

## SOME NEW CONCEPTS IN ANTIBACTERIAL DRUG THERAPY

K.K. SHARMA, H. SANGRAULA, P.K. MEDIRATTA\*

Department of Pharmacology, B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

\*Department of Pharmacology, University College of Medical Sciences & G.T.B. Hospital, Delhi 110 095

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**ABSTRACT** The goal of antibacterial therapy is to eradicate tissues of infecting organisms. However, achievement of desired outcome will depend on a number of drug-, pathogen- and patient-related factors. Neither microbiological pharmacodynamic activity (as measured by minimum inhibitory concentration [MIC] or minimum bactericidal concentration [MBC] *in vitro* conditions) nor pharmacokinetic data of drug in the host alone can adequately describe the complex interaction between the antibacterial agent, the invading bacteria and the host, culminating in successful bacterial elimination. Accumulating contemporary data especially in the last one-and-half decades from *in vitro* studies, animal models of infection and clinical trials have shown that bacterial killing may be described as a function of either drug concentration (concentration-dependent killing; CDK) or time of exposure (time-dependent killing; TDK). Since the duration of exposure is a function of drug disposition in the host and is measured by pharmacokinetic parameters of serum drug concentration ( $C_{max}$ ), simple correlations can be made to optimize antibacterial chemotherapy. These evidence-based correlations have shown that  $C_{max}$  and area under the curve (AUC) when integrated with an antibacterial pharmacodynamic parameter of MIC or MBC, the ensuing kinetic-dynamic hybrid parameters, like  $C_{max}/MIC$  or AUC/MIC ratios and the time during which the antibacterial concentration remains above the MIC or MBC ( $t > MIC$  or  $MBC$ ) become important determinants of deciding the dose regimens of an antibacterial agent which shows CDK (e.g. aminoglycosides; fluoroquinolones; metronidazole) or TDK ( $\beta$ -lactam; macrolide; oxazolidinone antibiotics) properties, respectively. The present communication describes how the new concepts of CDK and TDK kinetics when considered and applied along with the property of post-antibiotic effect (PAE), displayed by certain antibiotics can make the antibacterial therapy cost-effective, safe and efficient. PAE not only can mediate an enhanced antibacterial efficacy but also prevent emergence of bacterial resistance.

**KEYWORDS** Antimicrobial therapy concentration-dependent effect microbial resistance post-antibiotic effect time-dependent effect

### Introduction

Making antibacterial drug therapy effective, safe and affordable has been the focus of interest during recent years. Antibacterial therapy, since its dawn in 1940s, is changing constantly and in the last fifteen years has undergone a tremendous change due to evolvement of new concepts in the pharmacokinetics of antibacterial agents and their pharmacodynamics in microbes<sup>1</sup>. Previously antibacterial agents were selected on the basis of their high degree of *in vitro* activity but currently antibiotic (*the term 'antibiotic' has been used interchangeably with the terms 'antimicrobial' and 'antibacterial'*) use is based on its ef-

fectiveness and cost in a given situation<sup>2</sup>. The important new concepts, which determine antibiotic use, revolve around the word "effectiveness". In the past, three basic principles, which were taken into consideration to define the effectiveness of an antibiotic were: (a) its bacteriostatic or bactericidal activity, (b) its spectrum of antibacterial activity, and (c) its pharmacokinetic characteristics. However, in present day and age a clinician should also appreciate the difference between "concentration-dependent killing (CDK) dynamics" versus "time-dependent killing (TDK) dynamics" of an antibiotic alongwith post-antibiotic effect (PAE), if any. These new concepts have impor-

Correspondence: K.K. Sharma  
e-mail: drkksharma2000@yahoo.com

tant ramifications on how to dose an antibacterial agent to make it efficient, safe and free from the development of bacterial resistance. Single dose aminoglycoside therapy and constant-infusion beta-lactam therapy are examples of applying these pharmacokinetic and pharmacodynamic principles to the clinical situation. Besides these, new understandings also guide the switch in therapy from intravenous to oral route. Conversion from intravenous (parenteral) to oral route therapy based on these pharmacokinetic principles is socio-economically effective and is well accepted by patients. The present review describes evolution of new concepts of CDK, TDK and PAE dynamics of antibacterial agents and would consider how application of these parameters make an antibiotic effective and safe.

### Antibacterial action

Generally if an antibacterial agent has to display activity against a specific organism, it must first reach the site of infection, it then needs to penetrate the target site in the bacteria, attach itself to the site in an adequate concentration, and remain there for a sufficiently long period of time such that the organism is inhibited from carrying out its normal life functions<sup>3</sup>. The pharmacodynamic properties or the correlation of drug concentrations and the clinical effect, *i.e.* bacterial killing of a specific antibiotic class are thus an integration of two related areas, pharmacokinetics and its microbiological activity. As drug concentrations cannot be measured at the biophase, *i.e.* the site of action, *in vitro* microbiological surrogate markers, such as the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) are typically used as means of assessing these pharmacodynamic relationships. *In vitro* continuous exposure of a relatively small number of bacteria to constant levels of a drug, however, can differ considerably from *in vivo* conditions where large numbers of bacteria are usually exposed to fluctuating levels of an antibiotic. Parameters that more accurately describe the time course of antibacterial activity in such a situation, as recent studies have shown, include rate of bacterial killing at different concentrations<sup>4,5</sup> and the presence or absence of persistent suppression of bacterial growth following antibiotic exposure after the agent has been totally washed out from bacterial environment<sup>4,6</sup>. The latter phenomenon is also referred to as the PAE<sup>7</sup>. It is, therefore inappropriate to choose an antibiotic or

antibiotic regimen based solely on the microbiological activity or pharmacokinetics. Instead these agents should be selected based on their individual pharmacodynamic properties which should be correlated with their pharmacokinetic profile.

### Post-antibiotic effect (PAE)

PAE is defined as persistent suppression of bacterial growth after a brief exposure (1 or 2 h) of bacteria to an antibacterial agent even in the absence of host defence mechanisms<sup>7-9</sup>. In PAE, inhibition of bacterial growth is seen when either the antibacterial agent is no longer present in bacterial medium or if present, its concentration is well below the MIC. Variables that affect PAE include the antibiotic type (*vide infra*), concentration and duration of antibiotic exposure, bacterial species and strain under investigation and culture media used<sup>10</sup>. This phenomenon was for the first time described for quinolones and aminoglycosides<sup>8,9</sup>. Ciprofloxacin, ofloxacin and lomefloxacin were found to be similar in producing PAE of about 2 h in Gram-negative and Gram-positive bacteria when exposed for 1 h to antibiotic concentrations 4-fold greater than MIC<sup>11</sup>. The duration of PAE was further increased when the time of fluoroquinolones exposure was increased to 2 h. The PAE for fluoroquinolones appears to be a concentration-dependent parameter<sup>9,12</sup>. The newer fluoroquinolone compounds have been reported to have PAEs of 1 to 6 h depending on the pathogen and drug studied<sup>13,14</sup>. For aminoglycosides, it was similarly noted that an initial high antibiotic concentration and increased time of exposure prolongs the PAE; therefore with a high, single, daily gentamicin dose, the PAE can be as long as 5-10 h<sup>8,15</sup>. The measured duration of PAE was found to be longer *in vivo* than *in vitro* and was also seen in neutropenic animals<sup>15</sup>. The PAE was further extended by higher doses of aminoglycosides and concurrent administration of cell wall active antibiotics<sup>15,16</sup>. Later studies revealed PAE activity in chemotherapeutic agents, such as metronidazole and rifampicin<sup>16</sup>. Out of all these drugs which showed PAE phenomenon, rifampicin was demonstrated to have two important features: (1) Unlike ciprofloxacin which did not show synergistic prolongation of PAE of other drugs, rifampicin was observed to prolong PAE in a synergistic fashion when combined with other PAE-producing agents; and (2) it had a prolonged and persistent PAE activity<sup>17</sup>. It is because of this reason,

intermittent (thrice-, twice- or once-a week) dosage regimens are advisable when other antitubercular or antileprotic drugs are used in combination with rifampicin. The success of directly-observed-treatment-strategy (DOTS) programme for the treatment of tuberculosis and leprosy has been possible only after understanding the PAE of rifampicin and its synergistic prolongation of PAE of other antitubercular and antileprotic drugs<sup>17</sup>. To explain the mechanism of action of PAE, it has been suggested that an alteration of DNA function is possibly responsible for this effect, since most inhibitors of protein and nucleic acid synthesis (aminoglycosides, fluoroquinolones, tetracyclines, clindamycin, certain newer macrolides/ketolides, and rifampicin and rifabutin) induce long-term PAE against susceptible bacteria<sup>18-21</sup>. Such a suggestion gets further credence with the observation that cell wall active agents (beta-lactams and vancomycin) either have no or very short PAEs against most Gram-negative bacilli or induce PAEs of about 2 hr against staphylococci<sup>19</sup>. Other mechanisms to explain PAE include post-antibiotic leukocyte enhancement (PALE) and exertion of antibacterial activity by post-antibiotic sub-MIC effects<sup>20-23</sup>. The drug concentration below the MIC have not only been shown to exert the inhibition of bacterial growth to induce PAE but also to alter microbial cell morphology to produce a suppression of virulence factors. The latter effect is another form of PAE, and has recently been shown by Ohta and coworkers and designated as the post-antibiotic suppression effect (PASE)<sup>24</sup>. The ability of an antibiotic to exhibit PAE, PALE or PASE on a particular organism is a theoretically attractive attribute, since antibiotic concentrations could fall below the MIC for the bacterium yet remain effective to suppress the growth or virulence of the pathogen. Results of a number of clinical trials have shown the importance of PAE in choosing the wide dosage intervals of such an antibiotic<sup>5,15,19</sup>.

### Concentration-dependent versus time-dependent killing (CDK vs TDK) efficacy of antibacterial agents

Bacterial cell death following antibiotic exposure can be classified as either concentration-dependent or concentration-independent (or time-dependent). Although the bactericidal activity of a given antibiotic is a function of several factors, *viz.* the selected an-

tibacterial drug, the pathogen species, and the exposure concentration, it is generally accepted that killing profile is always the same, *i.e.* the agent always shows CDK. However, some antibacterials display a ceiling effect to this CDK, *i.e.* once a serum concentration for near maximum effect is reached it is more important to sustain it rather than increase the concentration. Agents showing this kind of antibacterial effect have been suggested to exhibit the TDK dynamics. When integrating the microbiological activity and pharmacokinetics of an antibiotic, several pharmacological parameters appear to be significant markers of drug efficacy. The pharmacokinetic parameters of area under the time-concentration curve (AUC), maximum observed concentration ( $C_{max}$  or peak concentration) after its administration and elimination half-life ( $t_{1/2}$ ) are often integrated with a pharmacodynamic parameter, MIC or MBC for the pathogen to generate several integrated pharmacodynamic clinical markers of antibacterial efficacy, such as:

- i) AUC/MIC ratio (also termed area under minimum inhibitory concentration [AUIC]). If a round the clock 24 h AUC is used to deduce this ratio, it is called AUIC<sub>(0-24)</sub>.
- ii)  $C_{max}$ /MIC ratio (also known as inhibitory quotient).
- iii)  $t > MIC$  or  $t > MBC$ , *i.e.*, the time (t) measured as per cent of time during which the concentration remains above the MIC between the two-dosage interval (total interval time taken as 100 per cent).

Integration between pharmacokinetic and -dynamic parameters is not surprising as both parameters have been related to the efficacy of antibiotic. As a result, it is often difficult to correlate a single pharmacodynamic parameter to the efficacy of an antibiotic. If it is assumed that the amount of drug delivered at the site of infection, *i.e.* available to the pathogen environment is proportional to the amount of drug delivered to the host (AUC), it can be concluded that the AUC is the primary pharmacokinetic parameter associated with antibacterial efficacy. Although AUC is considered as the primary pharmacokinetic parameter, this entity is a product of concentration and time. Therefore, under certain conditions, the influence of concentration appears to be a predominant factor, whereas under different set of conditions, the time

of exposure to the drug or the time  $>$ MIC or MBC may play a larger role. For agents that exhibit CDK and a relatively long PAE, *viz.* aminoglycosides, fluoroquinolones and metronidazole, the influence of  $t >$ MIC is small when compared with the influence of  $C_{\max}$ . If an antibacterial agent does not exhibit CDK and does not produce sustained PAE (e.g. beta-lactams, which demonstrate TDK with no or minimal PAE; actually  $\beta$ -lactam antibiotics exhibit moderate, about 2 hr PAE against staphylococci and other Gram-positive bacteria but negligible PAE against Gram-negative bacteria, except carbapenems which have some PAE for these organisms), the time of exposure or the  $t >$ MIC contributes more to the killing process than does drug  $C_{\max}$ .

### Pharmacodynamic classification of antibiotics

Antibacterial agents can be classified into three groups on the basis of their pattern of bactericidal activity as shown by their CDK or TDK dynamics and whether they exert persistent PAE, PALE or PASE (Table 1).

#### Group I. Agents that show concentration-dependent killing (CDK) efficacy with persistent PAE

Aminoglycosides, fluoroquinolones, metronidazole and other nitroimidazoles display CDK pharmacodynamics with a prolonged and persistent PAE. All these agents eliminate bacteria more rapidly when their concentrations are appreciably above the MIC of the organism, *i.e.* the rate of bactericidal activity is maximum at the peak serum concentration ( $C_{\max}$ )<sup>12,15</sup>. As the drug concentration decreases, the rate of antibacterial activity decreases. Higher doses of the drug increase the peak and all subsequent drug levels, and thus there is not only an increase in the rate and extent of bacterial killing but also in length of time of drug exposure to bactericidal concentrations. This implies that the clinical efficacy of this group of agents is influenced by both the  $C_{\max}$  and the AUC considered in relation to MIC. Since agents of this group display a powerful PAE, duration of which is also concentration ( $C_{\max}$  and AUC profile) dependent, the residual bacterial population is less at the time of next dose. This suggests that wide dosage intervals can be chosen with this group of drugs. With respect to aminoglycosides, landmark studies of Moore *et al*<sup>25</sup> (other studies cited therein) suggested that  $C_{\max}$ /MIC ratio of at least 8 to 10 were necessary for achieving an optimal clinical response in 90% of patients treated

for Gram-negative bacterial infection. In addition,  $C_{\max}$ /MIC ratios of this magnitude in another study prevented the development of resistance<sup>26</sup>. This suggestion gets further credence from a previous study by Keating *et al*<sup>27</sup> who observed an aminoglycoside response rate of 57%, 67% and 85% in neutropenic patients with mean serum  $C_{\max}$ /MIC ratios of 1 to 4, 4 to 10, and greater than 10, respectively. Taken together, several investigators have opined that both  $C_{\max}$ /MIC ratio and the AUC/MIC ratio are effective predictors of therapeutic outcome in patients receiving aminoglycosides<sup>19</sup>.

Accordingly, to take advantage of the CDK and PAE dynamics of aminoglycosides, the concept of once-daily dose regimen has been introduced in clinical practice<sup>28</sup>. The drug is administered in a single dose (gentamicin, 7 mg/kg, q 24 h) rather than in divided doses (1.5 mg/kg, q 8 h) over a 24 h period. Similarly the promoted single dose for tobramycin and netilmycin is in this range, whereas for amikacin it is 10-20 mg/kg. The single dose regimen optimizes the bactericidal activity and reduces potential toxicity of aminoglycosides by taking advantage not only of its CDK ability but also of two other important characteristics, *i.e.* time-dependent toxicity and prolonged concentration-dependent PAE<sup>29,31</sup>. Besides being safe and effective, once-daily regimen of aminoglycosides also reduces the cost on therapeutic drug monitoring and injection devices<sup>28</sup>.

For fluoroquinolones Forrest *et al*<sup>32</sup> by using ciprofloxacin for serious infections found that clinical and bacteriological response rates of  $<$ 50% were achieved (in 7 days) when the  $AUC_{(0-24)}$  was  $<$ 125. However, when a higher  $AUC_{(0-24)}$  ( $>$ 250) was obtained, the response rate rose to 80% within 2 days. Thus, these results suggest that antibiotics which show CDK efficacy, an  $AUC_{(0-24)}$  of  $>$ 125 can achieve a better and rapid clinical cure using dosage regimens that produce high initial concentrations. Further emergence of resistance can be prevented if doses of these agents that optimize the values of  $C_{\max}$ /MIC or  $AUC_{(0-24)}$  are used<sup>26,33</sup>.

#### Group II. Agents that show time- (or duration) dependent killing (TDK) efficacy with minimal PAE

$\beta$ -lactam antibiotics, clindamycin, and macrolides, except azithromycin exhibit TDK with minimal PAE.

**Table 1.** Pharmacodynamic classification of various antibacterial agents which determine their dosage regimens for efficient clinical use along with pharmacodynamic markers to measure clinical efficacy

Antibacterial agent	Aim of dosage regimen for efficient use	Pharmacodynamic marker(s) of clinical antibacterial efficacy*
I. Agents with concentration-dependent killing with persistent PAE		
1. Aminoglycosides	Maximise drug concentration	Peak concentration ( $C_{max}$ )/
2. Fluoroquinolones	(applicable to 1 to 4)	MIC ratio (should be >8-10)
3. Metronidazole		24 h AUC/MIC ratio [AUC <sub>(0-24)</sub> , which should be >125 for Gm-negative bacilli and considerably less, perhaps 25-50 for <i>S. aureus</i> / <i>S. pneumoniae</i> ] (applicable to 1 to 4)
4. Streptogramins		
a. Quinupristin/Dalfopristin (Synecid)		
II. Agents with time (duration)-dependent killing with short or no PAE		
1. $\beta$ -lactam antibiotics	Maximise exposure time	$t > MIC$ or $MBC$
a. Penicillins	(applicable to 1 to 4)	(applicable to 1 to 4)
b. Cephalosporins		
c. Carbapenems**		
d. Aztreonam		
2. Macrolides***		
3. Clindamycin		
4. Oxazolidinones		
a. Linezolid		
b. Eperezolid		
III. Agents with time (duration)-dependent killing with persistent PAE		
1. Macrolides	Maximise daily amount of dose	$t > MIC$ or $MBC$
a. Azithromycin	(applicable to 1 to 4)	(applicable to 1 to 4)
b. Clarithromycin		24 h AUC/MIC ratio (only for newer macrolides and tetracyclines)
2. Ketolides		
a. Telithromycin (HMR 3647)		
3. Tetracyclines		
4. Vancomycin		

\*for abbreviations see text; \*\*show short-duration PAE; \*\*\*except azithromycin, clarithromycin and other newer macrolides.

With these agents, the bactericidal activity is not enhanced by increasing the concentrations above MIC or MBC and the action is relatively slow. The bacterial killing rate reaches a ceiling at serum concentrations about 4 to 5 times the MIC and bac-

terial growth promptly resumes when serum and tissue concentrations fall below the MIC because there is either no or short PAE for most of this group of agents<sup>4,34,35</sup>. Therefore, in this group the time needed for serum concentrations to exceed the MIC or MBC

is an important determinant of efficacy. Thus the aim of therapy with these agents is to maintain serum concentrations above the MIC or MBC for as long as possible during the dosing intervals. Although the infecting organisms are located in the interstitial space, drug concentrations in the interstitial fluid are generally in equilibrium with that of serum. Thus, by increasing the time duration when serum levels remain above the MIC, would concomitantly increase the drug concentration proportionally at the site of infection.

Although there is no consensus on the optimal duration of time that serum antibiotic concentration should remain above the MIC, it has been observed that the range of suprainhibitory serum concentration for 40 to 50% of the duration of dosage interval provide a minimum threshold for this group of agents<sup>5,11,35-36</sup>. This view is supported by the study of Schentag *et al.*<sup>37</sup> who reported that in patients with nosocomial pneumonia the number of days of cefmenoxime therapy required to eradicate pathogens from sputum was inversely correlated with the proportion of time during which serum drug concentrations exceeded the MIC. Ten to 13 days treatment was required if concentrations exceeded the MIC for less than 50% of the dosage interval, whereas this time was reduced to between one and six days when drug concentrations exceeded the MIC for all or most of the dosage intervals<sup>37</sup>. Supporting observations from other studies<sup>38,39</sup> further reiterate that for maximal efficacy, serum drug levels of this group of agents had to be above the MIC for nearly all of the 24 h treatment period. Since, the optimal duration of dosage interval for a given antibiotic varies depending upon the infecting organism, site of infection, inoculum effect, and immunocompetence of the host, with this concept, it is clear that the pharmacodynamic marker:  $t > \text{MIC}$  with an efficacy break point value of  $>50\%$  is important for clinical success with this group of antibiotics; closer is the value towards 100%, greater will be the success rate. For  $\beta$ -lactams with short half-lives, it is important to maintain drug concentrations above the MIC against infecting pathogens during most of the dosage interval. This can be done by using smaller fractions of the total daily dose given at frequent intervals or the use of  $\beta$ -lactams with long serum half lives such as ceftriaxone ( $t_{1/2}$  of 6-8 h). A number of experimental and clinical studies comparing efficacy of intermittent dosing with that of continuous infusion suggest the importance of this ap-

proach for successful treatment of serious infections with  $\beta$ -lactam drugs<sup>34,40-42</sup>. In a study, Bodey *et al.*<sup>43</sup> compared carbenicillin plus either intermittent or continuous infusion cefamandole in febrile cancer patients. Evaluation of 235 infections revealed that 65% receiving continuous infusion were cured against 57% receiving intermittent dosing. In addition, the continuous infusion regimen was significantly ( $p=0.03$ ) more effective (65% cure) than intermittent regimen (21% cure) for the treatment of infections in profoundly neutropenic patients<sup>43</sup>. Data concerning with continuous infusion studies further reiterate the importance of  $t > \text{MIC}$  and suggest that maintaining the MIC for the entire dosing interval should ensure optimal efficacy with very short half life antibacterial agent that show TDK dynamics with minimal PAE<sup>3-5,40-43</sup>. Besides, the concept of  $t > \text{MIC}$  can be used to compare the effectiveness of different time-dependent antibiotics within a class, and as a corollary those drugs having lower MIC, *i.e.* greater potency would be anticipated to have longer time above MIC and therefore greater effectiveness.

### **Group III. Agents that show time- (duration) dependent killing (TDK) with prolonged PAE**

Antibacterial drugs, such as newer macrolides, *e.g.* azithromycin, clarithromycin, *etc.*, vancomycin, and tetracyclines, like agents of Group II exhibit TDK efficacy but differ in that they have a prolonged and persistent PAE. For these agents, although the duration of antibacterial exposure is important, clinical efficacy is not compromised if concentration falls below the MIC as they possess persistent PAE. Thus for this group of agents both  $t > \text{MIC}$  and 24 h AUC/MIC ratio [ $\text{AUC}_{(0-24)}$ ] play an important role in planning the dosage regimens<sup>44</sup>. For vancomycin, when used for severe life threatening situations  $t > \text{MIC}$  marker is more important; otherwise for azithromycin, clarithromycin and tetracyclines, and even vancomycin when used for less severe infections  $\text{AUC}_{(0-24)}$  can be used as pharmacodynamic marker to predict the antibacterial concentration at the infection site<sup>1,44</sup>.

The PAE-inducing property of vancomycin appears to be related to its hitherto unimportant inhibitory effect on RNA synthesis<sup>45</sup>, since another glycopeptide antibiotic teicoplanin which acts as bactericidal, like vancomycin by inhibiting cell wall synthesis, does not show this effect.

**Table 2.** Recommended dosage intervals for parenteral antimicrobial agents in the treatment of serious infections.

## Agents that can be given once daily

1. Aminoglycosides
2. Ceftriaxone
3. Vancomycin\*
4. Teicoplanin
5. Pefloxacin
6. Fleroxacin

## Agents that can be given twice daily

1. Cefazolin†
2. Cefotetan
3. Cefonicid
4. Cefepime\*
5. Cefpirome\*
6. Meropenem†
7. Synecid\*

## Agents usually given three-times daily

1. Cefazolin
2. Cefotaxime
3. Ceftazidime
4. Aztreonam
5. Carbapenems
6. Most penicillins

## Agents that can be given by continuous infusion

1. Beta-lactams

\*In very severe or life-threatening situations including bacteraemia, especially in immunocompromised patients (difficult-to-treat infections in critically ill patients with normal renal function) an 8 h (8 gm, q8h) dose is advised.

†Less-frequent administration is found to be effective.

### Other drug and disease-related pharmacokinetic factors in selection of antibacterials and their dosage

Since aminoglycosides have half-lives ranging between 2 and 8 h, it may be difficult to obtain  $C_{max}/MIC$  ratio of >8-10 h, *i.e.* peak concentration 8-10 times greater than the MIC without reaching toxic concentration. Since, these ratios are also important in preventing the development of resistance, there is currently a trend towards single daily administration<sup>15,26</sup>. This regimen has been shown to be more effective and possibly less toxic than traditional 8-hourly ad-

ministration (*vide supra*)<sup>26,28-31</sup>. There is also evidence that administration of subsequent aminoglycoside doses, while there is still detectable aminoglycoside present, may inhibit their bacterial killing capacity. This phenomenon is called "adaptive resistance after first exposure". Bacteria are no more sensitive to bactericidal activity for several hours before gradually returning to their full sensitivity<sup>46-47</sup>. The mechanism for this adaptive resistance is thought to be down-regulation of aminoglycoside uptake by energy-dependent drug transport into the bacterial cell<sup>46</sup>. Accordingly the once daily dose regimen of aminoglycoside antibiotics appears to be more rational.

As discussed above for  $\beta$ -lactams, it is important to maintain drug concentration above MIC against the infecting pathogen over much of the dosage interval. Therefore, agents with long half-lives can be given less frequently (Table 2), *e.g.* ceftriaxone which has the longest half-life among the  $\beta$ -lactams (approximately 8-10 h) can be given once daily. Cefotetan, cefoperazone and cefonicid have  $t_{1/2}$  of >2 h and can be given twice daily. Cefazolin, cefotaxime, ceftazidime and aztreonam have short  $t_{1/2}$  of 1 to 2 h and generally need to be given 3-times daily<sup>42</sup>. Other cephalosporins and penicillins have a half-life of only 0.5 to 1 h and are generally required to be given 4 times daily or more frequently.

The carbapenems (imipenem+cilastatin; meropenem; biapenem) also have short half-lives of approximately 1 h, thus, 3 times-daily administration may not provide concentrations above the MIC throughout the dosage interval. However, since these agents show some amount of PAE albeit of short duration<sup>1</sup>, this persistent effect allows a longer dosage interval. Indeed, twice-daily administration of meropenem has been shown to be as effective as 3-times daily administration in patients with urinary tract infection or respiratory tract infections<sup>48</sup> as has been twice daily administration of cefazolin for cellulitis<sup>49</sup>.

Certain disease states, such as sepsis and burns produce hyperdynamic circulation where there may be an increase in volume of distribution, glomerular filtration and rapid renal elimination of certain antibiotics<sup>50</sup>. Therefore, drugs whose MIC can be affected by such a change in haemo-renal dynamics (aminoglycosides, cephalosporins and vancomycin, *etc.*) should be administered initially during the course

of the disease in high doses, *i.e.* on day 1 and/or 2. Later the dose and/or frequency of administration, as the patient condition improves, may be downgraded<sup>50,51</sup>. The antibacterial effectiveness of aminoglycosides is diminished by low pH, oxygen tension and osmolality, an intrinsic environment always present at the site of infection, specially if the latter also involves anaerobic microorganisms, *e.g.* intra-abdominal sepsis. In such situations and other mixed (aerobic-anaerobic) infections, an aminoglycoside agent should be combined with an appropriate  $\beta$ -lactam or glycopeptide antibiotic to limit the spread of infection and tackle Gram-negative septicaemia. Also in mixed infections such a combined use would break aerobic-anaerobic synergy for optimal outcome.

### Conclusion

Clinically, pharmacodynamic effects of antibacterial agents are difficult to assess because of the intricacies in determining the bacterial load at the site of infection and antibiotic concentrations repetitively during the dosing interval. However, these difficulties can be overcome by understanding the pharmacodynamic factors in developing optimal treatment strategies as has been confirmed in a number of studies using models of infection in animals and clinical situations. These models attempt to simulate human infections and can predict how best the microbiological activity (an *in vitro* phenomenon) and antibacterial pharmacokinetic data in host (*in vivo* parameters) can be used to select an antimicrobial agent as well as its dosage regimen for successful therapy of infection. It can be deduced from these models that the requirement for bactericidal therapy for bacterial endocarditis, meningitis and developing synergistic combinations to treat enterococcal septicaemia or to shorten the course of antibacterial therapy it is necessary to obtain  $C_{max}/MIC$  ratios greater than 10, or 24 h, AUC/MIC ratios greater than 125 for antibiotics that show concentration-dependent killing dynamics, and time above the MIC longer than 40 - 50% of the dosing interval for agents that exhibit time-dependent killing dynamics. If an agent shows considerable PAE, the dosage interval can be less stringent as compared to those which show minimal PAE. These pharmacodynamic models provide a unique approach to determine the likely *in vivo* activity of individual antibacterial agents and prediction of clinical outcomes.

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***For further details, please contact:***

Dr. C.G. Agarwal  
Department of Medicine  
CSJ Maharaj Medical University,  
Upgraded K.G.M.C.,  
Lucknow-226 003.  
E-mail: med.kgmc@satyam.net.in