Pharmacological indices in antibiotic therapy

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After 60 years of antibiotic treatment, attempts to rationalize it have culminated in the use of pharmacological indices. These indices facilitate comparison of the activity of different antibiotics and serve as a sound basis for antibiotic dosing. Pharmacokinetic parameters (e.g. AUC, $C_{\text{max}}$) and pharmacodynamic parameters (mostly MIC) are used for this purpose. For the so-called concentration-dependent antibiotics, the pharmacological indices AUC/MIC and $C_{\text{max}}$/MIC are used, whereas for time-dependent antibiotics, the pharmacological index $T_{\text{MIC}}$ is used. Some authors believe that the index AUC/MIC can be used as a universal index, but, not all experts accept this generalization. As the various pharmacological indices have been defined inconsistently in the literature, the International Society for Anti-Infective Pharmacology (ISAP) has published a paper on the terminology of pharmacokinetic and pharmacodynamic parameters and the pharmacological indices. This paper will help to ensure uniform use of terminology. In addition, we point out that the use of pharmacological indices should consider the differences in pharmacokinetics (patient characteristics and localization of the infection) and the differences in pharmacodynamics of antibiotics (beyond MICs) with different pathogens (e.g. Gram-positive and Gram-negative).

Keywords: pharmacokinetics, pharmacodynamics, $C_{\text{max}}$/MIC, $T_{\text{MIC}}$, AUC/MIC

Historical development of the pharmacological indices

With the introduction of sulphonamides in 1935 and of penicillin in 1942, a basis of safe antibiotic therapy began. Initially, dosage schedules of anti-infectives were empirical, ascertained through animal experiments and through the success or failure of a treatment in patients.

A relationship between the therapeutic efficacy of penicillin and its concentration in the serum was observed by Eagle et al.1 in 1950. These authors realized from experiments in mice and rabbits that ‘the bactericidal action stopped abruptly as soon as the serum penicillin fell to ineffective levels’. Furthermore, they observed ‘a close parallelism between the aggregate time for which penicillin remains at bactericidal levels and the therapeutic efficacy of the particular schedule’. Penicillin concentrations higher than the ‘effective level’ did not expedite the cure of the animals. These investigations generated the basis for the pharmacological index $T_{\text{MIC}}$ (Figure 1), and recognized the time-dependent efficacy of penicillin.1–3 The term pharmacokinetic, which describes the concentration–time profile of drugs in humans, was first used by a paediatrician, F. Dost,4 in 1953.

During the early years of antibiotic therapy, the terms ‘susceptible’ and ‘resistant’ were vague. Rodger et al.5 criticized the fact that the definition of resistance had not been standardized and that ‘each laboratory may modify a standard test to suit its particular need, and therefore there is no standard in relation to therapy or for comparing results of percentages of resistant strains from different parts of the country’.

At the end of the 1950s and in the 1960s, as the pharmacokinetics of antibiotics were studied in more detail, first insights into the concentration–time profiles of antibiotics in patients became apparent. The relationship between the various routes of administration of antibiotics and the influence of body weight on serum concentrations were examined by many authors.6–10 Most linked the observed blood or serum concentrations in the patients with the therapeutic efficacy of the antibiotic. Goodman & Gilman11 stated that therapeutic blood levels should be sustained at two to five times the minimal inhibitory concentration (MIC) found in vitro.

A connection between the antibiotic concentration achieved in a patient and the susceptibility of a pathogen was put forward by Naumann12 in 1971. He suggested that the efficacy of an antibiotic in a particular infection could be defined in terms of the drug concentrations in vivo and the antibacterial activity of a substance determined by the MIC. The appropriate blood level for defining susceptibility was related to the average drug level in the middle of the dosing interval ($t = \tau/2$). According to Naumann, a pathogen is susceptible if the MIC of the pathogen is equal to or lower than the $\tau/2$-blood level. The breakpoint between intermediate and resistant is defined by the mean $\tau/2$-blood level using high dosages.13

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In 1974, Klustersky et al. examined the bacteriostatic and bactericidal activity of the serum and urine of 317 cancer patients with a bacteriologically proven infection. They recognized that ‘when the peak titre of bacteriostatic activity in serum was ≥1:8, the infection was cured in ≥80%… The response to therapy of patients with urinary tract infections correlated best with the inhibitory level found in the urine; clinical cure was observed in at least 90% of the patients who had a titre of bacteriostatic activity in urine ≥1:4’. The ‘peak titre of bacteriostatic activity’ has been developed into the pharmacological index $C_{\text{max}}/\text{MIC}$ (Figure 2), and many authors still associate a $C_{\text{max}}/\text{MIC}$ ratio of ≥8 with an improved clinical outcome.

In 1979, Jaffe et al. first related the area under the concentration-time curve (AUC) with the MIC. They investigated the cure of gonococcal urethritis treated with penicillin. In total, 45 male volunteer prisoners were experimentally infected with strains of Neisseria gonorrhoeae. A good correlation between cure and the index $\text{AUC} > \text{MIC}$ was found. Craig divided the pharmacology of antibiotics into pharmacokinetics (PK) and pharmacodynamics (PD). The former describes the concentration–time profile of drugs in the host, whereas pharmacodynamics describes the antimicrobial effect of an antibiotic at its target pathogen.

The International Society for Anti-Infective Pharmacology (ISAP) is an interdisciplinary scientific society that promotes the study of the PK and PD of antibiotics so as to improve dosing regimens. Since the foundation of the ISAP in 1991, the study and use of pharmacokinetic and pharmacodynamic principles in antibiotic therapy has increased greatly. Based on their mode of action, antibacterial drugs are divided into time- and concentration-dependent antibiotics.

Variation in the definition of pharmacological indices used in published materials has caused confusion. In order to avoid this, the ISAP published a paper about the PK/PD terminology for anti-infective drugs, in which the PK and PD parameters and the PK/PD indices are defined.

### PK/PD terminology according to the ISAP

The following list contains a selection of the more commonly used definitions according to the ISAP (in italic style) for PK/PD indices.

**Time>MIC (to be written as $T_{>\text{MIC}}$)**

*Definition*: the cumulative percentage of time over a 24 h period that the drug concentration exceeds the MIC.

*Note*: if the period is other than 24 h, this should be stated explicitly.

$T_{>\text{MIC}}$ (the expression $T_{\geq \text{MIC}}$ would be more accurate) is mainly used to predict the efficacy of time-dependent antibiotics (e.g. β-lactams, glycopeptides, macrolides, clindamycin and oxazolidinones).

Drugs that belong to these classes show no or little enhancement of the effect with an increase in antibiotic concentration. The optimal concentration is mostly the two- to four-fold MIC of the pathogen.

### Peak/MIC ($C_{\text{max}}/\text{MIC}$) (ratio)

*Definition*: the peak level divided by the MIC.

In the literature, $C_{\text{max}}/\text{MIC}$ is also denoted as peak/MIC, inhibitory quotient (IQ) or inhibitory rate (IR). This index is used to predict or describe the antibacterial effect of concentration-dependent antibiotics. Aminoglycosides and quinolones show such an enhanced activity with increasing concentrations.

### AUC/MIC

*Definition*: the area under the concentration–time curve over 24 h divided by the MIC. If a subscript indicating another time period is not present, the AUC is assumed to be the 24 h value at steady state.

*Note*: For all practical purposes, the expression AUC/MIC should be used to show PK/PD relationships involving the AUC and MIC.

The PK/PD index AUC/MIC (Figure 3) is used to predict the efficacy of concentration-dependent antibiotics (see also $C_{\text{max}}/\text{MIC}$). Some authors use AUC as a universal index. Because of the diverse definitions of the AUC/MIC and AUC in the literature, an
PK/PD-index is calculated, when bacterial killing is observed, or clinical cure is obtained in clinical trials. Using a given dosage of an antibiotic (resulting in known AUC and $C_{\text{max}}$), PK/PD breakpoints can be used for the calculation of a value that can serve as a breakpoint for susceptibility.

Table 2 shows PK/PD breakpoints suggested by various authors that can be applied for the calculation of MIC breakpoints. Although the PK/PD breakpoints are based on experimental data determined in animal models or in vitro models, they are claimed to predict with a high probability the success of a therapy in patients. Only a few clinical trials are taken into account, and these are often retrospective studies with a small number of patients.

A clinical MIC breakpoint, derived from pharmacological indices, can be used to divide the pathogens into the categories of clinically susceptible or clinically resistant. Table 3 shows these MIC breakpoints using as an example amoxicillin at a dosage of 1000 mg orally twice daily. The MIC breakpoints are based on PK/PD breakpoints, which are 125 h for AUC/MIC, 10 for $C_{\text{max}}$/MIC and 60% for $T_{\text{MIC}}$. The breakpoint of $T_{\text{MIC}}$ was graphically determined from the concentration–time profile. The breakpoints of 0.6 and 1.1 mg/L agree with the Swedish SIR breakpoint of ‘susceptible’ at 1 mg/L.

Adelman & Schentag have developed a computer program especially for healthcare professionals who wish to use pharmacological indices clinically. The program A.U.I.C (antibiotic utilization information and consultation) is ‘designed to educate and assist clinicians in the management of bacterial infections in patients’. The program calculates antibiotic specific AUC/MIC values for a given dosage by using standard parameters for renal function and organism MIC. On the other hand, based on an AUC/MIC value of 125 h it calculates the dose of the antibiotic also using the same standard parameters for renal function, etc. Each parameter can be modified by the user to suit the patient or the clinical situation in question. Based on diagnosis, demographic data and so-called infection factors, the program selects possible infecting organisms on a ranked scale of probability of most likely, less likely and least likely pathogens. For each antibiotic, the user can customize antibiotic- or organism-specific susceptibilities, and can also obtain information about antibiotic cost. The authors state: ‘The program provides an objective analysis of underlying patient conditions, infection site specifics, nosocomial and community epidemiology and antibiotic susceptibility data, and the program will alert the user to the likely causative bacteria and indicate appropriate antibiotic regimens’.

**Conclusion**

Looking at the PK/PD breakpoints for AUC/MIC in Table 2, it becomes obvious that the breakpoints fluctuate depending on the authors’ points of view. For the index AUC/MIC, Jacobs et al. published a breakpoint of 25–30 for all antibiotics and all pathogens for less severe infections. Hyatt et al. believe that an AUC/MIC ratio from 350 to 500 is necessary for successful antibiotic therapy. This example shows a disagreement between AUC/MIC values by a factor of 20 and exemplifies the different opinions concerning the PK/PD breakpoints.

By applying mean PK/PD breakpoints to the calculation of MIC breakpoints, as in Table 3, the MIC breakpoints of amoxicillin are 0.6 or 1 mg/L. If the MIC for the pathogen does not exceed this value, therapy should be successful. The main indications for amoxicillin are respiratory tract and urinary tract infections. The most likely pathogens are *Streptococcus pneumoniae* and *Haemophilus influenzae*.
for respiratory tract infections, and *Escherichia coli* and *Proteus mirabilis* for urinary tract infections. Whereas the MIC values for the natural population (susceptible) of *S. pneumoniae* and *H. influenzae* are well below the MIC breakpoint of 0.6 mg/L (Table 3), the MIC values for the natural population (susceptible) of *E. coli* and *P. mirabilis* are well above this MIC breakpoint. Nevertheless, if the therapy with amoxicillin is successful, this is as a result of the high concentration of amoxicillin in the urine. This example shows that a direct transfer of the PK/PD breakpoints can result in wrong conclusions, when looking at different infection sites and different pathogens.

The criticism by Naber & Wiedemann\(^3^8\) of Naumann’s breakpoint \(\frac{C_{\text{max}}}{MIC}\) can also be applied to the pharmacological indices. Depending on the patient and the infection, PK can vary enormously, resulting in different concentration–time profiles. The calculation of most pharmacological indices is usually derived from plasma concentrations. In addition, the tissue penetration of various antibiotics varies and is, furthermore, influenced by the infection. Thus, at the site of infection, the concentrations often are completely different from those in the plasma of a patient. For example, during therapy of meningitis, the antibiotic has to pass the blood–brain barrier and therefore the dosage of the antibiotic has to be high and sustained. Circumstances like these can profoundly affect the pharmacokinetic parameters.

The MIC for a pathogen, which is a PD parameter used in most pharmacological indices, can also vary markedly depending on whether it is determined in plasma, in urine or in broth. Usually, it is done in broth and the inoculum is in the exponential growth phase. It is well known that physiological conditions in vitro, such as nutrient supply and pH, do not correspond with those in vivo. In addition, the results of MIC determinations depend on the methods used. Even though essential methodical steps like inoculum, source of the broth, incubation temperature, and incubation time are standardized by the NCCLS or BSAC, variations (for example in the cation concentration in the medium) can result in considerable fluctuations in the MIC values.\(^3^9\)

The media used allow optimal growth, but the generation time of bacteria at the site of infection or in biofilms, which can exist on tissue surfaces or on plastics, is much longer. Nevertheless, it is assumed that the effect of an antibiotic is the same. Furthermore, the MIC indicates only the concentration that inhibits the visible growth of

### Table 2. PK/PD breakpoints

<table>
<thead>
<tr>
<th>(C_{\text{max}}/MIC) (no units)</th>
<th>AUC/MIC (h)</th>
<th>(T_{\geq MIC}) (%)</th>
<th>Antibiotic class</th>
<th>Data determined from</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–12</td>
<td>125</td>
<td>50–60</td>
<td>all</td>
<td><em>in vitro</em> model; animal model; patients</td>
<td>15</td>
</tr>
<tr>
<td>&gt;8–10</td>
<td>125</td>
<td></td>
<td>all</td>
<td>patients(^c)</td>
<td>33</td>
</tr>
<tr>
<td>10–12</td>
<td>25–30(^a); 100–125(^a)</td>
<td>40–50</td>
<td>all</td>
<td><em>in vitro</em> model; animal model; patients</td>
<td>35</td>
</tr>
<tr>
<td>&gt;8</td>
<td>40(^a); 100–125(^d)</td>
<td>40–70</td>
<td>all</td>
<td><em>in vitro</em> model; animal model; patients</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>30–50</td>
<td></td>
<td>quinolones</td>
<td><em>in vitro</em> model; animal model; patients</td>
<td>28</td>
</tr>
<tr>
<td>&gt;10</td>
<td>40(^a); 100–125(^d)</td>
<td>60–70(^d); 30–40(^d)</td>
<td>cephalosporins</td>
<td>murine thigh and lung model</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>350–500</td>
<td></td>
<td>all</td>
<td>healthy volunteers</td>
<td>36</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>quinolones</td>
<td>rat model</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^a\)Less severe infections.  
\(^b\)Severe infections.  
\(^c\)Gram-positive pathogens.  
\(^d\)Gram-negative pathogens.  
\(^e\)Eradication of pathogens in bronchitis patients.

### Table 3. MIC breakpoints for oral amoxicillin 1000 mg twice daily calculated with PK/PD breakpoints

<table>
<thead>
<tr>
<th>MIC breakpoint (mg/L)</th>
<th>(C_{\text{max}}/MIC) = 10</th>
<th>AUC/MIC(^{b}) = 125 h</th>
<th>(T_{&gt;MIC} = 60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}C_{\text{max}} = 11.4\) mg/L.  
\(^{b}AUC_{24} = 75.52\) mg h/L.
bacteria after 18–24 h incubation. The effect of antibiotics in the same antibiotic class can be considerably different although the MIC may be the same. For example, erythromycin shows a bacteriostatic and telithromycin a bactericidal effect. Thus, the MIC cannot provide any indication of the type of action of an antibiotic.

The increase in the PK/PD breakpoint given by a higher dosage suggests that a higher dose should always result in a better efficacy. But an increase in the dosage usually correlates with increasing efficacy only within a narrow concentration range. Some antibiotics even show a reduced activity at high concentrations. This phenomenon was originally observed by Eagle et al. in 1948 with penicillin and is known today as the Eagle effect.

The A.U.I.C. program of Adelman & Schentag is a good attempt to use pharmacological indices in routine clinical work in a fast, easy and practical way. However, as the authors suggest, the program should be used critically. To optimize the clinical cure rate, calculations of the antibiotic dosage are based on an AUC/MIC value of 125. This is independent of whether a time-dependent or a concentration-dependent antibiotic is chosen. The program gives the user an opportunity to enter demographic data and so-called infection factors, such as underlying diseases, renal and hepatic failure, etc. These data influence the list of the most likely causative pathogens. Demographic data, such as body weight or age, change the AUC value via the clearance. If the clearance of the antibiotic in the patient is unknown, the program calculates a standard clearance by using the Cockcroft–Gault equation. The program could be further enhanced by allowing changes in the AUC value derived from antibiotic concentrations at the specific site of infection, as suggested by the infection factors.

Furthermore, as far as the incidence of resistance is concerned in determining the choice and the MIC values for the pathogens, it is not clear to which international or national database the program refers. However, the program is a useful tool for healthcare professionals although all results obtained from the program should be examined critically, as the authors emphasize by their statement ‘the decisions of the program are not liable for the work of the physician’.

In this context, it is questionable if the pharmacological indices really improve the dosing of antibiotics. The risk of under- or over-dosing is evident, as variability in the PK and PD parameters in themselves leads to considerable diversity in PK/PD breakpoints. It is difficult to reduce the complex situation existing in the body during an infection simply to only one value. Thus, it is far too optimistic to generalize the PK/PD indices down to one universal PK/PD index for all antibiotics, species and infection sites, that guarantees a clinical cure. Dealing with PK and PD aspects of antibiotic therapy helps to determine the correct dosage, but for the clinical application of PK/PD breakpoints, further investigations are necessary. The breakpoints have to be verified in prospective clinical trials that include a large number of patients, as in the work of Preston et al. Recent retrospective studies do not usually give precise evidence for the prediction of the efficacy from pharmacological indices. For example, a retrospective analysis of clinical trials by Sánchez-Reato et al. showed that successful therapy with ciprofloxacin was observed in 100% of the treated patients even though the index AUC/MIC varied from 3.6 to 5675.

Furthermore, the evaluation of clinical trials using Monte Carlo Simulation has enabled a specification of the parameters that are responsible for the value of the pharmacological index since details of the pharmacokinetics can be incorporated into the evaluation. Thus, an adjustment of the PK/PD breakpoints to the severity of an infection, to Gram-negative and Gram-positive pathogens, to a concentration-dependent and a time-dependent antibiotic effect and to the site of infection seems to be the way forward.

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