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REVIEW

Rina Mehrotra
Raffaele De Gaudio
Mark Palazzo

Antibiotic pharmacokinetic and pharmacodynamic considerations in critical illness

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R. Mehrotra · M. Palazzo (✉)
Department Critical Care Medicine,
Charing Cross Hospital,
London, UK
e-mail: m.palazzo@ic.ac.uk
Tel.: +44-20-8846-7017
Fax: +44-20-8846-7585

R. De Gaudio
Department of Critical Care,
Section of Anaesthesiology,
University of Florence,
Florence, Italy

Abstract *Background:* Many factors over which there may be little control may influence the response of a patient to therapy. However, therapy with antibiotics can be readily optimised. *Discussion:* Concentration-dependent agents such as aminoglycosides appear effective and to entail fewer side effects when given in large, infrequent doses. There is also evidence that time-dependent antibiotics often fail to reach adequate concentrations throughout the treatment period. To date no randomised controlled prospective trial has demonstrated improvement in clinical outcome following infusion rather than intermittent boluses of time-dependent antibiotics. Critical illness alters antibiotic pharmacokinetics principally through increases in volume of distribution. Other than glycopeptides and aminoglycosides, antibiotic blood concentrations are rarely monitored and therefore adequate concentrations can only be inferred from clinical response. *Conclusions:* Failure to respond within the first few days of empirical treatment may be due to antibiotic resistance or inadequate doses. Therefore the same rigor should be applied to achieving adequate antibiotic concentrations as is applied to inotropes, which are titrated to achieve predetermined physiological targets

Keywords Antibiotic activity · Critical care patients · Dose optimasation · Pharmacodynamics · Pharmacokinetics

Introduction

Care of the septic patient is based on supportive management, while surgery and appropriate antibiotics provide specific therapy. Although it would seem obvious that antibiotics benefit patients with infection, the high hospital mortality associated with antibiotic-treated sepsis in critically ill patients is not always so convincing. The likely success of antibiotics is influenced by immunocompetence, severity of insult, timing of treatment, and physiological reserve. For ethical reasons studies evaluating the impact of antibiotics in these patients have been retrospective, and based on patients who received antibiotics judged either to be appropriate or inappropriate. McCabe and Jackson [1] provided the first convincing study in patients with Gram-negative bacteraemia. They classified patients according to their underlying condition as rapidly fatal, ultimately fatal or non-fatal. Among those with a rapidly or ultimately fatal condition, as might be expected, there was no impact of antibiotics on mortality. However, for those with a non-fatal condition appropriate antibiotics made a highly significant difference. In addition, it has been shown that prompt administration of empirical antibiotics reduces the frequency of shock associated with bacteraemia [2]. More recent intensive care studies have re-emphasised the importance and impact on hospital mortality of both early administration and appropriate antibiotic use, where appropriateness was based on in vitro sensitivities [3, 4, 5]. Although the choice of an antibiotic is clearly important, their doses and methods of administration are also considered relevant and are the subject of this review.

Antibiotic activity

Measurement

Quantification of micro-organism susceptibility to antibiotics has been measured classically by in vitro determination of the minimum inhibitory concentration (MIC). Unfortunately MIC may fail to reflect in vivo activity in part due to failure to account for variation in organism growth phases, antibiotic tissue penetration and protein binding which may modify antibiotic effectiveness. In order to provide clinicians with more useful measures of susceptibility many institutes such as the National Committee for Clinical Laboratory Standards in the United States and the British Society for Antimicrobial Chemotherapy in the United Kingdom have suggested the use of breakpoint minimum inhibitory antibiotic concentrations (breakpoint MIC) for susceptibility testing. The latter have been based on known pharmacokinetic and pharmacodynamic data for each antibiotic and organism combination [6]. Organisms are classified as being susceptible, resistant or intermediate susceptible to an antibiotic at breakpoint concentrations. Intermediate susceptibility implies that although standard antibiotic dosing may not be effective, in some circumstances higher doses might. Many laboratories have now automated breakpoint based antibiotic susceptibility testing.

There is good evidence in immuno-competent patients that antibiotic concentrations in excess of susceptibility breakpoint concentrations are well correlated with in vivo responses [7, 8]. However, in conditions such as endocarditis, cystic fibrosis, meningitis and osteomyelitis where tissue penetration might be limited, breakpoint MIC has not proved to be as predictive of in vivo outcome as time-kill studies. The latter measure the rate of killing over 48 h with a particular antibiotic concentration.

Mode of action

Concentration-dependent, time-dependent, post-antibiotic effect

It is now well recognised that the rate of kill for some antibiotics is closely related to peak concentration above breakpoint (concentration-dependent activity), while others have kill rates better related to the length of time concentrations are sustained above breakpoint MIC (time-dependent activity).

Soon after Florey's introduction of penicillin in 1940, Eagle et al. [9] showed that it is the aggregate time that penicillin remains above bactericidal levels that determines therapeutic outcome. A number of investigators have since confirmed that β-lactam efficacy is closely related to the time that its concentration remains above the MIC [10, 11, 12]. Penicillins, cephalosporins, macrolides, carbapenems, clindamycin, linezolid and glycopeptides are all characterised by time-dependent killing although the latter may also show concentration-dependent properties.

The precise concentration target above the MIC for time-dependent antibiotics remains a matter of controversy and may also depend on host factors. It is generally thought that concentrations should be four to six times the MIC [13, 14, 15]. In addition, there is evidence that higher concentrations above MIC add little more to micro-organism kill rates [10]. In fact an interesting observation was made by Eagle and Musselman [16] in 1948 in this regard. They unexpectedly observed that blood concentrations beyond the minimum bactericidal concentration (MBC, the lowest antibiotic concentration which kills 99.9% of the inoculum, usually 2× MIC) paradoxically resulted in increased rather than decreased bacterial survival. This "Eagle effect" has since been noted with penicillin and cephalosporins particularly at 50 and 500 times the MIC. This appears to be an in vitro phenomenon confined to Gram-positive organisms [10]. While β-lactams have time-dependent activity, aminoglycosides, fluoroquinolones, amphotericin B and metronidazole typically exhibit concentration-dependent killing [17].

In order to quantify the likely effectiveness of antibiotics various relationships between drug concentration and MIC have been proposed. Concentration-dependent antibiotics are best monitored by the ratio of peak serum antibiotic concentration to MIC, or the ratio of area under the concentration time curve (AUC) to MIC (AUC/MIC) while time-dependent drugs by the time that the serum concentration exceeds MIC (T>MIC) [18].

A number of antibiotics also demonstrate the ability to suppress bacterial re-growth after their concentrations have fallen below the MIC. This post-antibiotic effect (PAE) has been most often demonstrated in vitro. This effect should not be confused with the effects caused by sub-minimum inhibitory concentrations (sub-MIC). The latter describes antibiotic concentrations which have failed to exceed MIC at any stage during treatment. Sub-MIC concentrations produce morphological and surface adherence changes and toxin release without inhibiting growth or killing the organism. The PAE was originally observed with penicillin against Gram-positive organisms over 50 years ago [19]. With the exception of the carbapenems, β-lactams have modest PAE against Gram-positive bacteria and little or no PAE against Gram-negative bacteria [20, 21, 22, 23, 24]. However, other time-dependent agents such as macrolides and glycopeptides may have PAE of up to 6 h against some Gram-positives such as *Staphylococcus aureus* [20].

Concentration-dependent antibiotics such as aminoglycosides and fluroquinolones show consistent PAE against Gram-negative and Gram-positive organisms lasting several hours. Metronidazole, clindamycin and chloramphenicol also have PAE against Gram-negative anaerobes. It appears that in general antibiotics with nu-

Table 1 Mode of activity and approximate pharmacokinetic values for some antibiotics used in the critically ill. The dosing goal for concentration-dependent drugs is to maximise concentrations estimated by peak/MIC or AUC/MIC. The goal for time-dependent drugs with little PAE is to prolong the time above four times MIC. The goal for time-dependent drugs with significant PAE is to maximise AUC (area under time concentration curve). A comprehensive list of typical peak concentration following standard dosing is outside the scope of this table but available from other sources [6] (*App Vd* apparent volume of distribution, $t_{1/2}$ elimination half-life, *PAE* significant post-antibiotic effect >2 h where known (no or yes), *T* time-dependent activity, *C* concentration-dependent activity, *PB* protein binding, *NK* not known)

Antibiotic (mol. wt.)	Action	PAE	PB (%)	App Vd (l/kg)	Metabolism (%)	Renal excretion (% unchanged)
Amoxicillin (419)	T	N	18	0.21	10	60
Cefotaxime (477)	T	N	38	0.3	40	60
Cefuroxime (424)	T	N	33	0.2	None	95
Ceftriaxone (598)	T	N	90	0.14	40	60
Ceftazidime (546)	T	N	17	0.25	None	90
Erythromycin (733)	T	N	18	0.72	65	15
Imipenem (317), cilastatin (380)	T	Y	20	0.26	25[a]	70
Meropenem (437)	T	Y	2	0.3	75	25
Benzyl penicillin (334)	T	N	60	0.2	20	80
Teicoplanin (1875–1891)	T	Y	89	1.0	2–3	97
Vancomycin (3300)	T	Y	50	0.8	None	100
Linezolid (337)	–T	–N	31	40	65	30
Gentamicin (463)	C	Y	<10	0.3	None	95
Tobramycin (467)	C	Y	<10	0.3	None	95
Piperacillin (539)	T	N	26	0.2	6	50
Tazobactam	–	–	31	–	26	26
Ciprofloxacin (331)	C	Y	40	2.1	30	50
Clindamycin (461)	T	N	90	1.2	90	10
Metronidazole (171)	C	Y	20	0.8	60	20
Amphotericin B (liposomal)	C	Y	90	131	NK	NK
Fluconazole (306)	T	Y	11	1.0	11	80

[a] Metabolised in kidney by dehydropeptidase; cilastatin blocks renal dehydropeptidase

cleic acid or protein synthesis inhibitory activity tend to have PAE.

Antifungal agents amphotericin B and 5-fluorocytosine also have significant post-antifungal effect against *Candida* spp. lasting up to 10 and 7 h, respectively, in in vitro preparations [25]. By contrast, the imidazoles have little in vitro but significant in vivo post antifungal effect [25, 26]. The importance of PAE particularly for drugs with time-dependent activity is that they may be given for sensitive organisms on an intermittent bolus basis without concern for therapeutic failure.

Table 1 outlines details of antibiotics commonly used in the critically ill. Further data on maximum plasma concentrations following typical dosing and their relationship to MIC has been comprehensively detailed elsewhere [6].

Critical illness and pharmacokinetic changes

General considerations

While many drugs such as inotropes or sedatives can be titrated to immediate clinical effect, antibiotics have a long lead time. Critical illness alters volume of distribution while hepatic and renal dysfunction additionally makes antibiotic pharmacokinetics unpredictable. Such changes might potentially influence an antibiotic's effectiveness. Lack of routine drug monitoring for most antibiotics makes it difficult for a clinician with a patient failing to respond to treatment to distinguish insufficient antibiotic concentrations from lack of in vivo organism susceptibility.

As a general rule volume of distribution is greater than normal in critically ill patients. Therefore for a given patient and dose, peak concentrations are lower. If antibiotic clearance (Cl) remains unchanged, the increased volume of distribution (Vd) proportionally decreases the elimination rate constant (Ke): clearance=Vd x Ke. Since Ke is related to half-life ($t_{1/2}$) by Ke=ln2/$t_{1/2}$, assuming no change in clearance, a rise in Vd prolongs $t_{1/2}$. An increase in Vd which prolongs $t_{1/2}$, might be a useful effect for time-dependent antibiotics but a major disadvantage for concentration-dependent agents which might achieve lower peaks. This is a good reason for monitoring aminoglycoside peak concentrations in some patients; there should be as much concern for insufficient dose and antibiotic failure, as there is for overdosing and toxicity.

Hepatic dysfunction and antibiotic concentrations

The effect of antibiotics on liver function are well documented. Some inhibit hepatic enzyme activity, which

potentially cause toxicity of concomitantly administered drugs. Erythromycin, clarithromycin, ciprofloxacin, isoniazid, fluconazole and itraconazole are potent enzyme inhibitors. Ciprofloxacin and erythromycin, for example, by inhibiting CYP1A2 interfere with theophylline metabolism and can lead to theophylline toxicity. Other antibiotics are enzyme inducers and can also cause potential problems. For example, rifampicin induces cytochrome P450 (CYP3A and other families) and may result in failure of concomitantly administered warfarin and HIV protease inhibitors.

The effect of liver dysfunction on antibiotic concentrations is less well defined. The net effect of changes in protein binding, apparent volume of distribution, hepatic blood flow, extent of hepatic extraction, enzyme induction and functional hepatic mass is potentially complex

Albumin concentrations fall with hepatic and catabolic states, while α_1-acid glycoproteins concentrations rise with inflammatory processes. Albumin, the most abundant protein, binds to acidic drugs and a fall in albumin potentially increases free drug. An increase in α_1-acid glycoproteins, which binds basic drugs, would reduce free drug concentration. Although reduced albumin binding results in more free drug, the latter leads to greater tissue distribution thereby reducing plasma drug concentrations. Concomitant rises in bilirubin concentration displace antibiotics from albumin binding sites further increasing free drug concentration and apparent volume of distribution. Such changes would normally expose the drug to further hepatic metabolism. The activity of cytochrome P450 may be unchanged, increased or decreased due to hepatocellular loss, enzyme induction or inhibition. These numerous interactions make it only possible to prescribe on an individual patient basis.

Fortunately, for the majority of antibiotics hepatic metabolism is limited and protein binding is low enough to make no difference to their effectiveness. There is therefore little need to alter doses. However, patients with severe hepatic disease would require some lowering of doses for the few antibiotics metabolised by the liver these include chloramphenicol, clindamycin, metronidazole, nafcillin, tetracycline, cefotaxime and erythromycin.

Renal dysfunction and antibiotic concentrations

Most antibiotics are removed from the body largely unchanged in urine. Consequently oliguria potentially leads to drug accumulation. An increased Vd due to critical illness and fluid overload at the onset of oliguria, however, would dictate that the normal loading antibiotic doses should at least remain unchanged if not increased, while subsequent doses are given less frequently. Most patients are supported by renal replacement therapy (RRT) which will clear antibiotics in a similar manner to a native kidney with glomerular filtration rates approximating 35 ml/min. Whereas aminoglycoside and glycopeptide dosage intervals are greatly simplified by routine monitoring of concentrations other antibiotics are not measured, and toxic levels may only be apparent with the onset of a complication such as seizures. Guidance to doses and dosing intervals are well established in acute renal failure; however, with very severe infections such as endocarditis and meningococcal septicaemia treated with penicillin the narrow line between ensuring effectiveness and toxicity is best managed by introducing synergy with a second antibiotic.

Guidance on antibiotic dosage intervals is based on estimations of the half-life. Half life is related to clearance and volume of distribution by $t_{1/2=}$ln2 Vd/Cl. Clearance while receiving RRT is the sum of clearance by dialysis machine and non-renal clearance (metabolism by liver or loss through biliary excretion). Clearance on dialysis is likely to be less than normal native kidneys; consequently $t_{1/2}$ is prolonged and dosage intervals need to be increased in patients who are dialysis dependent. Typically penicillins, aminoglycosides, cephalosporins, carbapenems, glycopeptides and fluconazole have prolonged $t_{1/2}$ on RRT and need increased dosage intervals, whereas chloramphenicol, ceftriaxone, clindamycin, erythromycin, metronidazole, itraconazole, amphotericin B, acyclovir, rifampicin and to a lesser extent ciprofloxacin have substantial non-renal clearances and $t_{1/2}$ during RRT is only marginally increased.

Clearance on RRT depends on the mode of RRT, flow of filtrate or dialysate, antibiotic molecular weight and sieving coefficients. Continuous veno-venous haemofiltration (CVVHF) antibiotic clearance is by convection. For this process sieving coefficient and ultrafiltration rate are considerably more important than molecular size. On the other hand, continuous haemodialysis (CVVHD) an entirely diffusive process is molecular weight sensitive and better suited to the removal of small molecules below 500 Da. Consequently clearance of some antibiotics such as glycopeptides with molecular weights in excess of 1100 Da is more efficient with CVVHF than CVVHD.

The sieving coefficient (S) is the fraction of a substance that passes through the filter and is calculated as: S=antibiotic concentration in filtrate/[0.5 (antibiotic concentration in afferent+efferent blood)].

For a given haemofiltration rate, clearance is most efficient for antibiotics with the highest sieving coefficients. These include aminoglycosides, carbapenems, metronidazole and vancomycin, all have sieving coefficients between 0.9 and 1. Cefuroxime, cefotaxime, ceftazidime also have moderately high sieving coefficients, 0.9, 0.62, and 0.86, respectively, and are efficiently cleared by haemofiltration. However, drugs with the highest sieving coefficients are also most influenced by changes in the filtration rate.

Most antibiotics other than vancomycin and teicoplanin are of low molecular weight and are also easily

removed by diffusion during CVVHD. Consequently most antibiotics are readily cleared by CVVHDF, and once creatinine clearances approach 35 ml/min, there may be little need to alter dosage intervals for standard doses for fear of toxicity. Antibiotics such as glycopeptides and aminoglycosides can additionally be monitored and provide an indication of what is likely to be happening to other concomitant antibiotics.

As a general rule severely infected patients with poor renal function or who are dialysis dependent should receive normal antibiotic doses given less frequently. Ideally these patients are monitored by post-dialysis troughs and post-administration peaks to avoid non-renal antimicrobial toxicity.

Antibiotic distribution in tissues

Successful eradication of deep-seated infections depends on achieving bactericidal concentrations at the infection source. The infecting agent may be either within cells or extracellular or both. *Mycobacteria*, *Salmonella*, *Listeria*, *Legionella*, *Chlamydia* and *Mycoplasma* spp. are found mainly in cells while pyogenic bacteria locate primarily in the extracellular space. The ability of antibiotics to penetrate such sites is related to the type of antibiotic, protein binding, tissue characteristics and method of antibiotic administration. Table 2 presents findings on the tissue penetration of some antibiotics.

Type of antibiotic

β-Lactams and aminoglycosides distribute primarily to extravascular fluid although aminoglycosides eventually accumulate by a process of endocytosis in cells and may reach two to four times extracellular concentrations. Their intracellular activity, however, is limited. Macrolides, lincosamides (mainly clindamycin), and fluoroquinolones are heavily concentrated in cells through a mechanism of simple diffusion, partition based on differences in intracellular and extracellular pH and in the cases of lincosamides and macrolides an active transport system. Macrolides have a significant intracellular activity which makes them potent agents for obligate intracellular organisms such as legionella. Lincosamides, however, fail to have enhanced intracellular activity despite achieving high intracellular concentrations. Therefore the degree of intracellular penetration is not necessarily correlated with antibiotic activity, probably because the sub-cellular location of antibiotic within the cell may not match that of the organism. Equally while agents with poor cellular penetration are likely to have limited activity against intracellular infections, when higher extracellular concentrations are achieved and time is allowed, treatment can

Table 2 Tissue penetration of some antibiotics. Note that many of these studies had small numbers; concentrations were measured from multiple sources, for example, bile was from T tube, gall bladder, or common bile duct. Dosing also varied, for example, single or multiple, oral, intramuscular or intravenous; Many antibiotics have no data on tissue penetration (*R* ratio of tissue/serum antibiotic concentration after a single dose, *I* tissue infected at the time of measurements)

	PMN cells		Skeletal muscle		Ascites		Lung tissue		Sputum		Bile		Pleural fluid		CSF	
	I	R	I	R	I	R	I	R	I	R	I	R	I	R	I	R
Gentamicin [93, 94, 95, 96]	–	21	No	111	Yes	90	I	NA	Yes	<8	–	64	No	57	Yes	2.5
Amoxicillin clavulanic acid [97, 98]	–	–	–	–	No	83	No	32	No	13	–	–	–	–	–	–
Imipenem [99, 100, 101, 102, 103]	–	33	No	5	No	85	No	60	No	20	–	48	–	–	Yes	8.5
Cefotaxime [104, 105, 106, 107, 108]	–	110	No	5	Yes	120	No	382	Yes	2	Yes	252	No	26	Yes	51
Cefuroxime [109, 110]	–	–	–	–	No	89	–	–	Yes	14	–	23	No	30	Yes	108
Ceftazidime [106, 111, 112, 113]	–	56	No	26	No	45	–	–	Yes	18	–	88	No	21	Yes	23
Teicoplanin [93]	–	6000	–	–	–	–	–	–	–	–	–	–	–	21	–	–
Vancomycin [114]	–	122	–	–	No	52	–	–	–	–	–	41	No	41	No	0
Amikacin [95, 115, 116, 117, 118]	–	–	No	15	No	58	No	40	No	21	No	54	No	40	Yes	35
Piperacillin [111, 119, 120, 121]	–	<10	Yes	32	No	55	No	92	Yes	4	–	468	–	–	–	–
Ciprofloxacin [111, 122, 123, 124, 125]	–	349	No	79	–	–	No	624	Yes	26	–	–	No	26	Yes	25

be effective. An example of this is ampicillin treatment of *Listeria monocytogenes* [27].

Influence of protein binding

Antibiotics principally bind to albumin to establish an equilibrium between bound and free antibiotic. Free antibiotic is able to diffuse into tissue and microbes. In vitro and in vivo studies suggest that high intravascular protein binding limits free antibiotic accessibility to tissues and reduces effectiveness [28, 29, 30]. Given the mode of action of time-dependent antibiotics with no PAE which rely on free concentrations to be consistently above MIC, it seems more prudent to choose a poorly rather than highly bound antibiotic. In an in vivo study Wise et al. [29] demonstrated the advantage of amoxicillin over flucloxacillin in a blister penetration model. However, they cautioned that the effect of protein binding is less relevant when the choice is between drugs of relatively low protein binding, i.e. less than 70%. Most β-lactams are time dependent with no PAE and are moderately bound (10–30%), but ceftriaxone and flucloxacillin are over 80% bound. Other antibiotics such as ciprofloxacin, vancomycin, tetracycline, and chloramphenicol are significantly bound (40–60%) while aminoglycosides are poorly bound (<10%). Consequently for the majority of drugs protein binding is sufficiently low to not to pose a problem of tissue antibiotic availability. Therapeutic failure has, however, been reported with a highly bound agent [31].

Differences between tissues

The disposition of antibiotics has traditionally been studied by comparing tissue to serum concentration ratios in infected and non-infected tissues. However, differing doses, administration methods and processing of specimens have resulted in wide variations in estimates of tissue distribution. Notwithstanding this, some broad trends can be observed. For example, antibiotic concentrations in ascitic fluid are about 50% those in serum, peak concentrations being achieved some hours after those in serum. A major determinant of relative antibiotic concentrations in serum and fluid filled cavities is the ratio of cavity surface area (SA) to cavity volume (V). High SA/V ratios more closely follow serum concentration fluctuations. Low SA/V ratios typically have dampened peaks and higher troughs [32].

Of particular interest are the relative antibiotic concentrations achieved in bronchial secretions, sputum and lung tissue. The antibiotic concentration achieved in sputum for most drugs is very low while lung tissue concentrations are considerably higher. Opinion is divided as to whether sputum concentrations are of any importance [33, 34]. Antibiotics such as ciprofloxacin, cefotaxime and erythromycin are concentrated in the lung to levels considerably higher than plasma and seem ideal agents for susceptible micro-organisms causing pulmonary infections. However, although one might expect a correlation between higher tissue concentrations and infection cure rates, there remain few data for most antibiotics other than ciprofloxacin [35, 36, 37, 38].

Mode of administration and antibiotic availability

Many authors have proposed that β-lactam tissue availability would be better served by continuous infusions rather than intermittent dosing [13, 39, 40, 41, 42, 43, 44]. Animal and human studies have explored these proposals. Although the animal studies have shown little methodological consistency, the balance of opinion is that continuous infusions are slower to achieve target concentrations but result in a higher average antibiotic tissue concentration over time [45, 46, 47]. The speed of achieving target concentrations is easily resolved with a loading dose. However, the clinical question remains whether this results in better treatment of infection. Roosendaal and Bakker Woudenberg [46] attempted to answer this in a series of rat studies using ceftazidime against *Klebsiella pneumoniae* infection. They initially observed that continuous infusion (without a loading dose) did not produce a significantly better response than intermittent treatment. However, further studies comparing normal and leucopaenic rats infected with *K. pneumoniae* showed that while continuous infusions were equally effective in both groups of rats, intermittent doses were considerably less effective in the leucopaenic rats. There is evidence that for many antibiotics prediction of clinical outcome with respect to blood antibiotic concentrations seems to be best correlated with the 24-h AUC/MIC ratio otherwise known as AUIC [38, 48].

Clinical experience with time-dependent antibiotics in the critically ill

The importance of appropriate antibiotic administration was first alluded to by Jawetz [49] in 1946 who suggested that the newly discovered penicillin was being given infrequently and at too low a dose, probably because of its wartime scarcity. Except for aminoglycosides and glycopeptides where blood concentrations can be routinely measured, inadequate concentrations of other antibiotics can go unrecognised and give rise to a clinical dilemma; is failure to respond to therapy due to wrong antibiotic or an inadequate dose of the right drug?

The effects of simple illness on the pharmacokinetics of ceftazidime was studied by Ljungberg and Nilsson [50] in ten febrile but otherwise healthy 80-year-old men.

They found that acute infection was associated with an increase in ceftazidime Vd and renal clearance. In the following year Shikuma et al. [51] examined piperacillin kinetics in 11 critically ill patients with previously normal renal and hepatic function and found a large variation in clearance, $t_{1/2}$ and Vd. The latter varied from 0.1 to 1.3 l/kg (normal value 0.18±0.03) and clearance from 7.3 to 56.4 l/h. The expanded volumes of distribution were thought to be due to the requirement for volume expansion therapy and changes in protein concentrations.

In a recent study among 15 critically ill patients receiving recommended doses of ceftazidime Gomez et al. [52] found that 50% of patients had concentrations below four times the MIC_{90} for *Pseudomonas aeruginosa* for a substantial period of the dosing interval; this was attributed to larger than expected volumes of distribution. Lipman et al. [53] reported similar findings using standard doses of the new cephalosporin cefepime and suggested that a 50% increase in dose (1 g every 4 h) would result in trough concentrations three times MIC_{50} for *P. aeruginosa* and perhaps be more effective. Similar problems have been noted among severe burns patients, in whom the resulting low antibiotic concentrations are sometimes difficult to correct even with higher doses [54, 55, 56].

Many investigators feel that antibiotic blood concentration should be at least four to five times MIC to control serious infections [13, 14, 40, 44, 57]. In view of the documented increases in Vd there is concern that patients might become particularly vulnerable with an intermittent dosing regimen [40, 53]. Some investigators have explored whether continuous antibiotic infusion could provide consistently appropriate blood concentrations. Benko et al. [13] in a cross-over design among 12 critically ill patients found that at steady state ceftazidime infusions achieved five times the MIC for 100% of treatment time whereas intermittent therapy achieved the same concentrations for 92% of the time. Others have had similar findings and indeed have demonstrated in an animal model that for the same daily dose continuous infusion of ceftazidime is more effective than intermittent doses [58, 59]. It has also been suggested in a study among critical care patients with nosocomial pneumonia that smaller doses of ceftazidime would be equally effective and provide a cost saving [60]. However, thus far there have been no definitive human studies which demonstrate a better outcome with continuous infusion regimens, although some studies are suggestive [61, 62].

There has been a concern that sub-therapeutic time-dependent antibiotic concentrations might favour the emergence of resistant organisms. Fantin et al. [57] showed in a rabbit model of endocarditis that the growth of mutants could be prevented if antibiotic concentrations remained above MIC for at least 61% of the time. Others have suggested that emergence of resistance can be prevented only if concentrations are maintained above MIC for 100% of the time [40].

It has been proposed that vancomycin, a time-dependent antibiotic albeit with a post-antibiotic effect, should be infused with the aim to achieve constant blood vancomycin concentrations. Two early studies demonstrated that clinical efficacy can be achieved when vancomycin is given by infusion. In the first, Brinquin et al. [63] reported cure of post-neurosurgical methicillin-resistant *Staphylococcus aureus* meningitis in eight patients with intravenous vancomycin infusion rates of 37–55 mg/kg per 24 h which achieved CSF penetration (4 −7 mg/l). In the second study Conil et al. [64] demonstrated in burns patients that vancomycin infusions after an initial loading dose achieved adequate blood concentrations where intermittent doses had failed. Cruciani et al. [65] reported that while single large doses of vancomycin achieved lung tissue concentrations between 25% and 40% those in blood, by 12 h 43% of patients failed to have any detectable vancomycin in lung tissue. Since these early studies others have demonstrated at least similar clinical outcomes when vancomycin infusion is compared to intermittent dosing, with no increase in toxicity, less variability in blood concentration and need for sampling and cost savings. Loading doses of 15 mg/kg followed by daily infusions starting at 15–40 mg/kg aimed at achieving plateau concentrations between 15 and 25 mg/l are generally accepted [66, 67, 68, 69, 70].

Among the newer antibiotics such as linezolid there is preliminary evidence not only that administration by continuous infusion is more effective than intermittent doses, but that in the case of linezolid, normally a bacteriostatic agent, it acquires bactericidal properties [71].

Notwithstanding the theoretic advantages of time-dependent antibiotic infusions, not all β-lactams are best infused. MacGowan and Bowker [44] has suggested that the carbapenems, unlike other β-lactams, also have a concentration effect with variable PAE particularly against Gram-negative organisms, and that they are not more effective by continuous infusion.

Clinical experience with concentration-dependent antibiotics in the critically ill

Aminoglycosides, fluoroquinolones and metronidazole all have concentration-dependent activity. Aminoglycosides combine concentration-dependent activity with a consistent PAE against Gram-positive and Gram-negative bacteria in vivo. Aminoglycosides are water soluble, mainly distributed to the extracellular space, minimally protein bound and are almost entirely excreted by the kidney. Pennington et al. [72] reported that simply inducing fever in healthy patients resulted in a fall in gentamicin concentrations. These changes were later supported by Triginer et al. [73] who showed that during septic epi-

sodes gentamicin concentrations were lower than expected. They also demonstrated that initiation of intermittent positive pressure ventilation can result in a fall in gentamicin concentrations [74]. It was suggested that the fall in gentamicin concentration can be explained by the increase in Vd associated with critical illness and he recommended larger initial doses.

The idea that gentamicin should be given in doses sufficient to reach high plasma concentrations was alluded to by Moore et al. [75] in a logistic regression analysis of four studies with 236 patients. They suggested that gentamicin with a peak plasma concentration (Cmax) to MIC ratio of 10:1 or more is predictive of a good outcome. Others have also shown that to eradicate the more serious infections and prevent emergence of resistance the goal should be a peak concentration at least eight times MIC [76, 77, 78]. Kashuba et al. [79] in a study among patients with Gram-negative nosocomial pneumonia reported that it was possible to predict a 90% probability of temperature and leucocyte resolution by the 7th day of treatment if the Cmax/MIC was equal to or greater than 10 within the first 48 h of starting aminoglycosides. These authors also suggested that by achieving early appropriate peak concentration, duration of therapy can be shorter and aminoglycoside exposure and toxicity minimised. In a number of meta-analyses the overall finding has been of marginally better clinical responses when large loading doses at extended intervals is compared to multiple dosing regimens [80, 81, 82, 83]. Although these studies showed little difference in the incidence of toxicity, a recent prospective randomised controlled double-blind study not included in these meta-analyses showed a significant decrease in nephrotoxicity with extended interval dosing [84]. However, some evidence suggests that excessive peaks or area under the plasma concentration-time curve (AUC) can result in proximal renal tubular damage, while high pitch deafness has been associated with the duration of therapy [84, 85, 86].

Among the many methods suggested for prescribing aminoglycosides it has become common practice to adopt the nomogram prepared by Nicolau and colleagues [87] at Hartford Hospital, Connecticut, as a guide to interval dosing of gentamicin. This method attempts to maximise clinical efficacy and reduce aminoglycoside toxicity. Gentamicin dosing has been aimed at achieving peak concentrations of 20 mg/l to ensure ten times MIC for the more difficult *P. aeruginosa*. The dose that consistently achieved this was 7 mg/kg actual body weight, where the latter excluded patients 20% over ideal body weight. The nomogram suggests dosing intervals of 24, 36 or 48 h depending on blood gentamicin concentration obtained at any time between 6 and 14 h after the dose. The authors suggest that patients with reduced renal function should have normal doses to achieve peak concentrations, but that repeat doses are given at extended intervals when concentrations fall to 1 mg/l. Nicolau et al. [87] reported that use of the nomogram in more than 2,000 patients reduced nephrotoxicity rate from a historical 3–5% to 1.2%, and in spite of high peaks only two patient had ototoxicity. Although the Hartford nomogram assumes that peak gentamicin concentrations of 20 mg/l are achieved after administration of 7 mg/kg, many critically ill patients have increased Vd that might diminish such peaks. It would therefore be prudent in the event of poor therapeutic response to measure peak concentrations before changing therapy.

Other concentration-dependent antibiotics are the 4-quinolones, of which ciprofloxacin is the best example. Some time after its introduction in 1985 the dose was questioned [35, 88]. Based on AUC the bio-equivalence of the clinically effective oral dose 750 mg was found to be closer to 600 mg intravenously than the 200 mg intravenously for which it had been licensed. Since the dose of 600 mg produced a Cmax that was considered toxic, the suggested dose was modified to 400 mg intravenously every 8 h in order to receive FDA approval. In the United Kingdom the recommendations for ciprofloxacin is 400 mg ever 12 h. Notwithstanding these recommendations ciprofloxacin continued to be administered intravenously at 200 mg for some time, and was frequently associated with emergence of resistance, sometimes within the treatment period. This was particularly true with *P. aeruginosa* and *S. aureus*, whose MIC values were some ten-fold those for *Moraxella* spp. or *Haemophilus* spp. Ciprofloxacin uniquely inhibits bacterial replication by interacting with the active subunit of DNA gyrase, a process which is pH and concentration dependent, and it is likely that emergence of resistance was related to inadequate peak concentrations. The postantibiotic effect of 4-quinolones have been well documented [89, 90, 91]. It is interesting to note that inadequate concentrations of ciprofloxacin have been shown not only to increase emergence of resistant strains to ciprofloxacin but also to increase emergence of resistant strains to antibiotics which have a different mode of action [92].

Studies have confirmed that ciprofloxacin 400 mg intravenously every 8 h is required to obtain a bacteriological and clinical cure [36, 37]. It has been suggested that the ratio of area under the curve to MIC (AUIC) is closely associated with the likelihood of clinical, or bacteriological cure. AUIC is measured in serum inhibitory units over time (SIT^{-1}) and break points for clinical cure have been identified at 72 SIT^{-1}. However, best results have been obtained at values between 250 and 500 SIT^{-1} [36, 38, 48]. It is notable that Forrest et al. [36] was concerned that for an organism with MIC above 0.25 mg/l, daily ciprofloxacin doses of 1200 mg might still be inadequate to achieve target AUIC between 250 and 500 SIT^{-1}. They suggested that there is no reasons to limit the daily dose to 1200 mg but conceded that a preferred approach might be to seek synergy by introducing another antimicrobial.

Summary

Many factors, over which there may be little control, may influence the response of a patient to therapy; however, one of these, specific therapy with antibiotics can be readily optimised. The evidence suggests that concentration-dependent agents such as aminoglycosides are effective with fewer side effects when given in large, infrequent doses. Equally there is evidence that time-dependent antibiotics often fail to reach adequate concentrations throughout the treatment period, and that this might be resolved by an initial loading dose followed by constant infusion. However, to date no randomised controlled prospective trial has been published demonstrating an improvement in clinical outcome following infusion rather than intermittent boluses of time-dependent antibiotics. There remains the theoretical risk that inadequate antibiotic dosing would not only lead to therapeutic failure but also encourage the emergence of resistant strains.

Critically ill patients with hepatic dysfunction do not normally need dosage adjustments for most antibiotics while patients with poor renal function or who are dialysis dependent should receive normal antibiotic doses given less frequently. Ideally these patients are monitored by post-dialysis troughs and post-administration peaks to avoid non-renal antimicrobial toxicity.

Critical illness can grossly alter antibiotic pharmacokinetics principally through increases in volume of distribution. Unfortunately, other than glycopeptides and aminoglycosides, antibiotic blood concentrations are rarely monitored and therefore adequate concentrations can only be inferred from clinical response. Failure to respond within the first few days of empirical treatment might be due to antibiotic resistance or inadequate doses. Therefore the same rigour should be applied to achieving adequate antibiotic concentrations as is applied, for example, to inotropes which are titrated to achieve predetermined physiological targets.

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