Importance and role of pharmacokinetics, pharmacodynamics and stability in nonhospital, community-based parenteral antimicrobial therapy

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Several variables including the likely infecting organism, pharmacokinetic (PK) and pharmacodynamic factors (PD), and drug stability must be considered when selecting antimicrobials. The goal of antibiotic therapy is to provide adequate drug concentration at the site of infection long enough to eliminate the pathogen. Almost any antimicrobial can be used for outpatient therapy, but drugs with long half-lives are the best suited. The use of agents that can be administered once or twice daily minimized the disruption of daily activities and limited the number of intravenous line manipulations, lessening the potential for catheter-associated complications (1-3). Ceftriaxone (Rocephin, Hoffmann La Roche Limited, Mississauga, Ontario) and other cephalosporins have been the most common drugs reported in the literature (4). If the antibiotic must be given every 2, 4, or 6 h, it may become impractical to give at home without the aid of an infusion pump. Not all Canadian centres use pumps because they are complicated for patients to use and are expensive (1,5).

PHARMACOKINETICS AND PHARMACODYNAMICS

New insights into PK and PD parameters have resulted in changes in antibiotic dosing (6). Bacterial killing can be classified as concentration dependent or time dependent, with spe-

cific differences among antibiotic classes. The antimicrobial activity of the drug may be assessed by several other PD criteria including minimum inhibitory concentration (MIC), postantibiotic effect (PAE) (ie, the extended suppression of bacterial growth after antibiotic exposure) and the postantibiotic leukocyte enhancement effect (in which pathogens become more susceptible to the activity of leukocytes). Major factors affecting the duration or presence of PAE are the type of microorganism and the type of antimicrobial used (6,7).

In general, the antimicrobial agents can be divided into three categories based on their PD activity (1,2) (Table 1). Whereas most other antimicrobials inhibit protein synthesis at ribosomal sites, the beta-lactam antibiotics interfere with the synthesis of antimicrobial cell walls. Unlike aminoglycosides, where serum concentration is important, the bactericidal action of beta-lactams is related to the time that the serum concentration is above the MIC. High doses do not increase their potency or rate of bactericidal activity. Once plasma concentrations of penicillins or cephalosporins fall below the MIC, susceptible organisms begin to reproduce within a few hours. Furthermore, the beta-lactam drugs, apart from the carbapenems, have little or no PAE with Gram-negative organisms (7). Therefore, certain cephalosporins and penicillins

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TABLE 1
Antimicrobial pharmacodynamics effect on dosing

Antibiotic	Pharmacodynamics	Goal
Penicillins Cephalosporins Aztreonam	Time-dependent killing, brief or no PAE	Maximize exposure time, Keep serum levels greater than MIC
Carbapenems Vancomycin Clindamycin Macrolides	Time-dependent killing, prolonged PAE	Maximize exposure time, serum levels can fall below MIC
Aminoglycosides	Concentration-dependant killing, prolonged PAE	Maximize concentration, attain peak serum level
Quinolones Metronidazole		

Adapted from reference 2. MIC Minimum inhibitory concentration;
PAE Postantibiotic effect

with half-lives of less than 60 mins need to be dosed frequently to maintain the trough concentration above the MIC for the majority of the dosing interval (2) (Table 2). It is suggested that these agents are more appropriately given by continuous infusion rather than in intermittent doses; however, this can be logistically impossible in the ambulatory setting. In this instance, a programmable pump that delivers a continuous infusion may be beneficial. Continuous infusion may also require less drug because there is no advantage to having maintenance levels greater than four times the MIC of susceptible organisms (3,8).

Ceftriaxone has a sufficiently long half-life to provide serum concentrations above the MIC for susceptible organisms for 24 h and, thus, can be given once daily. This pharmacokinetic property makes ceftriaxone's use advantageous because it can be used in the emergency room for patients who will not be admitted to hospital to provide them with 24 h of intravenous antibiotic coverage. The drug also is conveniently administered in the patient's home environment.

Other categories of antibacterial agents that are also effective above the MIC include the carbapenems, vancomycin, clindamycin and the macrolides. These drugs have more persistent PAE and, therefore, serum levels may be allowed to drop below the MIC. The carbapenems have exhibited PAEs of up to several hours with Gram-negative bacilli (7). Carbapenems attain their maximum efficacy when serum levels are above the MIC for only about 50% of the dosing interval (5). Vancomycin, with a long half-life and persistent PAE, only requires dosing every 12 h to 24 h and, therefore, is very convenient in the outpatient setting. However, increasing concern about vancomycin-resistant enterococci and *Staphylococcus aureus* has limited vancomycin therapy to selected situations to deter its overuse. Vancomycin should no longer be used simply because it is convenient to give in the setting of impaired renal function when one can dose the drug only every few days (9).

The aminoglycosides, quinolones and metronidazole have concentration-dependent killing and a prolonged PAE. Once

TABLE 2
Half-lives of common parenteral antibiotics

Drug	Half-life (h)
Amikacin	2–3
Ampicillin	1–1.5
Aztreonam	1.7
Cefazolin	1–2
Cefotaxime	1–2
Ceftazidime	1.5–2
Ceftriaxone	5.5–11
Cefuroxime	1–2
Ciprofloxacin	3–5
Clindamycin	2–3
Cloxacillin	0.5
Doxycycline	14–25
Ganciclovir	2.9
Gentamicin	2–3
Imipenem/cilastatin	1
Meropenem	1
Metronidazole	6–14
Penicillin	0.5
Piperacillin	0.5–1.5
Piperacillin/tazobactam	0.7–1.2
Ticarcillin	1
Ticarcillin/clavulanate	1
Tobramycin	2–3
Trimethoprim/sulphamethoxazole	8–15
Vancomycin	4–6

Adapted from reference 1

daily administration of aminoglycosides has become popular in most institutions due to its practicality. The rationale for once daily aminoglycosides is fourfold. First, aminoglycosides demonstrate concentration-dependent bacterial killing, meaning that the greater bactericidal activity is achieved with higher concentrations. Second, they possess a prolonged PAE for most Gram-negative organisms. This PAE has been demonstrated to increase with increasing doses. These two properties alone are advantages to administer larger doses less frequently (7,10). Third, aminoglycosides induce adaptive resistance in Gram-negative bacteria. Adaptive resistance allows bacteria previously exposed to the continued presence of aminoglycosides to downregulate drug uptake. Once daily administration may lead to more effective killing by allowing less contact time between the antimicrobial and the organism, thus allowing less opportunity for postexposure resistance to develop (11). Finally, it appears that nephrotoxicity is a result of the accumulation of the aminoglycoside in the renal cortex. The uptake of aminoglycosides into the renal tubular cells appears to be a saturable process. Animal and human studies have shown that the aminoglycoside concentration in the renal cortex is lower when administered as a single dose than when the same dose is given in multiple doses given more frequently. Clinical studies have demonstrated a decrease in nephrotoxicity or no significant difference compared with conventional

dosing. The use of once daily aminoglycosides in pregnant women, children, burn patients, and patients with ascites and endocarditis, however, has not been intensively studied (10,12,13).

STABILITY

To ensure the safety and efficacy of a nonhospital, community-based parenteral antimicrobial program, stability of the antimicrobial in question must be assured (Table 3). A drug is considered stable in solution if it retains 90% or more of its original concentration for a minimum of 24 h at room temperature (25°C) and four to seven days under refrigeration (3 to 5°C). Imipenem/cilastatin (Primaxin, Merck Sharpe & Dohme Canada, Kirkland, Quebec), ampicillin and trimethoprim/sulfamethoxazole (TMP/SMX) are stable for less than 24 h in solution, which is of some concern unless the patients themselves are reconstituting the antimicrobials before infusion. The stability of TMP/SMX is reduced because the concentration is increased; therefore, this combination should not be used in devices with reservoir volumes less than 250 mL unless it is reconstituted and infused immediately. Furthermore, this drug may precipitate at temperatures of 3 to 5°C (14,15). Imipenem is stable at room temperature for 10 h and in the refrigerator for two days. Meropenem (Merrem, Astra Zeneca, Mississauga, Ontario) the newest carbapenem, has prolonged stability at lower temperatures and requires little intravenous solution for infusion due to its hydrophilicity. One gram can be administered in as little as 20 mL of sterile water over 5 mins or it can be hung as a regular infusion over 20 to 30 mins. In addition, it does not appear to share with imipenem the high incidence of nausea when given rapidly (16). These attributes may, therefore, make its use more attractive in the outpatient setting for complicated polymicrobial infections.

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TABLE 3
Antimicrobial stability

Antibiotic	Dilution		
	NS or D5W	5°C (days)	25°C (days)
Amikacin	0.25–5 mg/mL	60	1
Ampicillin	30 mg/mL (NS)	2	8 h
Aztreonam	20 mg/mL	7	2
Cefazolin	10–20 mg/mL	10	1
Cefotaxime	10 mg/mL	22	1
Ceftazidime	1–40 mg/mL	7	1
Ceftriaxone	10–40 mg/mL	10	3
Cefuroxime	5–10 mg/mL	30	1
Ciprofloxacin	1–2 mg/mL	14	14
Clindamycin	6–12 mg/mL	32	16
Cloxacillin	20 mg/mL	14	1
Doxycycline	0.1–1 mg/mL	3	2
Ganciclovir	1–10 mg/mL (D5W)	35	–
Gentamicin	1–5.5 mg/mL (D5W)	4–30	2–30
Imipenem/cilastatin	2.5–5 mg/mL (NS)	2–7	10 h
Meropenem	1–40 mg/mL	14	3
Metronizaxole*	Premixed	7	1
Penicillin	0.2 million U/mL (SW)	7	1
Piperacillin	10–80 mg/mL	7	1
Piperacillin/tazo	10–80 mg/mL	–	2–6 h
Ticarcillin	10–100 mg/mL (NS)	4	2
Ticarcillin/	10–100 mg/mL (NS)	14–63	1–17
clavulanate			
TMP/SMX*	0.65–1.1 mg/mL (TMP)		
Tobramycin	0.2–3 mg/mL (D5W)		
Vancomycin	2.5–10 mg/mL		

*Adapted from references 1,14. *Do not refrigerate. D5W Dextrose in water; NS Normal Saline; SW Sterile water; TMP/SMX Trimethoprim/sulphamethoxazole*