Clinical practice review

Towards Better ICU Antibiotic Dosing

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ABSTRACT

Objective: *To review the recent pharmacokinetic and pharmacodynamic reports of some of the commonly used antibiotics in critically ill patients and recommend alterations in their administration to improve their efficacy.*

Data sources: *Relevant articles and published reviews on aminoglycoside, third and fourth generation cephalosporins, vancomycin and ciprofloxacin dosing in critically ill patients.*

Summary of review: *Antibiotic regimens are derived from non-critically ill volunteers. To optimise antibiotic administration in the intensive care unit, the different 'kill-characteristics' of the antibiotic classes and the altered drug pharmacokinetics in critically ill patients should be considered together to re-evaluate the currently recommended regimens.*

Aminoglycosides require high peak levels to be most effective, hence large single daily doses are important. With the increased clearances in the critically ill patient, particularly those who have normal renal function, a more frequent administration than single daily dosing may be optimal (e.g. 18-hourly). Increased clearances of β-lactam antibiotics result in low troughs causing a reduced duration of antibiotic levels above the minimum inhibitory concentration (i.e. the suggested pharmacological target for these drugs). In critically ill patients, frequent dosing or even continuous infusions of the β-lactam antibiotics may increase their effectiveness by maintaining blood levels above the minimum inhibitory concentration (MIC) for longer periods. Vancomycin has a high volume of distribution in the critically ill patient, thus the currently recommended maximum daily dose may lead to inadequate serum levels. Suggested targets for quinolone therapy involve more than just high peak levels. A ratio of area under the serum concentration time curve (AUC) to MIC of >125 has been shown to correlate with better clinical outcomes. Ciprofloxacin when given intravenously at 400 mg 8-hourly should achieve this, which is a regimen that has been shown to be safe.

Conclusions: *Applying pharmacokinetic and pharmacodynamic principles to critically ill patients will lead to better antibiotic use and hopefully a better outcome.* (**Critical Care and Resuscitation 2000; 2: 282-289**)

Key Words: Intensive care, critical illness, antibiotics, aminoglycosides, β-lactam antibiotics, vancomycin, fluoroquinolones

Antimicrobial dosing regimens are often designed to maintain active drug concentrations above the minimum inhibitory concentration (MIC) or above the minimum bactericidal concentration (MBC) for nearly the entire dosing interval.[1] These recommendations are based on research from animal models obtained more than 40 years ago. Newer insights into antibiotic activities and their kinetics cast doubt on these guidelines.

The inflammatory response associated with infections involves cytokine and other mediator release,

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endothelial damage and increased capillary permeability. The acute phase response also produces a rapid fall in serum albumin levels. Included in the overall inflammatory response are fluid shifts, third space losses and, initially, a high cardiac output. These changes result in a creatinine clearance that is higher than normal unless renal dysfunction ensues, as severe sepsis may result in a decrease in renal and hepatic function.

This article attempts to incorporate basic pharmacokinetic and pharmacodynamic principles of aminoglycosides, vancomycin (i.e. glycopeptides), third and fourth generation cephalosporins (i.e. β-lactam antibiotics) and ciprofloxacin (i.e. fluoroquinolones) with the clinical effects of severe sepsis to give a rationale for more effective dosing regimens in critically ill patients. To explain these concepts we will assume relatively normal renal and hepatic function, for where this is not so, the serum half-lives of all these antibiotics will be prolonged and clearances will be diminished resulting in accumulation of all these drugs.

PHARMACODYNAMIC AND PHARMACOKINETIC PRINCIPLES

Understanding how antibiotics kill bacteria (or looking at their 'kill characteristics') in experimental models can give one insight into how dosing intervals may differ between antibiotic classes. For example, β-lactams have a characteristic slow, continuous kill, characteristic. This contrasts with the kill characteristics of the aminoglycosides, which are concentration dependent.[2-9] Experimentally, high peak concentrations of aminoglycosides provide a better killing effect on standard bacterial inocula. The higher the aminoglycoside concentration above the MIC of the microorganism, the quicker the kill. Moore *et al*,[10] demonstrated unequivocally in a retrospective study analysing clinical outcome after aminoglycoside usage, that a high peak concentration of aminoglycoside relative to the MIC for the infecting organism was a major determinant of the clinical response to aminoglycoside therapy.

Understanding and utilizing serum half-life effects of aminoglycoside antibiotics cannot explain the inability of Gram-negative organisms to grow in serum subsequent to the exposure to high concentrations of these antibiotics, even after serum concentrations have been unmeasurable for some time. This effect is called the post-antibiotic effect (PAE).[2-6,11,12] All aminoglycosides exhibit a significant PAE, the in-vitro duration of which is extended by higher serum concentrations (i.e. the PAE is concentration dependent).[2-4] It is from these pharmacokinetic and pharmacodynamic principles that the philosophy of single daily dosing arose.

In-vivo animal experiments demonstrate that the killing effect of β-lactam antibiotics on bacteria is significantly different to that of the aminoglycosides. Bacterial killing is almost entirely related to the time that the levels in tissue and plasma exceed a certain threshold. β-lactam antibiotics lack a significant post-antibiotic effect, particularly against Gram-negative organisms. Also, if the concentration of antibiotic falls below the MBC, any bacteria left in the inoculum proliferate almost immediately.[2-9,13] A study in rabbits with experimental aortic endocarditis due to *Pseudomonas aeruginosa* investigated development of resistance to cefpirome and ceftazidime, and showed that resistance developed only in animals whose plasma concentrations exceeded the MIC for less than half the dosing interval.[14] Roosendaal *et al*,[7] using a rat model, reported better results in treating sepsis with continuous infusions of ceftazidime.

However, defining pharmacokinetic criteria to assess dosing regimens is a contentious issue. It may be argued that the criterion of exceeding the MIC for 60% or more of the dosing interval is not optimal for two reasons. Firstly, experimental studies have demonstrated that maximum killing of bacteria occurs at 4 to 5 times the MIC, while higher levels do not produce added efficacy. Mouton and den Hollander, in an *in vitro* pharmacokinetic model using resistant *Pseudomonas* strains, demonstrated the need for sustained ceftazidime concentrations above 4 to 5 times the MIC.[13] When antibiotic concentrations fell below this threshold in the models, bacterial growth resumed immediately.[13,14] This necessity for a relatively high threshold concentration is supported by a recent *in vitro* study of *Pseudomonas* isolates obtained from cystic fibrosis patients.[15] It has been suggested by some researchers that concentrations of any β-lactam should be maintained above 4 to 5 times the MIC for long periods.[2,3,5] Secondly, it has been proposed that for pathogens for which the β-lactam does not exhibit a post-antibiotic effect, the plasma concentration should exceed the MIC for 90% to 100% of the dosing interval.[16] Consequently, dosing regimens of β-lactam antibiotics are being re-evaluated to optimise the time that the levels exceed the MIC during the dosing interval.[13,16-19]

The above data support the concept of administering β-lactams in a way that maintains a constant plasma concentration above the required threshold i.e. maintaining trough levels, while eliminating the high peak serum concentrations that are not important. In clinical terms this would mean that smaller, but more frequently dosed amounts of β-lactam antibiotics could be advantageous and should be investigated. Pharmaco-

kinetic and pharmacodynamic modeling using different bacterial growth models for optimising dosage regimens also support a loading dose and an infusion regimen, provided that concentrations greater than the required threshold are achieved.[20]

In contrast, ciprofloxacin has a combination of both of the above effects. It has some concentration-dependent kill characteristics, and hence one suggested 'target' parameter for a good clinical bactericidal effect is a C_{max} of up to 8 x MIC.[21] Quinolones also have some time-dependent kill characteristics,[22-24] and as well exhibit a PAE.[22-26] Therefore, peak concentrations alone may not correspond with optimal *in vivo* killing. A combination of peak concentrations and time above MIC (i.e. the whole area under the concentration time curve) experimentally corresponds best with ciprofloxacin efficacy. A ratio of the area under the serum concentration time curve (AUC) to MIC (i.e. AUC/MIC or AUIC) of >125 has been shown to correlate with better clinical outcomes.[21,23,27-29] It is noteworthy that under-dosing can be a potential problem. There is general concern about the emergence of resistance related to inappropriately low doses of ciprofloxacin particularly with enterococci, *Pseudo-monas* species and methicillin resistant staphylo-cocci.[27,30]

APPLIED CLINICAL ISSUES

Aminoglycosides

The narrow therapeutic index of aminoglycosides has continued to cause reticence in using high doses. There is now, however, much evidence that if smaller, more frequent dosing (but the same total daily dosing) of aminoglycosides is given compared with the daily dosage given once a day, there is more renal and ototoxicity.[31-37] It is therefore felt that it is the troughs (more particularly the area under the concentration-time curve) that are more incriminatory in the renal and ototoxicity of these drugs.[31-37]

When given intravenously, peak aminoglycoside levels are achieved at about thirty minutes. The plasma half life ($t_{1/2}$) of aminoglycosides varies with renal function but both the naturally occurring and semi-synthetic agents have a $t_{1/2}$ of between 2 and 3 hours, in patients who have normal renal function.[38] From a practical point of view, this means that six to eight hours (3 to 4 times $t_{1/2}$) after a dose of aminoglycoside there will be very low serum levels of aminoglycoside in patients with normal renal function.

The volume of distribution, (Vd - the apparent volume required to contain the entire amount of drug in the body at the same concentration as in the blood or plasma) of aminoglycosides are from 0.2 to 0.3 L/kg in patients with normal renal function. This means that these drugs are almost exclusively maintained in the extracellular space. The Vd is altered in some disease states, such as leukaemia, where it is increased[39] and in critically ill patients, where it has been shown that the sicker the patient, the larger the Vd.[40] Aminoglycosides are excreted unchanged and almost entirely by glomerular filtration.[41] Thus, high renal and urinary concentrations of aminoglycosides occur.

Another problem with the aminoglycoside dosage is patient variability in achieving adequate peak serum concentrations.[41-51] Considering the fact that amino-glycosides are minimally protein bound, they will distribute into the extravascular space.[41,52] Depending on various factors such as inflammatory processes, vascular permeability, fluid extravasation, 'third space' losses, etc, this distribution will differ in the critically ill patient.[51,53,54] Furthermore, some data show that the sicker the patients are, the greater the volume of distribution of aminoglycosides.[40] Importantly, the critically ill patient with a high APACHE II score, but normal renal function will not only have low trough levels, but also lower peak levels than a less unwell patient. I believe that this (i.e. the severity of illness) variation in different studies explains, at least to some extent, the wide variability of dosages needed to achieve therapeutic levels and the differences in volume of distribution during the course of therapy.[42-51]

Optimisation of dosage schedules, reducing the toxicity, yet retaining a high kill rate has been the subject of at least 50 studies, and almost a dozen meta-analyses.[55-57] Many trials set out to obtain high peak (at 1 hour) and a 4-hour antibiotic free period,[58] which is felt to reduce the incidence of toxicity. Whilst being 'antibiotic free' for a couple of hours, there is still significant antibacterial action, explained by the post antibiotic effect (PAE).[59]

The phenomenon of PAE is much more prevalent in the aminoglycosides than in other antibiotics and more prevalent with Gram-negative bacilli than with other bacteria. It refers to the continued suppression of bacterial growth despite immeasurable concentration of antibiotic by normal assays. The duration of this effect is variable (e.g. between 2 and 8 hours) and is dependent on several factors, the most important of which is the preceding peak of aminoglycoside.[4] This allows drug concentration to fall significantly below MIC of the pathogen without compromising antibacterial efficacy. It is noteworthy that in this context the synergism of aminoglycosides with β-lactams may help counter any adverse effect the low levels may produce.

These three functions of aminoglycoside antibiotics, i.e. high and widely spaced doses causing less toxicity than smaller more frequent doses, high doses producing better kill curves and the prolonging of the PAE,

promoted the philosophy of large, single daily doses of aminoglycosides.[60,61] We ,[62,63] and others,[64,65] have now shown in prospective human clinical trials, that these principles are correct, i.e. that large single daily doses of aminoglycosides produce a better clinical outcome, with less toxicity.

In designing the dosage of aminoglycosides for single daily administration, the dosage was calculated by multiplying the 'old' 8-hourly dose (i.e. 1 to 1.5mg/kg) by three, thus giving a 24-hour dosing schedule. This technique is still used successfully by a large number of centres. However, the largest single series, reported by Nicolau *et al*,[58] used a single daily administration of 7 mg/kg if the creatinine clearance was greater than, or equal to, 60 mL/min. With lower creatinine clearances (i.e. 59 to 40 mL/min) the same dose was suggested at an interval of every 36 hours, and with even lower clearances (i.e. 39 to 20 mL/min the dose was reduced to once every 48 hours. This study used a higher than previous suggested dose, aiming for a greater peak/MIC ratio. They showed no apparent deterioration in cure and a reduction in toxicity compared with a historical comparison at the same institution.

Recently the results of many smaller trials have been amassed and subjected to meta-analysis by a number of different groups. In one meta-analysis involving over 2000 patients, a once daily administration was found to be more efficacious (odds ratio 1.47).[66] Whilst other meta-analyses have been less optimistic as to the increased efficacy, they have all shown an improvement in terms of toxicity and at least no reduction in efficacy.[55-57] These benefits are significant; reduced toxicity, higher peak/MIC ratios, further prolonged PAE and reduced ancillary costs.

β-lactam antibiotics (e.g. third and fourth generation cephalosporins)

In common with the aminoglycosides, it is becoming increasingly apparent that the pharmaco-kinetics of the β-lactam antibiotics in the ICU patient is also different compared with the ward patient.[67,68] Many studies now have demonstrated lower serum concentrat-ions of antibiotics than expected, occurring in the critically ill.[6,11,12,41,43,44,67-74]

In a number of studies, we have demonstrated a common trend, namely low serum β-lactam concentrat-ions at the end of the standard dosing regimen.[71-74] One of the inclusion criteria for all of these studies was a normal serum creatinine level (i.e. a relatively normal renal function). During our studies we measured creatinine clearances and documented these to be unexpectedly high.[71-74] We assumed that as patients with sepsis required fluid loading, this resulted in high creatinine clearances. In two of these studies we found that clearances of cefepime and cefpirome to be linearly related to creatinine clearance.[73,74] In clinical terms this means that patients with high creatinine clearances will have low serum levels of these antibiotics.[73,74]

Our studies have shown that bolus dosing of cephalosporins produces peaks that are unnecessarily high and troughs that were often below the MIC for much of the dosing interval.[71-74] We believed that either more frequent dosing[16,73] or continuous infusions[16,17,20,67, 71-73] provide more sustained levels for longer.

Conceptually, in the early phases of sepsis, patients develop a high cardiac output.[75] This is often maintained unless there is significant myocardial depression. In this state if renal function is not compromised, creatinine clearances will be high, as will be the clearances of many of the renally excreted antibiotics. When either renal dysfunction (e.g. acute tubular necrosis) occurs or when renal blood flow diminishes, creatinine clearances will decrease and serum levels of the β-lactam antibiotics will be maintained at higher levels.

Vancomycin

There is other supportive data that the volume of distribution of drugs that distribute into extracellular water changes in the critically ill, particularly in patients with burns.[68,69,76-80] For example, vancomycin, which is poorly protein bound (similar to the aminoglycosides), will distribute into the extravascular space and will need higher doses in conditions where there is an increase in capillary permeability.[53,54] We have demonstrated in one of our studies on vancomycin an increased volume of distribution in infants with the systemic inflammatory response syndrome (SIRS).[81] We have also demonst-rated a significantly lower peak serum concentration for a given dosage (based on weight) on day 2 of therapy compared with the same dose on day 8 of a therapeutic course.[81] To achieve optimum therapeutic levels of vancomycin in this study we often had to give doses higher than the recommended daily dose (i.e. > 40 mg/kg/day).

Ciprofloxacin

Like many other antibiotics the optimal intravenous dose of ciprofloxacin is unknown.[82] Various theoretical suggestions have been put forward for optimal dosing regimes. Considering the fact that high peak serum concentrations/MIC and AUIC (area under inhibitory curve - AUC/MIC) >100-150 have been suggested as surrogate targets for the quinolones,[21-24,27-29] from a theoretical point of view, high peak serum levels (C_{max}) would help kill, as would the time above MIC and the AUC. All of this information has been integrated into

one value, known as the AUIC (i.e. area under inhibitory curve). Any PAE of the quinolones would be an added benefit to the kill characteristics.

There is general concern about the emergence of resistance related to inappropriately low doses of ciprofloxacin, particularly with enterococci, *Pseudomonas* species and methicillin resistant staphylococci.[27,30] Organisms are usually regarded as sensitive to ciprofloxacin if their minimum inhibitory concentration (MIC) is less than 1 mg/L and resistant if the MIC is greater than 4 mg/L.[83] We have recently published data using ciprofloxacin 400mg given 8-hourly to critically ill septic patients with normal renal function.[84] We found that this dose was safe and provided not only a high C_{max} but also satisfactory AUC levels. A large multicentered clinical trial has recently confirmed the efficacy of this dosage regimen and documented very few side effects.[85]

We are in the process of finalising other ciprofloxacin data that shows that its Vd differs from that of vancomycin and aminoglycosides. In particular, ciprofloxacin Vd does not significantly change with third space losses, nor does it change with time. We believe the differences are due to the fact that ciprofloxacin penetrates tissues better than vancomycin and aminoglycosides. The latter two distribute into extravascular space but not into 'whole body water' compared with ciprofloxacin. This latter compartment will not change with an acute disease process nearly as much as extravascular or extracellular water.

CONCLUSION

The inflammatory response involves cytokine and other mediator release, endothelial damage and an increase in capillary permiability. These aspects have specific effects on antibiotic pharmacokinetics and pharmacodynamics. With fluid shifts, the volume of distribution of antibiotics that distribute into the extracellular space (e.g. aminoglycosides and vancomycin) is high, therefore peak serum antibiotic levels for any dose will be lower than that found in patients with a normal Vd. The distribution phases of antibiotics will also be altered, as will clearances of renally and hepatically cleared antibiotics. Obviously hepatic and/or renal dysfunction will decrease clearances of those antibiotics metabolised and/or excreted by these organs.

Antibiotic regimens are derived from trials on non-critically ill volunteers. In order to optimise antibiotic regimens in the ICU, the specific differences in fluid compartmental changes in these patients, in conjunction with the different kill characteristics of the various antibiotic classes, should be used to determine doses and regimes that may well differ from more common antibiotic prescribing practices.

Large doses of aminoglycosides separated by longer intervals have been shown in experimental models to be more efficacious and less toxic. This animal work has now been clinically adapted to large single daily doses. Once daily dosing of aminoglycosides now has evidence based data to confirm its benefits.

This is in contrast to β-lactam antibiotics where in vitro models have demonstrated increased efficacy with continuous infusions that maintain lower serum levels for most of the dosing interval. Serum levels of these antibiotics fall to low levels between conventional dosing regimes. Renal elimination of these drugs is almost linearly related to creatinine clearances, so with renal dysfunction serum levels will accumulate. In contrast, with high creatinine clearances that can occur with significant fluid loading in the initial phases of sepsis or SIRS, drug clearances will be high, resulting in low serum levels of these antibiotics. Initial clinical data demonstrate at least equivalence between continuous infusions and bolus dosing.

Vancomycin and aminoglycosides distribute into extravascular and extracellular water. With the common abnormalities associated with critically ill patients particularly in fluid shifts into interstitial spaces, larger than conventional doses may be needed to optimise serum levels and therefore clinical efficacy.

Ciprofloxacin has some characteristics of each of the above classes of antibiotics. High peak levels are needed for optimal effects, but in view of its ability to penetrate into tissues, the acute changes in the volume of extracellular water will have little impact on dosing requirements.

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