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### Impact of Pharmacokinetics of Antibiotics in ICU Clinical Practice

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#### Introduction

The efficacy of a drug is mainly dependent on its ability to achieve an effective concentration in the target tissue. However the risk of toxicity limits the dose that can be administered.

Critically ill patients often have increased cardiac output, capillary leak, modification of proteins serum levels and binding properties. Additionally increased renal and hepatic clearance or, on the contrary, organ failure, are common and lead to significant pharmacokinetic (PK) changes (Roberts and Lipman 2006). Antibiotic dosing is especially challenging in these patients, due to increased volume of distribution (Vd) and changes in clearance (Cl). Besides antibiotics killing kinetics is dependent on drug class, and different patterns of exposure are necessary for antimicrobial success (Drusano 2004).

Unfortunately, therapeutic drug monitoring is only available for a small number of antibiotics. Nevertheless knowledge of PK may help to select appropriate dosage and schedule intervals that might contribute to therapeutic success.

#### Principles of Pharmacokinetics

Pharmacokinetic refers to the study of drug concentration during a timeframe and its distribution in different tissues of the body, namely its absorption, bioavailability, distribution, protein binding, and also its metabolism and excretion. Clinical PK is the application of these principles to design individualised dosage regimens, which optimise therapeutic response while minimising the chance of an adverse drug reaction.

Bioavailability is the drug proportion, which actually reaches systemic circulation (usually 100% for intravenous route). Distribution occurs when drug molecules leave the vascular system to different compartments, either tissues or organs. Their chemical conversion is called metabolism. Excretion is the irreversible elimination of a drug from the body.

Most drugs follow a linear PK (its concentration changes proportionally with dose). However, some, like phenytoin, presents non linear, Michaelis-Menten, PK (Bauer 2008).

Pharmacodynamics (PD) relates drug concentration to the pharmacological response. However, drug effect may not be proportional to drug concentration because the pharmacological drug effect depends on its ability to form a complex with a receptor. Once these are saturated, a maximum response will be obtained. Often adverse effects of drugs follow the same type of concentration response relationship.

#### Volume of Distribution

Serum concentration of a drug depends of the amount delivered, its bioavailability and the Vd. The Vd is a mathematical construct and refers to the size of a compartment necessary to account for the total amount of the drug, assuming that its concentration in the whole body is the same as the measured in plasma [ $Vd = (\text{dose} \times \text{bioavailability}) / \text{concentration}$ ]. Drugs that distribute mainly in the extracellular fluid have low Vd (0.2-0.3L/kg), whilst drugs that have rapid cellular uptake have high Vd (in excess of 0.6 L/Kg).

In general, Vd is above normal in critically ill patients. Volume resuscitation, blood products, vasopressors, positive pressure ventilation, surgical procedures, capillary leak and reduction in albumin serum concentration, all contribute to this increase in Vd. Therefore with the same dose, peak concentrations are usually lower. This is especially important after the first dose of a drug, when the drug concentration is only dependent on the Vd. If a lower dose is given (namely to adjust for renal failure), a lower concentration will be obtained, which may contribute to therapeutic failure. Nevertheless maintenance doses should be reduced (or intervals enlarged) to avoid accumulation and toxicity.

When drug Cl remains unchanged, a rise in Vd, although associated with a lower concentration, proportionally increases the  $t_{1/2}$ , since  $t_{1/2} = Vd / (Cl \times 0.693)$ . This might be a useful effect for antibiotics that depend on time to act (like  $\beta$ -lactams), but a major disadvantage for concentration-dependent agents (like aminoglycosides).

Drug doses may need to be adjusted depending on its tissue penetration and the intended effect. Many antimicrobials do not penetrate well in cerebrospinal fluid and higher doses may be necessary to treat meningitis. By contrast, at excretory sites, such as the urine, drugs may concentrate and use of lower doses may be appropriate (Estes 1998).

### Excretion

In the hyperdynamic septic patients, there is commonly an increased renal and hepatic blood flow and often an increased drug CI (Weinbren 1999; Roberts and Lipman 2006; Baptista et al. 2009). To achieve adequate therapeutic levels some antibiotics may need higher than usual doses (Pea and Viale 2009). Oliguria inversely leads to drug accumulation and toxicity.

Prescription guidance is well established in chronic renal failure. However in acute renal failure there is often a narrow therapeutic range between ensuring effectiveness and preventing toxicity. Under modern renal replacement therapy, there is a significant risk of underdosing, when doses previously defined for stable chronic renal failure patients are used (Fish et al. 2005).

The effect of liver dysfunction on drug concentrations is less well defined, with numerous interactions, which make it only possible to prescribe on an individual basis. Of note, patients with liver disease often have decreased renal CI, although with a normal serum creatinine. Thus dose reduction may be necessary even for drugs essentially cleared by the kidneys (Morgan and McLean 1995).

### Antibiotic Pharmacokinetics

One of the major characteristics of these drugs, which determine their timeframe activity, is whether its killing rate depends on drug concentration or on the duration of exposure (Craig 2003). The second major characteristic is the post antibiotic effect (PAE), the persistent effects that last after antimicrobial concentration fall under the minimal inhibitory concentration (MIC). Antibiotics that inhibit nucleic acid or protein synthesis tend to have larger PAE (Mehrotra et al. 2004).

However antibiotic PK changes in critically ill patients, especially the increase of both the Vd and the CI, makes its concentration difficult to predict (Figure 1), especially those of hydrophilic antimicrobials (e.g.  $\beta$ -lactams, aminoglycosides, glycopeptides) that distribute mainly in the extracellular space. Moreover, antibiotic efficacy is not easily assessed, as its effects are usually unnoticeable before 48 h of therapy. Therefore failure of the antimicrobial treatment may occur because of the inability of the antimicrobial to achieve adequate concentrations at the infection site.

When choosing a drug dose to attain the desired target, it is important to recognise the range of MICs that might be found clinically. The higher the MIC, the lower the probabilities of attaining its PK/PD target. Consequently high antibiotic doses, according to their PD profile, should be used to ensure bacterial killing, especially in critically ill patients. However these high antibiotics doses also increase the risk of toxicity.

### Time Dependent Antibiotics

$\beta$ -lactams attach and block penicillin-binding proteins, responsible for the stability of bacterial cell wall peptidoglycan. Bacteria death occurs when a considerable portion of these proteins are occupied. As the drug concentration increases, its effect quickly maximises and higher drug concentrations do not result in significantly greater bacterial killing. On the opposite, if antibiotic concentration falls, bacteria proliferate almost immediately, especially Gram-negative organisms. Therefore  $\beta$ -lactams are time-dependent antibiotics and its T>MIC is the major PK/PD parameter that correlates with efficacy (Craig and Ebert 1992).

The administration of this class of antibiotics with short time intervals or the use of continuous infusion maximises time of bacteria exposure to adequate drug concentration and may improve patient outcome. Despite clinical trials failed to show a clinical benefit from this strategy, there are theoretical arguments, results from animal studies and case reports supporting the efficacy and safety of continuous or prolonged infusions (Mouton and Vinks 1996). Moreover, prolonged infusion (4 h) of piperacillin tazobactam in patients with severe *Pseudomonas aeruginosa* infections was associated with a significant reduction in mortality (12.2% vs. 31.6% with conventional administration schedule; p=0.04) (Lodise et al. 2007). The same was noted with continuous infusion of ceftriaxone in critically ill patients (Odds Ratio for survival with continuous infusion - 22.8; p=0.008) (Roberts et al. 2007).

In severe infections, where the risk of underdosing is higher, continuous infusion of  $\beta$ -lactams has proven to be safe, with at least a comparable therapeutic efficacy and may even improve patient survival and help prevent the emergence of resistant strains.

### Concentration Dependent Antibiotics

Some antibiotics, like aminoglycosides, show rapid concentration dependent killing and have a large PAE. This PAE increases with the ratio between peak concentration and MIC (Peak:MIC) (Moore et al. 1987).

Aminoglycosides are extracellular drugs, poorly bound to proteins and therefore, also susceptible to PK changes occurring in the critically ill

patients. Therefore, even with high antibiotic doses, the increased Vd of critically ill patients may preclude the achievement of a high Peak:MIC ratio. In a study from our group (Goncalves-Pereira et al. 2010), despite a gentamicin median loading dose of 7.4 mg/kg, only 31.3% of patients achieved a gentamicin peak concentration above 20mg/L. This was due to a marked increase in Vd, 0.41 L/kg, without any correlation with SOFA score, Charlson score, age, or renal failure. The same increased Vd (0.41L/kg) was found following the first dose of amikacin (Tacccone et al. 2010) and, consequently, 30% of the patients did not achieve their therapeutic target, 64mg/L.

The fear of oto and nephrotoxicity may prevent the use of these high aminoglycoside doses. However in a study of 373 patients treated with gentamicin, despite a decrease of 0.5% per day in creatinine clearance, these changes did impact neither patient outcome nor the incidence of clinical significant renal failure (Buchholtz et al. 2009).

#### **Exposure Dependent Antibiotics**

Fluoroquinolones have a high Vd and present both renal and hepatic Cl. Therefore their PK parameters are not significantly affected by critical illness. Also renal failure is not associated with significant drug accumulation, unless the patient has also concomitant liver pathology. These antibiotics are concentration dependent and a Peak:MIC ratio of 10 predicts bacterial eradication (Roberts and Lipman 2006). However, concerns about neurotoxicity of such high doses, may preclude its use. Therefore, the AUC:MIC is the parameter usually associated with outcome.

However, a ciprofloxacin dose of 400 mg bid only achieved an effective AUC:MIC for bacteria with a MIC less than 0.25 mcg/ml (van Zanten et al. 2008). Using the same antibiotic in critically ill patients, Lipman et al. showed that 400 mg tid was both safe and provided an AUC:MIC bactericidal ratio against most organisms (Lipman et al. 1998). These higher AUC:MIC may also reduce the risk of selecting resistant mutants, a major concern with fluoroquinolones (Andes et al. 2004).

Vancomycin is also an AUC:MIC ratio dependent antibiotic. Nevertheless in one study of MRSA hospital-acquired pneumonia no correlation was found between the outcome and vancomycin AUC (survivors 351; non survivors 354mg\*h/L; p=0.941) (Jeffres et al. 2006). However the authors failed to provide the MICs. Therefore, it was not possible to rule out a correlation between survival and AUC:MIC.

#### **Can We Use Pharmacokinetics to Guide Antibiotic Therapy?**

Antibiotic PK variability is largely unpredictable at the individual level. Therapeutic monitoring is therefore desirable and had been shown to facilitate the achievement of adequate serum levels (according with PK/PD targets), to decrease toxicity and even to contribute to prevent resistance development (Burgess 1999). Unfortunately dosing of antibiotics is only largely available for aminoglycosides and vancomycin.

Pharmacokinetic studies on  $\beta$ -lactams had also shown potential benefit from real time application of therapeutic drug monitoring. Serum ceftazidime concentration was measured in a cohort of 92 patients receiving continuous infusion (Aubert et al. 2010). The mean serum ceftazidime concentration was 46.9 mg/L but with a very large range of concentrations (7.4–162.3 mg/L). Dosage modification was necessary in a large number of patients, both with low concentration (36.9%) or potentially toxic levels (27.2%).

Pharmacodynamic modelling was also used to empirically treat VAP in critically ill patients in ICUs with a high prevalence of antibiotic resistant *Pseudomonas aeruginosa* (Nicasio et al. 2010). A 3-hour infusion regimen of either cefepime or

meropenem at high dose (2 g every 8 hours) was used followed by both antibiotic and dose deescalation, when a low MIC was identified. With a before and after design, an infection-related relative mortality reduction of 69% was found (8.5% vs

21.6%; p=0.029) and fewer superinfections were observed.

#### **Conclusion**

Changes of the antibiotics PK in critically ill patients, puts such patients at risk for either underdosing or prolonged drug exposure. Therefore, conventional dosing should be replaced by strategies aiming to tailor concentration to the individual patient. Microbiological and pharmacokinetic data may help to improve clinical outcome and to prevent resistance.

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