Pharmacodynamics and alternative antimicrobial dosing regimens

Many years have passed since the discovery of penicillin by Fleming in 1929 and, although many other antimicrobials have since been discovered, the debate regarding optimal doses and dosing regimens continues. Antimicrobial therapy is unique in many respects since the ‘receptors’ to which the anti-microbial is directed is a living microorganism that may be found in virtually any location in the body. The determinants of outcome of the infectious process have been well described and include a complex interaction among the microorganism (bug), the antimicrobial (drug) and the infected individual (host). The bug-drug-host interaction may be described in terms of the pharmacokinetics of the drug, pharmacodynamics of the bug-drug interaction and the host response. Pharmacokinetics deals with the disposition of the drug in the body and the provision of active drug at the site of the infection, whereas pharmacodynamics deals with the time course of drug activity and the mechanisms of action of drugs on the microorganism. The host response is probably the most important variable in any bug-drug-host interaction since it is the ability of the host to destroy or contain the microorganisms that ultimately leads to recovery.

It is the interplay of drug pharmacokinetics, pharmacodynamics and the host response on which dosing regimens of antimicrobials are proposed. The concept of a therapeutic level with respect to penicillin was discussed as early as 1944 (1). It was suggested that continuous therapy with penicillin was necessary to maintain a critical level during therapy. Studies conducted in the early 1950s using a mouse model demonstrated that intermittent therapy was as effective as continuous therapy (2,3). The success in these early trials with intermittent dosing was thought to depend on the length of the dosage interval and the amount of time during which drug levels remained effective in the serum. Based on these early studies most antimicrobials have been given as intermittent doses with usual dosage schedules of three or four times daily. With beta-lactam agents it was also thought that some bacterial regrowth was necessary to obtain bactericidal activity.

During the past decade factors governing the pharmacokinetic parameters of antimicrobials (distribution into tissues, free versus bound antimicrobials, effect of dosage on half-life) have been further clarified and attention has shifted towards new pharmacodynamic parameters other than the traditional in vitro and static minimal inhibitory concentration (MIC). New data have accumulated on the dynamic interaction of the bug-drug interaction, including the rate of bacterial killing, the postantibiotic effect (PAE), the influence of subinhibitory drug concentrations, effective regrowth time and postantibiotic leukocyte enhancement (4). The pharmacodynamic activity of a specific antimicrobial may vary considerably depending on the microorganism and the setting in which it is used. The different pharmacodynamic parameters among classes not unexpectedly will have a major impact on the determinants of optimal dosing regimens. As information has accumulated from in vitro kinetic models, animal models and, to a lesser extent, human clinical trials, the traditional approaches to antimicrobial dosing are being questioned, and alternative dosing regimens are being proposed and implemented in many Canadian hospitals.

For example, both in vitro models and animal studies have demonstrated that the most reliable predictor of in vitro activity for beta-lactams is the time during which the antimicrobial serum concentration exceeds the MIC of the offending pathogen (5-11). The very high initial serum concentrations obtained after parenteral administration do not appear to contribute to the efficacy of these agents. The bactericidal activity of the penicillins and cephalosporins does not increase with increasing serum concentrations, provided the MICs of the microorganism are exceeded. The PAE (suppression of bacterial growth that persists after brief exposure of organisms to antimicrobials) for beta-lactams has been observed since the initial discovery of antimicrobials (12). Most beta-lactams have in vitro PAEs of 1.5 to 3 h against most Gram-positive microorganisms but relatively short or no PAE (less than 0.5 h) against Gram-negative microorganisms (4). The carbapenems (imipenem) are an exception to this general rule for Gram-negatives, exhibiting a PAE of more than 1 h (4). Furthermore, it must be emphasized that in vivo PAEs are more prolonged than in vitro PAEs (13), likely due to the presence of neutrophils and serum factors (14). Since the time during which drug concentrations exceed the MIC appears to be a major determinant of efficacy of beta-lactams, continuous infusion of agents with very short half-lives but modest antibacterial activity or intermittent infusion of agents with longer half-lives but with very high antibacterial activity may
be the preferred routes of delivery. Another important observation is that, with the exception of endocarditis and perhaps meningitis, no additional benefits are seen with extremely high concentrations of beta-lactams. The relevant impact of these findings to the practicing clinician is that the large multigram dosages of the newer extended spectrum penicillins and the second- and third-generation cephalosporins commonly used during the 1980s are no longer generally necessary. Specific examples include the use of piperacillin every 6 to 8 h, ceftazidime 1 to 2 g every 24 h, cefotaxime 1 to 2 g every 12 h and ceftazidime 1 to 2 g every 12 h (15-20). These dosing regimens take advantage of the excellent antibacterial activity (extremely low MICs) and extended half-lives of the parent compound or of an active metabolite as in the case of ceftaxime.

The aminoglycosides, quinolones and metronidazole are examples of antimicrobials that exhibit major concentration-dependent killing and that produce prolonged PAEs. These agents have a kill rate that is greatest at high concentrations (4,21). Several animal models and clinical data have correlated peak aminoglycoside serum concentrations with outcome (22-26). It has been suggested that peak levels eight- to 10-fold higher than the MIC are capable of preventing any regrowth of resistant organisms (27). The in vitro PAEs for aminoglycosides against most Gram-positive and Gram-negative organisms are at least 2 to 3 h, and the in vivo PAEs have been recorded to be as high as 12 h (13). Similarly, quinolones have in vitro PAEs from 1.5 to 3 h for Gram-negative bacilli, whereas metronidazole has a prolonged PAE (greater than 3 h) versus anaerobic bacteria (4). The relevant impact for the clinician has been the advent of once-daily dosing of aminoglycosides at a dose of 5 to 7 mg/kg (28,29) for gentamicin and tobramycin and twice-daily dosing of metronidazole in conventional doses, which has been adopted by many hospitals.

In the future, it is likely that further refinements to antimicrobial dosing will occur not only for specific agents but also for specific patient populations. Trials are underway with continuous low dose infusions of beta-lactams, and the first large randomized prospective trial of once- versus multiple-daily aminoglycoside dosing in febrile neutropenic patients has been completed (30). Not only are we likely to see further new developments in the dosing and delivery of established antimicrobials, but characterization of the optimal dosing parameters for newer agents will likely also occur during their premarketing evaluation. We hope that all of these developments will continue to move towards improved clinical outcomes and reduced toxicity in the patient populations that we serve.

REFERENCES
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