed by CRRT and higher maintenance doses are required to assure a therapeutic effect. In the past, it has been proposed to administer fluconazole during different CRRT modes at the same loading dose as in patients without renal failure, followed by a maintenance dose adjusted for anuria by multiplying with a (different) factor accounting for the extracorporeal elimination of the absorbed dose [39]. Calculations based on PK/PD analysis from the above mentioned studies, however, suggest a dose of 500–600 mg fluconazole every 12 h in all CRRT-treated subjects [40–42].

PEAK DEPENDENT ANTIMICROBIALS

AMINOGLYCOSIDES

Concentration-dependent killing of aminoglycosides is maximally exploited at least toxicity when the Cpeak/MIC ratio is at least 8–10. Aminoglycosides are administered once daily and are easily removed by CRRT [43].

The "standard" 15 mg kg^{-1} amikacin dose was found to be largely insufficient to obtain the required PK/PD target in CRRT-treated patients. Loading doses of 25 to 35 mg kg^{-1} have been proposed [44, 45]. Doses as high as 80 mg kg^{-1} (!) may even be necessary to treat infections caused by multidrug-resistant Gram-negative (MDR-GN) infections only susceptible to amikacin. High-dose amikacin treatment obviously increases the risk of AKI and, in the longer term, may even cause permanent loss of renal function. In this particular setting, CRRT might be used as an aid to prevent renal toxicity. Brasseur et al. first applied this "prophylactic" CRRT concept in 15 patients infected with MDR-GN bacteria [46]. Amikacin was administered in 11 patients. Initially, a loading dose of 25–30 mg kg^{-1} was given. Subsequent dosing was adapted to obtain a Cpeak/MIC between 8 and 12. High-flow CVVHDF was initiated after the Cpeak of the loading dose was sampled and continued over the entire duration of amikacin therapy. Maximal median daily amikacin dose was 29 (26–67) mg kg^{-1}. This approach appeared to beneficially affect overall clinical outcome and incidence of nephrotoxicity for the whole patient group but requires further evaluation in larger studies.

Gentamycin PK/PD behaviour has only been studied in peritoneal dialysis [47]. A Cpeak/MIC gentamycin concentration of ≥ 30 mg L^{-1} is needed to assure optimal therapeutic efficacy. Studies in IC patients with normal renal function showed that this target was achieved in only 4% of patients after an initial dose of 6 mg kg^{-1} [47], in 59% of patients after 8 mg kg^{-1} [48], and in 100% of patients after infusion of at least 11 mg kg^{-1} [49]. It is conceivable that equally high doses should be administered in a CRRT-treated population.

METRONIDAZOLE

Metronidazole is extensively removed by IHD [50] but no data are available in CRRT. A once daily 1500 mg dose of metronidazole resulted in more optimal tissue concentrations than a 3 × 500 mg daily regimen [51]. Awaiting more PK/PD data, we recommend administration of a single 1,500 mg dose during CRRT.

PEAK AND TIME DEPENDENT ANTIMICROBIALS

COLISTIN

Although colistin possesses rapid concentration-dependent bacterial killing activity against susceptible strains, the AUC/MIC ratio is the PK/PD parameter that correlates best with its antibacterial effect [52]. Colistin is commercially available as colistimethate sodium (CMS). CMS is an inactive prodrug that is hydrolyzed to a series of sulfomethylated derivatives and to colistin that exhibits antibacterial activity. CMS is predominantly cleared by the kidneys whereas colistin undergoes extensive renal tubular reabsorption and mainly is non-renally eliminated [53]. Colistin is bactericidal when a steady-state plasma concentration of at least 2 mg L^{-1} is achieved. It is important to note that CMS and colistin follow a different elimination pattern during CVVH. A decay in CMS elimination from plasma was seen after each dose which pleads for convective elimination. In contrast, colistin removal followed an asymptotic curve compatible with slow elimination and accumulation as seen with adsorption. This supports the concept that CMS is eliminated by convection whereas colistin removal is determined by the adsorptive capacity of the CRRT membrane [54].

Implementation of predicted PK/PD modelling on plasma CMS/colistin concentrations, suggests a loading dose of 12 million international units (MIU) CMS followed by a maintenance dosage of 6.5 to 7.5 MIU every 12h [55]. We recently evaluated clinical outcome and microbiological efficacy of this treatment regimen in 16 critically ill patients infected with MDR-GN infections only susceptible to colistin [56]. CVVH was performed under regional citrate anticoagulation (RCA) using a highly adsorptive membrane. A loading dose of 9 MIU CMS was administered followed by 4.5 MIU $8h^{-1}$. A favourable clinical response was obtained in 14 (88%) patients. Microbiological eradication was complete in 10, presumed in 4 and absent in 2 subjects. Seven (45%) patients left the hospital alive. Renal function was preserved in 6 patients. One patient required intermittent dialysis at IC discharge. Thus, CMS given as a loading dose of 9 MIU followed by a divided maintenance dose of 13 to 15 MIU daily, guarantees adequate and safe treatment in patients undergoing CRRT. We suggest that CRRT should be equipped with highly adsorptive filters to avoid colistin accumulation and performed under RCA to preserve functional membrane capacity [57].

CIPROFLOXACINE

Ciprofloxacin PK/PD targets for optimal therapeutic efficacy are either a Cpeak ≥ 10 mg L^{-1} [58] or an AUC/MIC ratio >100 [59]. Ciprofloxacin elimination is highly variable during CRRT. Nonetheless, a dose of 400 mg day^{-1} was considered to be sufficient to maintain effective drug concentrations in the plasma of patients undergoing CVVH or CVVHDF [60]. Shotwell *et al.* [61] studied 14 patients on CVVHD treated with ciprofloxacin without dose adjustment for kidney failure. Only 1 patient attained a peak ciprofloxacin concentration ≥ 10 mg L^{-1} whereas AUC/MIC values > 100 were obtained in 8 subjects. Significant dependence of Cpeaks on CRRT was observed [61]. Several small studies also suggested that greater than traditional daily doses of 400–800 mg ciprofloxacin are required to achieve optimal bactericidal activity during CRRT [62, 63]. We currently prescribe ciprofloxacin at a dose of 400 mg $8h^{-1}$ during CVVH.

CONCLUSIONS

A PK/PD directed approach for optimal dosing of antimicrobials during CRRT is progressively gaining a clinical

Table 1. Antimicrobial dose recommendations for continuous veno-venous hemofiltration

Antimicrobial	Loading dose	Maintenance dose
Amikacin	30–35 mg kg^{-1}	TDM (Cpeak 8–10)/15 mg kg^{-1}
Meropenem	2 g	2 g over 8h (prolonged infusion)
Piperacillin-tazobactam	4 g/0.5 g	16 g/2 g (continuous infusion)
Vancomycin	35 mg kg^{-1} over 4h	TDM (Css 20–30 mg L^{-1}) (continuous infusion)
Teicoplanin	15 mg kg^{-1} 3 × every 12h	600 mg od
Linezolid		600 mg tid or continuous infusion of 1200 mg after a loading of 600 mg in 60 min
Ciprofloxacin	800 mg	400 mg tid
Tigecyclin	150 mg	100 mg bid
Colistin	9 MIU	4.5 MIU tid
Voriconazole	8 mg kg^{-1} bid	6 mg kg^{-1} bid
Fluconazole		600 mg bid
Cefepime		2 g tid
Gentamycin	11 mg kg^{-1}	7 mg kg^{-1} od
Co-trimoxazole	1200 mg/240 mg	800 mg/160 mg tid
Clindamycine		900 mg qid

MIU — million international units; TDM — therapeutic drug monitoring; C_{ss}: steady-state concentration; od — once daily; bid — twice daily; tid — three times daily; qid — four times daily

foothold and has already resulted in significant dose adaptations of crucial IC antibiotics such as piperacillin-tazobactam, amikacin and colistin. For the majority of drugs, however, adequate CRRT dosing still is confined to "trial and error" or "educated guessing", with any new PK/PD studies being eagerly awaited. We included Table 1 to summarize CVVH dose recommendations for some relevant antimicrobials. TDM may be an important aid to optimize individual dosing regimens during CRRT. TDM already "finetunes" aminoglycoside and vancomycin treatment in current daily practice and is expected to cover, in due course, also the beta-lactams and a variety of drugs with either a narrow therapeutic range (e.g. colistin) or marked pharmacokinetic variability (e.g. linezolid).

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