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## Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs

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### Abstract

Over the last decades, the interest in the relationships between the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents has increased and, therefore, the use of PK/PD indices and expressions has spread widely. The appropriate definition and use of these parameters is a matter of controversy. This paper contains a proposal to use PK/PD expressions for antimicrobial agents and their units in a uniform manner. © 2002 Published by Elsevier Science B.V. and International Society of Chemotherapy.

**Keywords:** Pharmacokinetic; Pharmacodynamic; Anti-infective drugs

### 1. Introduction

Over the last decades, interest in the relationships between the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents has increased. One of the characteristics of a rapidly evolving field is that definitions and expressions used by various authors differ in their meaning and that authors use different expressions to indicate the same meaning. Thereby, it becomes difficult to compare the results of various experiments. In view of this well recognized problem, during a meeting arranged by the International Society of Anti-infective Pharmacology (ISAP) in Nijmegen July 2002, a document was discussed that outlined proper use and expression of commonly used expressions in pharmacokinetic and pharmacodynamic research.

This paper contains the view of the discussion group. We hope that by referring to this paper, the use of PK/

PD terminology will be used more uniformly and consistently. Perhaps even more importantly, we have indicated the conditions of testing and/or analysis to be reported so that the results of various authors may be compared more efficiently.

Since the Nijmegen meeting, a consensus group has been formed with the aim of developing a document to standardize pharmacodynamic research. That document will be discussed at the Interscience Conference of Antimicrobial Agents and Chemotherapy 2002, in San Diego.

### 2. Definitions

#### 2.1. General remarks

- The quantitative relationship between a pharmacokinetic and a microbiological parameter is called a PK/PD index.
- All PK/PD indices should be expressed as or referred to by the unbound (non-protein bound) fraction of the drug or the degree of protein binding should be stated in such a way that the concentration of the

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unbound fraction of the drug can be readily calculated. This is particularly important for comparisons between members of the same class of drugs acting by the same mechanism.

- In all expressions, when reporting, it should be stated whether pharmacokinetic parameter values (and derivatives such as PK/PD indices) were determined at steady state or after a single dose.
- If increasing doses are given, linearity between dose and pharmacokinetic parameter has to be stated. If the drug follows nonlinear PK, it has to be stated how this was analyzed.

## 2.2. List of definitions

### 2.2.1. PK/PD index

*Definition:* composite of a pharmacokinetic parameter (such as AUC, peak level) and a microbiological parameter (such as minimum inhibitory concentration (MIC)).

*Note:* these include, but are not limited to, AUC/MIC, AUIC, Peak/MIC,  $T_{>MIC}$ .

### 2.2.2. MIC

*Definition:* minimum inhibitory concentration.

*Note:* any calculation or expression of the MIC should include a description of the method by which the MIC was determined or a reference to a published method (e.g. NCCLS [1] or BSAC [2]) should be given.

*Dimensions:* concentration (e.g. mg/l or  $\mu\text{g/ml}$ ).

### 2.2.3. AUC

*Definition:* the area under the concentration–time curve at steady state over 24 h.

*Note:* the AUC in PK/PD calculations is used as a reference value. If a subscript indicating another time-period is not present, the AUC is assumed to be the 24 h value at steady state. It should be stated how the AUC is determined, based on the trapezoidal rule (regular or log-linear); based on dose; clearance and bioavailability or based on micro-constants.

*Dimensions:* concentration  $\times$  time (e.g. mg.h/l or  $\mu\text{g.h/ml}$ ).

### 2.2.4. 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:* publications on PK/PD relationships involving the AUC in relation to MIC should use this expression. The time-period of reference should be stated.

*Dimensions:* time (e.g. h).

### 2.2.5. AUIC

*Definition:* the area under the inhibitory curve. If a subscript indicating another time-period is not present, the AUIC is assumed to be calculated over 24 h at steady state.

*Note:* the AUIC has been ambiguously applied and at least three different definitions exist. It was originally used as the area under the curve of the reciprocal values of the serum inhibitory titre (SIT) versus time [3] and some authors still use that definition [4,5]. A few years later, in 1991 it was used as the AUC for the period of time the concentrations were above the MIC divided by the MIC [6], and a few years later yet the AUIC was defined as the total AUC divided by the MIC [7,8]. To avoid further confusions, the AUIC should be reserved for those cases where actual inhibitory titres have been measured and used in the calculations. In any case, it should be defined if used. Statements such as AUIC (AUC/MIC) should be avoided. For all practical purposes the expression AUC/MIC should be used to show PK/PD relationships involving the AUC and MIC. See also the definitions and notes under AUC.

*Dimensions:* time (e.g. h).

### 2.2.6. Peak or $C_{max}$ (level, concentration)

*Definition:* the highest concentration reached or estimated in the compartment of reference.

*Note:* it should be stated how the peak-level was determined and its relevance to the compartment of infection. If the peak-level is measured in the (post) distributional phase, specifics regarding distribution and elimination should be stated. In most cases, during extra-vascular routes of administration the peak level can be taken as being equal to the highest concentration in plasma/serum.

*Dimensions:* concentration (e.g. mg/l or  $\mu\text{g/ml}$ ).

### 2.2.7. Peak/MIC ( $C_{max}/MIC$ ) (ratio)

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

*Note:* there are no dimensions, as the units cancel.

*Dimensions:* no dimensions.

### 2.2.8. Time $>$ MIC (to be written as $T_{>MIC}$ )

*Definition:* the cumulative percentage of time over a 24 h period that the drug concentration exceeds the MIC at steady state pharmacokinetic conditions.

*Note:* if the period is other than 24 h, this should be stated explicitly. When a drug is given by a route other than intravenous bolus-injection (e.g. oral dosing), the time-period that drug concentrations remain below the MIC during the ascending portion of the concentration–time curve, should be considered in calculating this index.

*Dimensions:* percentage.

### 2.2.9. $E_{max}$ model

**Definition:** a three parameter logistic equation or sigmoid  $E_{max}$  model (four parameter if inhibitory sigmoid) or modified Hill equation, e.g.:

$$E = E_{max} \times \frac{C^s}{(C^s + EC50^s)}$$

where  $E_{max}$  is the maximum effect,  $C$  the concentration,  $EC_{50}$  the concentration where 50% of the maximum effect is measured, and  $s$  the Hill or sigmoidicity coefficient.

**Note:** when referred, it should be mentioned whether the three parameter equation (or four parameter if inhibitory sigmoid) or Hill equation is used. If the two parameter  $E_{max}$  model (the same model without the Hill factor,  $s = 1$ ) is used, this should be stated explicitly. The  $E_{max}$  model also can be used to describe the relationship between dose and a cumulative effect,  $E = E_{max} \times D^s / (D^s + ED_{50}^s)$ , where  $D$  is the dose and  $ED_{50}$  is the dose that results in 50% of the maximum cumulative effect. Similarly, the  $E_{max}$  model can be used to describe the relationship between a PK/PD index and effect.

### 2.2.10. Static dose

**Definition:** the dose, dosing regimen or value of a PK/PD index required to obtain a net static effect over a period of 24 h.

**Note:** the time period over which the net static effect is measured should be stated explicitly.

**Dimensions:** amount (e.g. mg or g, sometimes expressed per kg body weight). If body weight is not used, the weight and a measure of dispersion of the experimental group should be stated.

### 2.2.11. 50% Effective concentration ( $EC_{50}$ )

**Definition:** the concentration required to obtain 50% of the maximum effect.

**Note:** this parameter is usually estimated from the Hill equation, probit, or logistic methods. The time-period over which 50% of the maximum effect is measured should be stated explicitly.

**Dimensions:** concentration (e.g. mg/l or  $\mu$ g/ml).

### 2.2.12. 50% Effective dose ( $ED_{50}$ )

**Definition:** the dose, dosing regimen or exposure required to obtain 50% of the maximum effect.

**Note:** the time period over which 50% of the maximum effect is measured should be stated explicitly.

**Dimensions:** amount (e.g. mg or g, sometimes expressed per kg body weight). If body weight is not used, the weight of the experimental group should be stated.

### 2.2.13. Maximum effect ( $E_{max}$ )

**Definition:** the maximum effect obtained when determining a dose–effect or concentration–effect relationship.

**Note:** this parameter is usually estimated from the Hill equation. In any expression, the limits of detection should be noted and the maximum possible (i.e. effect which can be determined) should be noted. In many cases the maximum effect measured and the maximum effect that can be measured are the same, but there is an essential difference.

### 2.2.14. Minimum effect

**Definition:** the minimum effect obtained when determining a dose–effect or concentration–effect relationship.

**Note:** in any expression, the limits of detection should be noted and the minimum detectable effect that can be determined should be noted.

### 2.2.15. In vitro PAE

**Definition:** the post antibiotic effect in vitro is defined as the period of suppression of bacterial growth after short exposure of organisms to an antimicrobial.

**Note:** when reporting, the following should be stated: antibiotic concentration, inoculum, exposure time, method to remove antibiotic and prevent carry-over, method to prevent an inoculum effect after exposure, time points measured and calculation method. The PAE using bacterial counts as a parameter is calculated by  $PAE = T - C$  where  $T$  is the time required for the bacterial counts of the exposed cultures to increase one  $\log_{10}$  above the counts observed immediately after washing/dilution and  $C$  is the corresponding time required for the counts of the untreated cultures [9].

**Dimension:** time (e.g. h).

### 2.2.16. In vivo PAE

**Definition:** the difference in time for the number of bacteria in a tissue of treated animals versus controls to increase 1  $\log_{10}$  over values when drug concentrations in serum or the infection site fall below the MIC. The in vivo PAE thus includes the effects of sub MIC concentrations.

**Note:** when reporting, the following should be stated, inoculum, exposure time, method to calculate half-life and time of falling below MIC, time points measured and calculation method.

**Dimension:** time (e.g. h).

### 2.2.17. SubMIC effect

**Definition:** any effect of an antimicrobial on a micro-organism at concentrations below the MIC.

**Note:** the effect can be described both morphologically as well as time to growth, growth rate etc. Details of the procedure have to be described exactly.

### 2.2.18. Post-antibiotic sub-MIC effect (PA SME)

**Definition:** the effect of sub-MIC drug concentrations on bacterial growth following serial exposure to drug concentrations exceeding the MIC.

**Note:** when reporting, the following conditions should be described, inoculum; antibiotic concentration and exposure time to induce the post-antibiotic phase, method to remove antibiotic, antibiotic concentration(s) to induce the PA SME, method to prevent an inoculum effect after exposure, time points measured and calculation method. The PA SME is calculated as  $T_{pa} - C$ , where  $T_{pa}$  is the time taken for the cultures previously exposed to antibiotics and then exposed to a sub MIC to increase by  $1 \log_{10}$  above the counts observed immediately after washing/dilution and  $C$  is the corresponding time for the unexposed cultures. [10]

**Dimension:** time (e.g. h).

### 2.2.19. Post MIC effect (PME)

**Definition:** the difference in time for the number of antibiotic exposed bacteria versus controls to increase  $1 \log_{10}$  over values after drug concentrations in serum or the infection site to fall below the MIC. The PME thus includes the effects of sub MIC concentrations (c.f. in vivo PAE).

**Note:** when reporting, the following should be stated, inoculum; exposure time; method to calculate half-life and time of falling below MIC, time points measured and calculation method.

**Dimension:** time (e.g. h).

### 2.2.20. Drug interaction effects

**Definition:** any effect of a combination of antimicrobials, of a combined effect of drugs. For the definitions of synergism, additivity etc. see the paper of Greco et al. [11].

**Note:** if an interaction is reported, the following should be stated: methods used, method used to calculate synergism, statistical analysis. Any value reported should state 95% confidence intervals of the interaction coefficient, FIC or other parameter.

**Dimensions:** none.

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