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Understanding PK/PD

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Introduction

Pharmacology is the science underpinning dosing, mechanisms of action and effectiveness of drugs. Central to pharmacology are the studies of pharmacokinetics (PK) and pharmacodynamics (PD).

What are PK, PD and PK/PD?

PK defines the time-course of drug concentrations in the body. On the other hand, PD describes the relationship between drug concentrations and pharmacological effects. In practice, PK is often referred as "what the body does to the drug" whilst PD as "what the drug does to the body". Thus, PK/PD describes the relationship between drug dose and pharmacological effects with changes in drug concentrations leading to different pharmacological effects.

Why is knowledge of PK/PD essential to optimising care in the intensive care unit (ICU)?

During drug development, from pre-clinical studies to Phase III trials, PK/PD is an essential consideration for maximising therapeutic effects whilst minimising any drug side effects. Critically ill patients are rarely included in dose-finding studies (Phase I and Phase IIa studies) and are usually poorly represented in later clinical outcome studies (Phase IIb and Phase III). From a PK perspective, the disposition of many drugs changes in the presence of critical illness, resulting in much more varied concentrations across patients and within the same patient during different phases of the disease (i.e. early vs. late therapy), leading to much more unpredictable pharmacological and toxicological effects. Therefore, when "standard" dosing regimens are used in ICU patients with the assumption that product information dosing is appropriate, sub-optimal concentrations and therapeutic failure can result. At the other end of

the spectrum, supra-therapeutic concentrations leading to drug toxicity are also possible.

Whilst altered PK/PD is common, for many drugs this is not a discernible problem because they are dosed to an "end-of-needle" effect; the clinician then titrates the dose for the patient at the bedside to the desired observable pharmacological target (e.g. vasopressors titrated to a target mean arterial pressure). However, other drugs, such as antibiotics and anti-epileptics, do not have an easily measurable bedside endpoint and a detailed understanding of PK/PD for these agents can enable physicians to ensure that individual patients receive the optimal doses. Below, we use the example of antibiotics to highlight the importance of an understanding of PK/PD.

Major concepts in PK affecting antibiotic dosing

Pathology-mediated PK variations are significant for antibiotics like the beta-lactams, glycopeptides and aminoglycosides in the critically ill, whereas some other agents have intrinsically high PK variability regardless of the patient (e.g. linezolid, colistin, triazole antifungals). The critical illness-related PK variations are caused by wide drug clearance possibilities as observed in patients with augmented renal clearance (ARC) [1] and, at the other end of the spectrum, acute kidney injury (AKI) [2]. The presence of renal replacement therapy (RRT) or extracorporeal membrane oxygenation [3] also introduces difficult-to-predict effects on antibiotic clearance. Further to this, changes in fluid balance associated with fluid resuscitation, oedema and obesity can affect the volume of distribution (defined as the apparent volume of fluid into which a drug has distributed to give it a concentration equal to that observed in plasma) of drugs. In particular, fluid balance fluctuations will affect the volume of distribution of the more water-soluble antibiotics like beta-lactams, glycopeptides and aminoglycosides. Taken together, these pathophysiological changes lead to a wide variation of resulting concentrations such that, in the DALI study, over 500-fold differences in plasma drug concentrations were observed for beta-lactams [4]. The variations in concentration in the interstitial fluid of tissues, where most infections typically occur, would be even greater. Indeed, the extent of altered plasma concentrations are impossible to predict with accuracy, and for this reason therapeutic drug monitoring is advocated for as many agents as possible, even though it may not accurately reflect the exact target site concentration [5].

Major concepts in PD affecting antibiotic dosing

PD changes are equally important in the ICU where less susceptible pathogens are commonly present. Data from epidemiological studies confirm that minimum inhibitory concentrations (MICs) for bacteria are commonly two–four times higher in the ICU compared to ward environments [6]. Therefore, when considering that the MIC is the denominator for each of the PK/PD ratios for the different classes of antibiotics [e.g. area under the concentration–time curve (AUC)/MIC antibiotics like quinolones], as this denominator increases, then the PK exposure (numerator) must also increase to ensure this optimal ratio is achieved for maximal clinical effectiveness (Fig. 1).

What happens when we use routine doses in ICU?

Data from the large multicentre DALI Study suggested that there is a very low variation ($\sim$2-fold) in the range of doses used for many beta-lactams [4] and glycopeptide antibiotics [7, 8], as well as triazole and echinocandin antifungals [9]. This "one dose fits all" approach would appear to be problematic in critically ill patients, as the DALI Study [4], among others [10–13], have demonstrated clear concentration–effect relationships for antibiotics where achievement of PK/PD targets is associated with improved clinical cure and/or patient survival. Moreover, drug accumulation may occur in those patients with organ dysfunction and potential side effects, such as AKI and/or neurotoxicity [14]. The challenge for clinicians is choosing doses that ensure achievement of these optimal PK/PD targets given that both PK and PD differences exist in critically ill compared with non-ICU patients.

Principles for minimising the effect of altered PK/PD

Estimating or measuring altered PK and PD is essential for dose optimisation. An increased volume of distribution is common in the ICU and, therefore, loading doses (e.g. vancomycin 30 mg/kg [15]) are required to rapidly achieve therapeutic concentrations. Maintenance doses should be based on estimations of drug clearance which are generally well correlated with renal function estimates (e.g. measured creatinine clearance) for many drugs. In the case of RRT, different settings in different ICUs mean that a standard dose is also impossible and, as such, careful research of the published literature to describe optimal doses for individual scenarios is required.

The future

Antibiotic PK and PD are difficult to predict if they are not measured. Therefore, the application of therapeutic drug monitoring to describe antibiotic PK and use of microbiology expertise to measure pathogen MIC is the only way to truly generate personalised doses that optimise patient outcomes. PK/PD studies are also able to define effective evidence-based dosing regimens for old

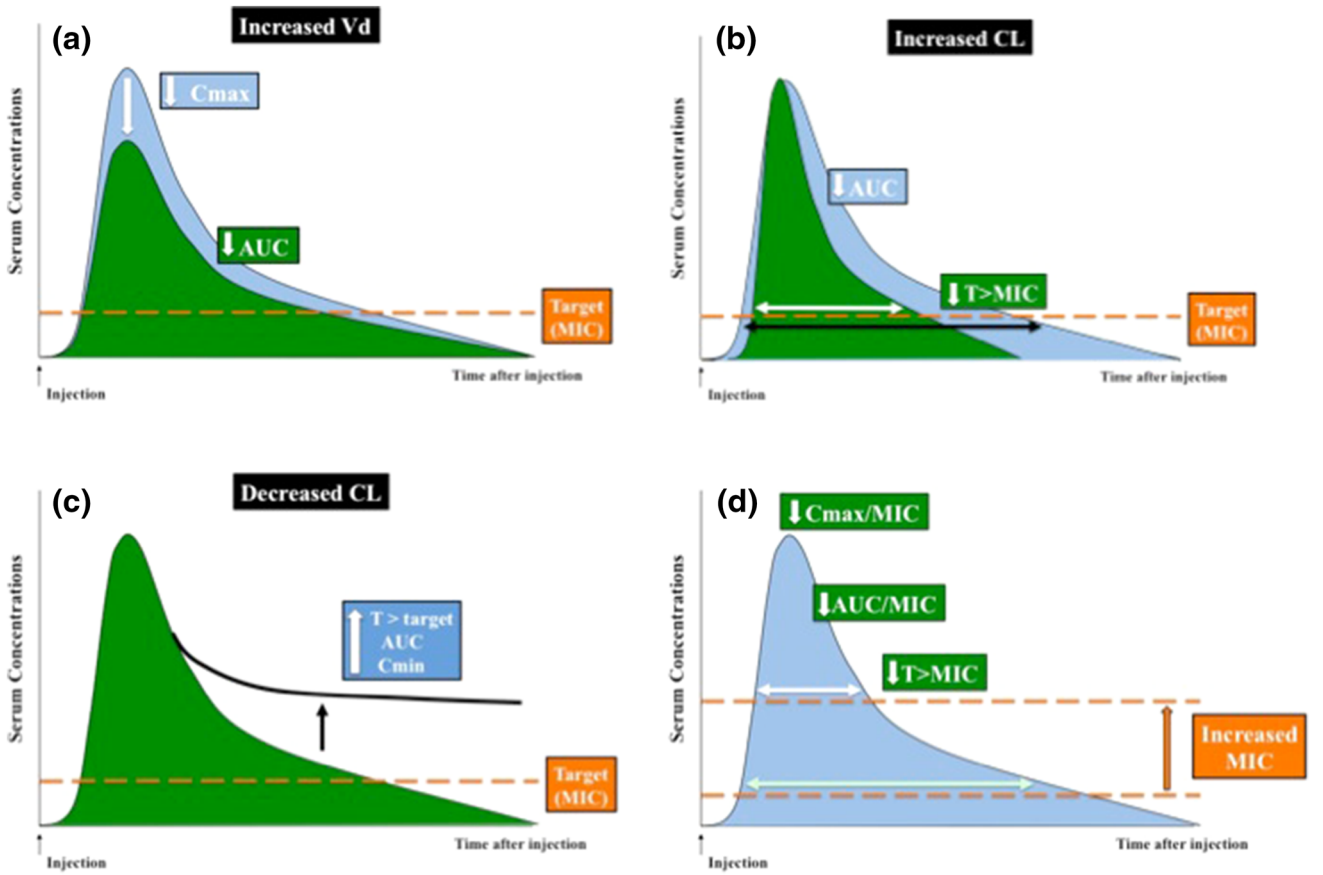

Fig. 1 Examples of PK/PD changes for antibiotics in critically ill patients. **a** Increased volume of distribution (V_d) will decrease the peak concentration (C_{max}; relevant for drugs like aminoglycosides) and the area under the curve of drug concentrations over time (*AUC*; relevant for drugs like quinolones) of the drug in the first dosing interval. **b** increased drug clearance (*CL*) will reduce the AUC and the time above the minimum inhibitory concentration ($T > MIC$; relevant for drugs like beta-lactams). **c** Decreased CL will increase the AUC, the T > MIC and the minimum drug concentration before the next administration (C_{min}). **d** Increased MIC of the pathogen will result in decreased PD targets (C_{max}/MIC, AUC/MIC and $T > MIC$)

antibiotics as well as antibiotic combinations, and these efforts serve to provide wider therapeutic options to treat infected critically ill patients.

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Compliance with ethical standards

Conflicts of interest None of the authors are aware of any actual or potential conflicts of interest associated with this work.

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