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To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: the eternal doubt

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Critical illness, acute renal failure and continuous renal replacement therapy (CRRT) are associated with changes in pharmacokinetics. Initial antibiotic dose should be based on published volume of distribution and generally be at least the standard dose, as volume of distribution is usually unchanged or increased. Subsequent doses should be based on total clearance. Total clearance varies with the CRRT clearance which mainly depends on effluent flow rate, sieving coefficient/saturation coefficient. As antibiotic clearance by healthy kidneys is usually higher than clearance by CRRT, except for colistin, subsequent doses should generally be lower than given to patients without renal dysfunction. In the future therapeutic drug monitoring, together with sophisticated pharmacokinetic models taking into account the pharmacokinetic variability, may enable more appropriate individualized dosing.

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Introduction

Optimal dosing of antibiotics is difficult because doses cannot be titrated to effect. Instead dosing should be designed to achieve pharmacokinetic targets associated with optimal killing. The pharmacokinetic parameters vary with the class of antibiotic and the target values depend on the organism and the susceptibility of the organism, as reflected by the minimum inhibitory concentration (MIC). Given that the targets are pharmacokinetic parameters, it is self-evident that appropriate antibiotic dosing in patients receiving continuous renal replacement therapies (CRRT) requires knowledge of the pharmacokinetic changes that occur in these patients as well as the clearances obtained by the specific CRRT used.

Continuous renal replacement therapies are modes of therapy which are applied almost exclusively in intensive care units. As a result drug pharmacokinetics in patients receiving CRRT are affected by changes due to critical illness, acute renal failure and the therapy. These issues have previously been reviewed by us [1] and will be dealt with only briefly here.

Pharmacokinetic changes due to renal failure

Changes in drug pharmacokinetics associated with critical illness and acute renal failure include increases in volume of distribution for some drugs (e.g. colistin [2], daptomycin [3,4], amikacin [5]) but not all. In general the volume of distribution of hydrophilic antibiotics (e.g. aminoglycosides, beta lactams, glycopeptides) increases more than lipophilic antibiotics (e.g. macrolides, linezolid and fluoroquinolones) which already have a large volume of distribution [6••]. Furthermore there may be increases in non-renal clearance [7] and some residual renal function despite the presence of acute renal failure and CRRT.

There are three main modalities of continuous renal replacement therapy (CRRT): continuous veno-venous haemodialysis (CVVHD), continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF). Clearance of solutes by these modalities is dependent on a number of factors as described in the following equations [1]:

$$\mathrm{Cl}_{\mathrm{CVVH(post)}} = Q_f \times S_c$$

$$\mathrm{Cl}_{\mathrm{CVVH(pre)}} = Q_f \times S_c \times \frac{Q_b}{Q_b + Q_{\mathrm{rep}}}$$

$$\mathrm{Cl}_{\mathrm{CVVHD}} = Q_d \times S_d$$

$$\mathrm{Cl}_{\mathrm{CVVHDF}} = (Q_f + Q_d) \times S_d$$

where $\mathrm{Cl}_{\mathrm{CVVH\ (post)}}$ = clearance by continuous veno-venous haemofiltration with replacement fluid infused

post-filter, $Cl_{CVVH\ (pre)}$ = clearance by continuous veno-venous haemofiltration with replacement fluid infused pre-filter, Cl_{CVVHD} = clearance by continuous veno-venous haemodialysis, Cl_{CVVHDF} = clearance by continuous veno-venous haemodiafiltration, Q_b = blood flow rate, Q_d = dialysate flow rate, Q_f = ultrafiltrate flow rate, Q_{rep} = replacement fluid flow rate, S_c = sieving coefficient, S_d = saturation coefficient.

From these equations it can be seen that the main determinants of elimination by CRRT are sieving or saturation coefficient and effluent flow rate (ultrafiltration rate, dialysate flow rate or the two combined). Blood flow rate plays a relatively minor role. The sieving coefficient and the saturation coefficient describe the ratio of solute concentration in ultrafiltrate (sieving coefficient) or the dialysate (saturation coefficient) to solute concentration in the blood. Drugs are often bound to plasma proteins which are large molecules that cannot cross the dialysis or haemofiltration membrane and therefore only unbound drug (free drug) is dialyzed or filtered. As a result sieving coefficient and saturation coefficient are related to the unbound fraction. Acute phase changes in plasma protein concentrations are common in critical illness, affecting the sieving and saturation coefficients [8]. Thus, in critically ill patients these coefficients may not reflect the unbound fractions normally measured in healthy volunteers. Furthermore there may be significant patient to patient variation in these coefficients (Table 1; a more conveniently formatted version of this table can be found in the online version of this paper). Different filter materials may also be associated with different coefficients [1].

Pharmacokinetic changes due to variability of CRRT

The issue is further complicated by the fact that continuous renal replacement therapy is not a single modality applied in a uniform way. Instead considerable variation in effluent rate between patients and between intensive care units is common, filter or dialyzer material may vary and replacement fluid may be infused pre-filter or post-filter. Furthermore it is frequently not continuous but is interrupted for technical reasons and to transport the patient out of the intensive care, for example, for imaging or surgery. During these periods of downtime there is no CRRT clearance and therefore the actual (or delivered) CRRT clearance may be considerably lower than prescribed.

Thus dosing of antibiotics should take into account changes in patient characteristics such as volume of distribution and changes in non-renal clearance, the killing characteristics of the antibiotic, the minimum inhibitory concentration of the target organism, the effluent rate and saturation or sieving coefficient as well as the fact that these coefficients may change with acute phase changes in plasma protein concentrations. Given this, it is not surprising that non-individualized dosing results in a large proportion of patients being either under or overdosed [9,10,11•] resulting in calls for more individualized dosing [9,12,13,14]. In our previous review we proposed an individualized approach based on both pharmacokinetic and microbiological considerations. We recommended an initial dose based on the published volume of distribution and subsequent doses be based on an estimate of total clearance — total clearance being the sum of residual renal clearance, non-renal non-CRRT clearance and CRRT clearance. We proposed that CRRT clearance should be calculated using the equations given above and data obtained from critically ill patients. This approach, like all other dose adjustments for CRRT, has not been formally validated. Nevertheless, since our previous review other authors have advocated a similar approach [15,16,17] and recent data provide some supportive evidence.

Prescription of initial loading dose and subsequent maintenance doses

Our recommendation is to base the initial dose on the published volume of distribution of each specific antibiotic in critically ill patients and the target concentration of that antibiotic. As volume of distribution is either unchanged or increased in the critically ill, this will lead to patients receiving at least the standard dose of antibiotic. Dosing that does not take into account changes in volume of distribution will lead to low initial serum concentrations [18].

Furthermore if our method of estimating CRRT clearance is correct then total clearance, half life and serum concentrations will be dependent, to some extent, on effluent rate. Yamamoto *et al.* found that ratio of predicted clearance (based on an *in vitro* measurement of unbound fraction and effluent rate) to actual clearance ranged from 0.67 to 1.5 [16]. Beumier *et al.* found that serum concentrations of meropenem, ceftazidime, cefepime and piperacillin-tazobactam were correlated with effluent rate despite the fact that only the initial drug dose was fixed (subsequent doses were adjusted according to serum concentrations) [11•]. Similarly, effluent rate has been shown to be associated with piperacillin clearance [7], doripenem clearance [19] and vancomycin serum concentration [20]. Jamal *et al.* systematically reviewed the literature and demonstrated that CRRT clearance of meropenem, piperacillin-tazobactam and vancomycin is associated with the effluent rate [21•]. However, this finding needs to be interpreted with some caution. In some cases CRRT clearance was derived from the equations given above and therefore CRRT clearance and effluent rate would have been mathematically coupled. In contrast, Roberts *et al.* found that trough concentrations of meropenem, piperacillin-tazobactam, vancomycin and ciprofloxacin were not associated with