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Optimising the administration of antibiotics in critically ill patients

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Optimal outcome and a reduction in the potential for resistance require that appropriate pharmacokinetic (PK) targets are achieved. Consequently, we need to target drug concentrations that are significantly higher than those conventionally presumed to be adequate.

Drug exposure varies according to the molecular weight, degree of ionisation, protein binding and lipid solubility of each agent. In critically ill patients, hypoalbuminaemia increases the free fraction of hydrophilic drugs, which in turn increases the volume of distribution and clearance (CL), both of which result in reduced drug levels. Similarly, augmented renal clearance (ARC), defined as a creatinine clearance (CLcr) of >130 mL/min/1.73 m^2, which occurs frequently in critically ill patients, particularly younger patients with normal or near-normal creatinine levels, may also significantly reduce drug exposure. Studies have demonstrated a greater mortality and lower cure with ARC, particularly with the additive effects of obesity, hypoalbuminaemia and increasing resistance, if conventional dosages are used. These concepts apply to antibiotics targeting Gram-negative and -positive organisms. Knowledge of PK and the resistance profiles of organisms in each environment is necessary to prescribe appropriately. This article discusses these issues and the doses that should be used.

Optimal outcomes require achieving appropriate pharmacokinetic (PK) targets relative to the minimum inhibitory concentration (MIC) of the organism for a specific antibiotic. Antibiotics may be classified as time dependent, where a specific time above the MIC (T>MIC) is required to ensure optimal efficacy, and as concentration dependent, where the ratio of the area under the curve (AUC) to the MIC, also known as the area under the inhibitory curve (AUIC) or the peak-to-MIC ratio, more accurately reflects efficacy (Fig. 1). The AUIC might also be the most accurate parameter for some time-dependent drugs, particularly those with longer half-lives, such as the glycopeptides and linezolid. The optimal T>MIC for the β-lactams is >50% for penicillins, >60% for the cephalosporins and >40% for the carbapenems. For concentration-dependent agents the AUIC should generally be >120 or the peak-to-MIC ratio >8 - 10.[1,2] For example, in a study of free antibiotic levels, 248 patients with infection were examined to establish whether or not a target of 50% or 100% T>MIC was achieved. Those who did not achieve the 50% T>MIC target were significantly less likely to have a positive clinical outcome (odds ratio (OR) 0.68; *p*=0.009), and a positive clinical outcome was associated with increasing 50% T>MIC and 100% T>MIC ratios (OR 1.02 and 1.56, respectively; *p*<0.03).[3] Whereas these parameters primarily reflect efficacy, there is also the possibility that not achieving them may increase the potential for resistance, as selective pressure increases when there is a prolonged period below the MIC. Organisms that are more resistant have a lower AUIC and/or shorter T>MIC and an increased likelihood of survival.[4,5] Therefore, we might need to target drug concentrations that are significantly higher than those conventionally presumed to be adequate.[6] The mutant prevention concentration (MPC) is the concentration above which selective proliferation of mutants is unlikely to occur. Mutants are members of the microbial population with inherently higher MICs than the population average. Antibiotic concentrations that are targeted to the overall MIC would potentially be less than the MPC, thereby providing a competitive advantage to the mutant members of the microbial population.[7] Therefore, it is critical that the dose be optimised; some recommendations advise that concentrations should be >4 times the MIC for specific periods to prevent selection of resistant organisms – an essential component of antibiotic stewardship. Fig. 2 illustrates the concept of MPC and potential pitfalls of MIC-based dosing.[8]

Factors impacting on antibiotic exposure

Drug exposure varies according to molecular weight, degree of ionisation, protein binding and lipid solubility. Lipophilic antibiotics, e.g. the fluoroquinolones, have a large volume of distribution (Vd) owing to significant tissue and intracellular penetration. Hydrophilic agents, however, distribute into the extracellular space only and have a much lower Vd. The latter is influenced by a number of factors, such as serum albumin level, augmented renal clearance (ARC) and fluid losses as occurs with an open abdomen and major surgery with blood loss.[9]

Albumin level is of particular relevance for highly protein-bound antibiotics such as teicoplanin (90 - 95% bound), especially in critically ill patients in whom hypoalbuminaemia frequently occurs. In this setting, the Vd and clearance (CL) of the unbound/free fraction are increased.[10,11] These PK changes could result in suboptimal drug exposure, which may necessitate dose adjustments to ensure that therapeutic exposures are achieved.[12] In this regard, Mimoz *et al.*,[13]
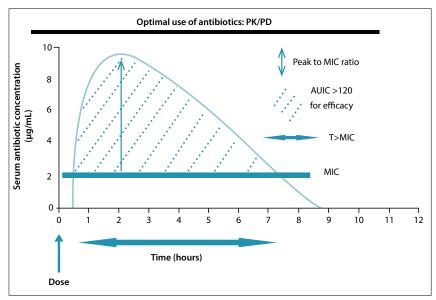
Fig. 1. The pharmacokinetics of antibiotics (MIC = minimum inhibitory concentration; T>MIC = time above the MIC; AUIC = area under the inhibitory curve).
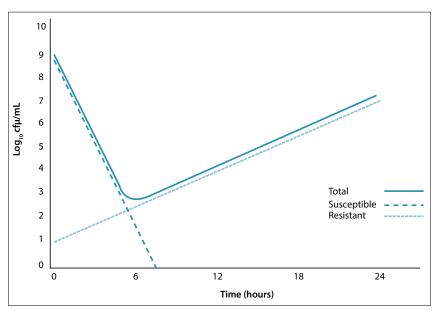

Fig. 2. Antimicrobial therapy rapidly reduces the total number of colony-forming units owing to a reduction in the number of susceptible organisms. Resistant organisms are afforded a competitive advantage and progressively constitute a bigger proportion of the microbial population.[8]

utilising a high-dose regimen of teicoplanin (12 mg/kg 12-hourly for 48 hours, followed by 12 mg/kg once daily) in critically ill patients with ventilator-associated pneumonia (VAP) and severe hypoalbuminaemia (median albumin concentration 16.1 g/L), observed variations in the fraction of unbound teicoplanin of 8 - 42%.

ARC is defined as a creatinine clearance (CLcr) >130 mL/min/1.73 m². The prevalence varies from 30% to 85% in critically ill and trauma patients and a normal or near-normal creatinine level may represent a high glomerular filtration rate (GFR). At-risk populations are those with good

physiological reserve, of a younger age and with lower illness severity scores. In this setting, dose increases are appropriate as the potential for subtherapeutic dosing is high. Increased β-lactam clearance in patients with sepsis, but without organ dysfunction, can lead to subtherapeutic levels for significant periods.[14-17] CLcr should be routinely measured if there is doubt about the GFR and evidence that an 8-hour collection may be just as accurate as a 24-hour one. A recent prospective, single-centre observational study of patients with VAP treated with doripenem or imipenem demonstrated a greater mortality and lower

cure with CLcr >150 mL/min. Separate PK/pharmacodynamic (PD) modelling suggested that daily doripenem doses (up to 2 g 8-hourly) might be required for adequate drug exposure, particularly with resistant organisms.[17-19] In 128 surgical and medical patients encompassing 599 antibiotic days, ARC, defined as more than one 24-hour CLcr >130 mL/min/1.73m², was present in 51.6% of patients and in 12% it occurred throughout the hospital stay. The median CLcr was 144 mL/min/1.73m² (interquartile range (IQR) 98 - 196), the ARC patients were significantly younger (*p*<0.001) and treatment failure occurred more frequently: 27.3% v. 12.9%; *p*=0.04.[17] We investigated ertapenem PK in 8 patients with severe sepsis (all of whom had normal renal function) after the administration of the conventional dose of 1 g daily. These patients had a lower maximum concentration (C_{max}), AUIC (0-∞), and higher Vd (26.8 L v. 5.7 L) than healthy volunteers, and in 4 patients time above 2 mg/L (the MIC breakpoint for Enterobacteriaceae) of the unbound fraction was <40% and in 2 it was <20%. These lower levels correlated negatively with low albumin, open abdomen and ARC.[20]

In summary, systemic inflammation increases the Vd of hydrophilic agents through capillary leak, large-volume crystalloid resuscitation and low albumin levels. Furthermore, altered organ per-fusion and therapeutic use of inotropes and vasopressors increase the potential for ARC. The additive effects of obesity and extracorporeal circuits reduce drug exposure in an environment where MICs are increasing inexorably. The overall effect is to increase the potential for treatment failure and select for resistance.[21]

What should be done to limit the impact of reduced drug exposure?

There are two obvious approaches, firstly to increase the dose and secondly to alter the methods of administration (infusion for time-dependent agents and, where possible, larger single daily doses for concentration-dependent drugs), both preferably guided by therapeutic drug monitoring (TDM).

β-lactams

In the abovementioned study by Claus *et al.*,[17] doripenem was administered at four times the recommended dose – with good outcome. There have been many similar case studies of the outcomes when treating resistant organisms. In a patient with cystic fibrosis infected with multidrug-resistant *Burkholderia cepacia*, who was treated with meropenem 2 g

8-hourly as a 3-hour infusion, concentrations >8 μg/mL were achieved for 52% of the dosing interval, with subsequent improvement.[22] In a study of 348 patients using β-lactam therapy (the Defining Antibiotic Levels in ICU (DALI) study – a PK point prevalence study using empirical therapy in the 'worst case' scenario), T>MIC was <50% of the dosing interval in 19.2% and <100% in 41.4% of patients. Intermittent infusion significantly increased the likelihood of reaching the target, whereas increased CLcr was independently associated with not reaching the 100% T>MIC target for free drug.[23] Similarly, using a Monte Carlo simulation, Nicasio et al.[24] determined that 3-hour infusions of cefepime or meropenem, both at 2 g three times daily, would be most likely to achieve optimal bactericidal *Pseudomonas aeruginosa* exposure. When this was implemented, infection-related mortality decreased by 69% (8.5% v. 21.6%; *p*=0.029), length of stay was reduced (11.7±1 v. 26.1±18.5; *p*<0.001), there were fewer superinfections, and many 'non-susceptible' *P. aeruginosa* infections were successfully treated.

Tigecycline

The efficacy of tigecycline (TGC) has often been questioned. Meta-analyses of monotherapy v. comparators such as the meta-analysis by Yahav et al.[25] have been done. The latter included 15 trials (*N*=7 654) where overall mortality was higher (relative risk (RR) 1.29 (1.02 - 1.64)), regardless of infection type; clinical and microbiological failure were higher (RR 1.16 (1.06 - 1.27) and 1.13 (0.99 - 1.30), respectively); and development of septic shock was significantly more frequent (RR 7.01 (1.27 - 38.66)). However, numerous recent studies using increased doses have shown improved outcomes. Patients with hospital-acquired pneumonia were randomised to a 150 mg bolus and 75 mg 12-hourly or a 200 mg bolus and 100 mg 12-hourly v. imipenem 1 g 8-hourly.[26] Clinical cure with the larger dose (17/20; 85.0%) was numerically superior to that with the lower dose (16/23; 69.6%) and to imipenem (18/24; 75.0%). Despite the increased dose, there were no new safety signals. Their conclusion was that higher AUIC ratios may be necessary to achieve clinical cure in hospital-acquired pneumonia. Similarly, in a retrospective study of patients with VAP, in which the main isolates were carbapenem-resistant *Acinetobacter* (blaOXA-58 and blaOXA-23) and *Klebsiella pneumoniae* (blaKPC-3), high-dose TGC was compared with standard dose TGC.[27] Organisms were said to be TGC sensitive if the MIC ≤2 mg/L and resistant if the MIC was ≥8 mg/L. The single independent predictor of clinical cure was high-dose TGC (OR 6.25 (1.59 - 24.57); *p*=0.009).

Fluoroquinolones and aminoglycosides

With regard to the concentration-dependent antibiotics, optimising the AUIC of fluoroquinolones reduced the development of resistance and was more likely to eradicate the pathogen.[28,29] Aminoglycosides are generally used suboptimally. To achieve appropriate targets, a much larger dose based on age and weight must be administered once per day and the MIC should be low.[30] In general, aminoglycosides are administered for short periods as empirical therapy to decrease the likelihood of inappropriate therapy for hospital-acquired infections. Peak and trough levels and the MIC of the organism (where possible) should be documented and subsequent doses titrated accordingly.[31] As with other hydrophilic agents where the Vd is increased and in the presence of ARC, concentrations may be suboptimal. Amikacin 15 mg/kg, for example, did not reach effective concentrations, with MICs of 8 mg/L, and it is possible that inconsistent concentrations may have contributed to the lack of effect in studies that investigated whether β-lactam-aminoglycoside combinations confer additional efficacy compared with β-lactams only.[32-35] Some reviewers have suggested that doses as high as 25 - 30 mg/kg for amikacin and

7 - 9 mg/kg for gentamicin or tobramycin should be administered initially, and thereafter a C_{max}/MIC ratio of 8 - 10 should be targeted.[36] Even then, levels might not be adequate; 33% of patients receiving 25 mg/kg total body weight amikacin load had a C_{max} of 60 mg/L, with positive fluid balance being the major negative predictive factor. To complicate matters further, Monte Carlo simulation of conventional v. high-dose extended-interval administration found resistance to be higher against pathogens with high MICs if T>MIC was <60%, even if C_{max}/MIC was high, and that treatment efficacy may not be guaranteed.[37] Illustrative dosing schedules for Gram-negative agents may be seen in Table 1.

Colistin

Colistin is a last-line drug and if used inappropriately resistance will develop rapidly. The form available in South Africa is a prodrug, colistimethate sodium or colistin methanesulfonate (CMS), which makes a bolus dose necessary to achieve therapeutic effect. It is effective against most Gram-negative bacilli, except *Proteus* spp., *B. cepacia*, *Providencia* spp., *Serratia marcescens* and *Morganella* spp.[38] The appropriate dose must exceed an MIC of 2 mg/L rapidly to prevent regrowth of more resistant organisms in heteroresistant populations, in which the PK target achieved would be insufficient for eradication.[39]

Consequently, a loading dose of 12 million units (MU) administered intravenously over 1 - 2 hours followed by 9 MU daily (4.5 MU twice daily or 3 MU three times daily) administered 12 hours after the loading dose is required.[38,40,41] Colistin is predominantly cleared by unknown non-renal mechanisms and undergoes extensive renal tubular reabsorption.[42] In renal dysfunction, elimination of CMS is decreased and a greater fraction of the administered dose is converted to colistin; however, a loading dose of 12 MU is still required, but maintenance doses are reduced according to CLcr (Table 2).[40] From murine AUC/MIC colistin data, it is estimated that an AUIC of total colistin of 60 is the average achieved without exceeding the dose recommended in the package insert (10 MU), particularly where CLcr is >70 mL/min.[40] Therefore, in an attempt to

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Table 1. Illustrative dosing and administration schedules for Gram-negative bacilli: Normal renal function

- Meropenem 2 g 8-hourly over 3 hours
- Imipenem 1 g 8-hourly over 3 hours
- Doripenem 1 g 8-hourly over 4 hours
- Ertapenem 1 g twice daily
- Cefepime 2 g bolus and 6 g daily over 24 hours*
- Ceftazidime 2 g bolus and 6 g over 24 hours*
- Piperacillin-tazobactam 4.5 g bolus and 18 g daily*

*Temperature ≤25ºC.

Table 2. Dosing of colistin

Load with 12 MU

- 60 kg: 3 MU 8-hourly/4.5 MU 12-hourly

Renal impairment – load with 12 MU, then:

- CLCr 20 - 50: 1 - 2 MU 8-hourly
- CLCr 10 - 20: 1 MU every 12 - 18 hours

CRRT – full dose; intermittent HD 1 MU 12-hourly and 1 MU after dialysis

- Never use colistin as monotherapy

MU = million units; CRRT = continuous renal replacement therapy; HD = haemodialysis.

reduce resistance, colistin is not administered as monotherapy and options include the carbapenems (provided the MIC is ≤32 mg/L (for carbapenem-resistant Enterobacteriaceae)), tigecycline (*Acinetobacter*), fluoroquinolones, rifampicin and others, even if the organism is resistant to these drugs.[43-45]

The glycopeptides, vancomycin and teicoplanin

These concepts regarding dosing are similar when using agents active against Gram-positive organisms. Vancomycin MICs have gradually been increasing, which appears to impact on outcome. In 158 patients with hospital-, ventilator- or healthcare-associated pneumonia caused by methicillin-resistant *Staphylococcus aureus*, 72.8% had vancomycin MIC ≥1.5 µg/mL. All-cause mortality at day 28 was 32.3%, but this increased as the MIC increased (p=0.001). Consequently, although controversial, it is recommended that other therapies be considered with MICs of 1 - 2 µg/mL.[46] Studies using higher troughs (15 - 20 mg/L), loading doses or continuous infusions differ with regard to improved clinical or microbiological outcome; however, it is hoped that higher dosing may delay resistance by not selecting those organisms with higher MICs.[47-50] In another study from the DALI group, 42 patients either received continuous infusions (CIs) (57%) or intermittent doses (43%) of vancomycin. The PK targets were a C_{min} ≥15 mg/L or an AUIC >400 (assuming the MIC was 1 mg/L). The C_{min} was highly variable and achieved in only 57% overall, and in 71% (CI) v. 39% (intermittent) (p=0.038). AUIC was achieved in 88% (CI) v. 50% (intermittent) (p=0.008). Whereas CI appeared to be superior, it was still not adequate in achieving targets, and multivariate analysis did not confirm CI as an independent predictor of either.[51]

Similarly, teicoplanin is unlikely to achieve therapeutic targets if administered in recommended doses as per the package insert. We performed a study in patients with normal renal function, in whom the standard dose of 400 mg twice daily × 1 day and 400 mg daily thereafter was compared with 400 mg twice daily.[52] With the latter, a C_{min} of 15 mg/L was achieved only on day 3, whereas with the former it was never achieved. In another study of 10 patients with chronic bone sepsis, 800 mg twice daily was administered for 48 hours and then 800 mg daily. Samples were taken 15 minutes pre-, and 30 and 120 minutes post-teicoplanin dose. The CL of the free fraction (f_f) was 33.5 L/hour (38.0 - 34.7) compared with the bound fraction 7.0 L/hour (6.8 - 9.8), and the major determinant of f_f was albumin with an OR of 0.120 (0.078 - 0.161; p<0.001), with a lesser effect of total dose. This emphasises that multiple factors impact on serum levels whether or not the patients are critically ill.[53]

Linezolid

Linezolid is a time-dependent antibiotic and efficacy improves as the T>MIC increases. However, it is probably only with CI that this can this be achieved when MICs are higher.[54] Boselli *et al.*[55] demonstrated that a loading dose followed by CI led to concentrations twice that of a linezolid MIC of 4 mg/L in serum and epithelial lining fluid for 100% of the time in critically ill patients with VAP. Why is this important? A recent prospective observational study of 30 critically ill patients showed that levels were frequently inadequate with standard dosing of 600 mg twice daily. The range of the AUC_{24} was 50.1 - 453.9 mg*h/L (median 143.3) and that of C_{min} 0.13 - 14.49 mg/L (median 2.06). Similarly AUC_{24} <200 mg*h/L and C_{min} <2 mg/L, both of which represent inadequate levels, were observed for 63% and 50% of patients, respectively.[56] As the achievement of PK targets is essential, the dose and method of administration must be optimised, and it seems reasonable to utilise TDM where available; where not, CI might significantly improve AUIC.[57] This is not a review of TDM,

but numerous other studies have proven its worth and it is probably the way of the future.[58] Illustrative dosing schedules for Gram-positive agents may be seen in Table 3.

Conclusion

There is currently a crisis with regard to antibiotic resistance. Every day that we delay ensures that we are further from a solution. We have to use antibiotics in an appropriate manner, reduce inappropriate use by all possible means, and reduce the incidence of infection, particularly in hospital. We are at the end of the antibiotic era – perhaps we can make it last a few more years to allow the introduction of new agents, particularly β-lactam antibiotics combined with β-lactamase inhibitors, or until new strategies can be devised.

Table 3. Illustrative dosing and administration schedules for Gram-positive organisms

Normal renal function

- Teicoplanin: 800 mg twice daily × 2 days, then 400 mg twice daily
- Vancomycin: 1 - 2 g stat, then infuse 2 g daily (target a trough of 15 - 20 µg/mL)

Renal dysfunction

- Teicoplanin: 400 mg twice daily × 1, then daily
- Vancomycin 2 g stat – maintain levels at 15 - 20 µg/mL

The following 3 drugs have the same dose, regardless of renal function

- Linezolid: day 1 – bolus 300 mg, then infuse 900 mg over 24 h, thereafter infuse 600 mg 12-hourly
- Tigecycline: 100 mg stat, then 50 mg twice daily
- Rifampicin: 600 mg twice daily

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