Role of Pharmacokinetics and Pharmacodynamics:
Does the Dose Matter?

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Antibiotic dose is important in determining serum area-under-the-curve (AUC) and peak serum concentration (Cmax), as well as the time the serum concentration remains over the pathogen minimum inhibitory concentration (T>MIC). However, dose is not the sole determinant of these factors; they are modified by absorption, clearance, and frequency of dosing. It is difficult to relate dose to clinical outcome in humans, but pharmacodynamic parameters (AUC/MIC, Cmax/MIC, or T>MIC) have been related to clinical and bacteriological efficacy or emergence of resistance to aminoglycosides, fluoroquinolones, glycopeptides, and β-lactams.

In this comment I will concentrate on human data to answer the question posed: “Does the dose matter?” There are a number of pharmacodynamic studies performed with human subjects that indicate that for aminoglycosides, glycopeptides, and fluoroquinolones, dose is not related to clinical and/or bacteriological outcome [1–4]. In some ways, this is an unexpected finding, because it is likely that the antimicrobial dose-to-outcome relationship in humans follows a sigmoid Emax curve. The reason why dose cannot be related to outcome in humans is 2-fold: first, the range of doses used to treat infection in humans is too narrow to establish the response curve; second, the effect that dose has on the antibiotic exposure at the site of infection is modified by tissue penetration and bacterial susceptibility. The serum area-under-the-concentration-time-curve (AUC) is a good index of antibiotic exposure, and it depends directly on dose, modified by absorption (F) and plasma clearance (Clp):

\[ F \times \text{Dose} = \text{Clp} \times \text{AUC}. \]

However, even AUC does not determine the outcome in all situations—the shape of the serum concentration time curve is important, and AUC provides no information on this topic. For those agents in which the amount of time that the serum concentration exceeds the MIC (T>MIC) determines the outcome, a low, flat profile will be best; however, if the peak concentration to MIC ratio (Cmax/MIC) is important, then high peaks will be useful. In addition, serum concentrations may not predict extra vascular concentrations that may be more relevant for the infection site.

The question then becomes, “Are antimicrobial concentrations or their pharmacodynamic derivatives that incorporate susceptibility related to outcome?” It has been known for more than 25 years that aminoglycoside post-dose concentrations are related to clinical outcome. When aerobic, gram-negative rods that cause urinary tract infection, skin and soft-tissue infection, or bacteremia were treated with gentamicin, a post-dose concentration of >5 mg/L given in the first 3 days of therapy was related to a good response. In patients with pneumonia caused by gram-negative rods, post-dose concentrations of >8 mg/L were related to beneficial outcome [5–7].

This work was confirmed by Moore et al. [8, 9] for gram-negative bacteremia and pneumonia. However, in...
an analysis of infection due to gram-negative rods in a wide variety of sites, the pharmacodynamic parameter of \( C_{\text{max}}/\text{MIC} \) was best related to clinical outcome. A ratio of >10 was optimum [10]. This was recently confirmed in a more homogenous group of patients with pneumonia caused by aerobic gram-negative rods, when a \( C_{\text{max}}/\text{MIC} \) ratio of >10 during the first 48 h of therapy was related to clinical outcome [2].

For fluoroquinolones, pharmacodynamic parameters have also been related to clinical and bacteriological outcomes in humans: either AUC/MIC or \( C_{\text{max}}/\text{MIC} \) are predictive of outcome for ciprofloxacin, grepafloxacin, or levofloxacin [3, 11, 12].

Data for glycopeptides are less compelling, but a review of cases published in the literature and a study of *Staphylococcus aureus* bacteremia treated with teicoplanin was able to relate serum concentrations to outcome [4, 13]. In the *S. aureus* bacteremia study, pre-dose concentrations and patient age predicted outcome after multivariate analysis [4].

As for glycopeptides, there are little good human data relating doses, serum concentration, or pharmacodynamic parameters to outcome for ß-lactams. However, it is known that cefamandole, when given by means of continuous infusion to patients with persistent neutropenia, was superior to the same agent given by means of intermittent infusion [14]. In addition, when cefuroxime was given by means of continuous infusion to achieve a steady-state concentration of 20 mg/L in patients with chest infection, the total daily dose was lower and there was a trend towards shorter duration of therapy and stay among patients in the continuous-infusion group, compared with patients in the intermittent-injection control group [15].

Finally, there are recent data that imply dose or drug exposure may be related to emergence of antibacterial resistance both in the hospital and in the community. An AUC/MIC ratio of <100 was associated with emergence of resistance in an intensive care unit pneumonia model that involved a number of different antimicrobial agents and pathogens [16]. In a community-based study of the carriage of penicillin-resistant *Streptococcus pneumoniae*, patients who received low dose ß-lactam therapy had a higher risk of carriage than did patients who received larger doses [17].

In conclusion, it is clear that dose is important in influencing drug concentration, but the impact of dose is modified by absorption, clearance, and, perhaps, tissue penetration and bacterial susceptibility. Human data indicate that dose is a poor predictor of outcome; pharmacokinetic parameters, such as \( C_{\text{max}}, \text{AUC}, \) and \( C_{\text{min}} \) are better predictors of outcome, but pharmacodynamic parameters are best.

### References


