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EDITORIAL

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Clinical measures for increased creatinine clearances and suboptimal antibiotic dosing

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Vancomycin, a glycopeptide, is still the mainstay for resistant gram-positive infections [1]. As a result of the worry about toxicity an easy-to-use assay was produced and is now in widespread use resulting in therapeutic drug monitoring [1].

The pharmacokinetic and pharmacodynamic (PK/PD) parameters of major importance for vancomycin optimisation are not that easy to define (Table 1). The best clinical study addressing clinical outcomes according to PK/PD parameters found that the clinical and bacteriological response to vancomycin therapy was superior in patients with higher AUC_{0-24}/MIC values ($\geq$400) ($p = 0.0046$) [2]. For various reasons the Infectious Diseases Society of America (IDSA) now recommends vancomycin trough concentrations of 15–20 mg/L for serious MRSA infections [3, 4] (Fig. 1).

Vancomycin is eliminated by the body mainly via the kidneys, more particularly by glomerular filtration. Creatinine clearance (CL_{CR}) is the clinical surrogate we use in ICU for glomerular filtration [5]. It is then not surprising that the estimates of CL_{CR} have been used as educated guesses for drug clearance, including those of vancomycin [6, 7].

Measurement of CL_{CR} as a clinical routine can be used not only to help vancomycin dosing, but to help dosing of all renally excreted drugs [5, 8].

Are there any more ubiquitous clinical data that can be used to predict drug clearance instead of measuring CL_{CR}?

This current study by Shimamoto et al. is impressive as it is a novel way of addressing the above question. It uses common clinically available data to predict low serum vancomycin concentrations resultant on high vancomycin clearances. The study uses 105 non-ventilated patients without neutropenia and shows that patients with increasing systemic inflammatory response syndrome (SIRS) criteria have lower serum vancomycin concentrations with standard dosing unless there is renal end-organ dysfunction (decreased glomerular filtration rate, GFR). They correlate these low vancomycin concentrations with increased estimated CL_{CR}.

We believe we can explain these results physiologically. It is the innate immune response that causes the SIRS. This same innate immune response results in increased renal blood flow [5]. With normal kidneys this increased renal blood flow translates into an increased GFR and subsequently increased CL_{CR}. "Augmented renal clearance" (ARC) is an evolving concept in critical care pharmacology. While data concerning specific drug clearances in the critically ill remains sparse, a timed urinary CL_{CR} represents a useful surrogate, allowing identification of patients 'at-risk' of sub-therapeutic antibacterial exposure. Specific thresholds remain uncertain, although CL_{CR} values of

Table 1 Simplified explanation of the PK/PD concept

	Time-dependent killing	Concentration-dependent killing	
PK/PD index	T > MIC	C_{max}/MIC	AUC/MIC
Antibiotics	Beta-lactams	Aminoglycosides	Fluoroquinolones
	Vancomycin (not concentration dependent yet still AUC/MIC)		
Optimizing antibacterial efficacy	Extended or continuous infusion, frequent dosing	High dosages once or twice daily	

While this model is generally accepted, many questions remain unanswered, such as the actual clinical targets for PK/PD indices and the association between blood and tissue concentrations

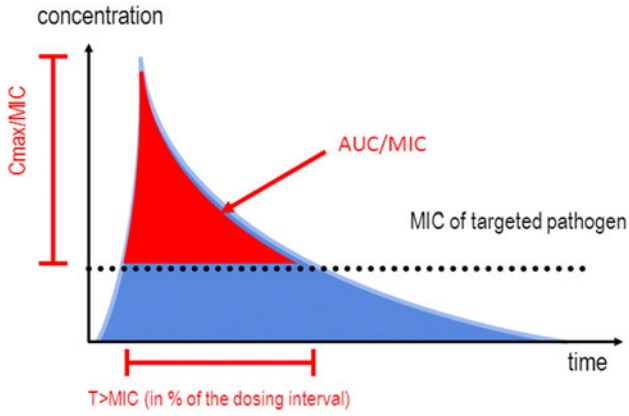

Fig. 1 Pharmacokinetic (maximal concentration—C_{max} and area under the curve—AUC) and pharmacodynamic (relationship to minimal inhibitory concentration—MIC) parameters and the resulting three different PK/PD indices (*red*)

130 ml/min/1.73 m^2 and higher have been strongly associated with sub-therapeutic beta-lactam concentrations. Age, multi-trauma, brain injury, sepsis, surgery, haematological malignancy, and ventilator-associated pneumonia have been identified as risk factors [5], although specific physiological and therapeutic drivers require additional study. ARC implies a more rapid decline in drug concentrations, other than what is usually observed in healthy volunteers. For agents that require adequate concentration throughout the dosing interval (such as time-dependent antibacterials), this may predispose to treatment failure, or the selection of drug-resistant strains, complications that may adversely impact the patients' clinical course.

In the recent past, there has been a growing body of evidence that regular dosing results in sub-inhibitory antibiotic concentrations in septic patients, e.g. Pletz et al. [9] found that the fixed dosage of 400 mg moxifloxacin resulted in sub-inhibitory plasma concentrations at steady state in one-third of patients with severe sepsis and septic shock. Taccone et al. [10] showed the same for the first 24 h of severe sepsis and septic shock for basically all beta-lactams that are recommended for empiric sepsis treatment. Years ago there was much concern on overdosing antibiotics in critically ill patients but more recently underdosing has been shown to be a problem. Udy et al. [11] have demonstrated underdosing when using beta-lactam antibiotics in a group of patients, largely those 50 years or under, with a normal serum creatinine and with an inflammatory response. Whilst Monte Carlo simulations may not always be performed using pharmacokinetics of ICU patients, even such studies provide evidence that sub-therapeutic concentrations occur following administration of recommended fixed dosages [12].

Underdosing may be even more life threatening than overdosing especially in patients with severe infections. A good example is the failure of tigecycline at a fixed dosage of 50 mg/bid (after 100 mg loading dose) versus imipenem/cilastatin in patients with nosocomial pneumonia [13]. Whereas there was no significant difference in non-ventilated patients, tigecycline resulted in a significantly lower rate of cure in ventilated ICU patients. A PK sub-study demonstrated that this fixed dosage resulted in significantly lower concentrations in ventilated compared to non-ventilated patients.

Finally, besides ARC, an increased volume of distribution (Vd) can contribute to low vancomycin concentrations [14]. Increased vascular permeability is correlated with the degree of inflammation. An increased Vd would particularly affect vancomycin, a large charged molecule with poor tissue penetration and a significantly lower Vd in healthy volunteers than what we find in sick ICU patients [15]. This phenomenon is particularly important as regards loading doses [14].

Who needs increased dosing of vancomycin—both loading dose and increased maintenance dosing? The paper by Shimamoto et al. [16] says those unventilated patients with SIRS criteria but without renal dysfunction.

This paper has the potential to be extremely important. If it could be translated into clinical practice, it would allow better vancomycin dosing and similarly all renally excreted drugs. However the study has some major limitations. It was performed merely in unventilated patients and hence generalisation into many multidisciplinary ICUs may be a problem. Validation needs to be performed in a wider group of ICU patients before widespread increased vancomycin dosing is given to any patient with SIRS. Increased dosing can then apply to any renally excreted drug.

Another feature of the study we are not in agreement with, is estimating CL_{CR} in ICU from various formulae derived from ward patients. The estimates of CL_{CR} from a

serum concentration of creatinine have been derived from non-ICU patients and not surprisingly these extrapolations of CL_{CR} to ICU populations are not particularly accurate [17, 18].

For future validation studies we would suggest a more accurate measure of CL_{CR} be used for ICU patients.

Concluding remarks

We compliment Shimamoto et al. [16] for pointing us in a new clinical direction of predicting underdosing of vancomycin. There is a group of patients in ICU that have significantly higher creatinine clearances than those patients in a general ward. These patients have ARC [8, 11]. The concept of patients without renal dysfunction but with increasing SIRS criteria being those that have increased CL_{CR} needs, however, to be validated by more extensive studies before becoming part of clinical algorithms.

Conflicts of interest None.

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