

Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update

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Interest in the relationships between the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents has increased over recent years. Since the appearance 2 years ago of our first article describing terminology in PK/PD, the field has continued to expand rapidly, urgently requiring an update. This paper describes in a uniform manner the use of PK/PD expressions for antimicrobial agents, and their units.

Keywords: AUC/MIC, $T_{>MIC}$, probability of target attainment, cumulative fraction of response, protein binding

Introduction

Two years ago, we issued a document outlining proper use and expression of commonly used terms in pharmacokinetic and pharmacodynamic research.¹ By publishing these definitions, it was our aspiration that the use of PK/PD terminology would be applied more uniformly and consistently. Over the past 2 years, numerous publications have referred to the document and there is a clear impression that the attempt at terminology standardization was helpful for the field.

As was stated in the original paper, one of the characteristics of a rapidly evolving field such as pharmacodynamics is that definitions and expressions used by various authors differ in their meaning, or that authors use different expressions to indicate the same meaning. As a consequence, it becomes difficult to compare the results of various studies. The field is still growing rapidly. In only 2 years, the use of Monte Carlo simulations for PK/PD analyses has become common, while the increasing use of bacterial kill kinetics to describe the interaction between drug and pathogens is rapidly evolving. Finally, although still an unproven concept, the introduction of the Mutant Selection Window for study of drug resistance with its associated parameters and issues warrants special attention. An update of the paper was therefore highly warranted to include terms used in these three areas.

In addition to the issues above, we took the opportunity to refine some of the definitions in the initial document. Last year (2003), a conference took place in Leiden (The Netherlands) where many of these parameters were re-evaluated. Importantly,

the use of the prefix *f* is introduced as an indicator that the free, unbound fraction is used or meant when using a pharmacokinetic parameter, e.g. *f*AUC.

We have chosen to structure the paper based on various topics rather than alphabetically because grouping of terms on a related subject seemed far more logical; related terms are then easier to find.

Not all terms and concepts have been sufficiently debated to justify a finalized definition. Some are tentative and open for discussion. These are indicated in a separate section 'Terms under consideration'. In addition, it is impossible to foresee the development in the field over the next few years, and undoubtedly there will be a requirement for updates of the present paper in the future, both for new terms as well as re-evaluating established terms. A new update will appear every 5 years, or earlier if warranted. We encourage readers to submit proposals or suggestions for future evaluation and description. A web page on the web site of ISAP (www.isap.org), is available to that purpose.

Terminology

General remarks

The quantitative relationship between a pharmacokinetic parameter (such as AUC, peak level) and a microbiological parameter (such as MIC) is labelled as a PK/PD index (PDI). Examples include AUC/MIC and $T_{>MIC}$. The term pharmacodynamic index was deliberately chosen above the sometimes-used term pharmacodynamic parameter to indicate that the associated

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value is a derived ratio or composite of a pharmacokinetic parameter and a microbiological parameter and not a property in itself.

It is strongly advocated to use the prefix *f* if the free fraction of the drug is used in calculations, e.g. *fAUC* indicating that it is the free, unbound fraction of the drug that is meant or used. In general, all PK/PD indices should be referenced to 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 unbound fraction of the drug can be readily calculated. This is particularly important for comparisons among 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 pharmacokinetic steady-state conditions or after a single dose. In general, the steady-state values should be used if multiple dosing regimens are applied.

If increasing doses are given, linearity between dose and pharmacokinetic parameter has to be stated. If the drug follows non-linear pharmacokinetics, it has to be stated how this was analysed.

PK/PD indices and related terms

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. NCCLS² or BSAC³) should be given. At present, the International Organization for Standardization (ISO) is redefining the MIC to a worldwide reference method.

Dimensions: Concentration (e.g. mg/L or µg/mL).

f

Definition: Prefix indicating that the pharmacokinetic parameter values or PK/PD index values used are unbound (free) fractions of the drug.

Note: This cannot be used by itself but should be used in conjunction with a pharmacokinetic parameter or pharmacodynamic index, e.g. *fAUC*, *fT_{>MIC}*.

Dimensions: Not applicable.

AUC

Definition: The area under the concentration–time curve at steady-state over 24 h unless otherwise stated. It is equivalent to a single dose $AUC_{0-\infty}$.

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 × time (e.g. mg·h/L or µg·h/mL).

AUC/MIC

Definition: The area under the concentration–time curve over 24 h in steady-state 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: In the initial definition document¹ the dimension was time. However, many consider the dimension in this case as meaningless and would prefer considering it a ratio as such. Since the MIC is measured after 18–24 h of incubation and therefore involves time as a dimension in a certain sense, although not expressed as such, the use of the ratio without dimensions seems justified. The time-period of reference should be stated. For unbound fraction of the drug, use *fAUC/MIC*.

Dimensions: No dimensions.

AUBC

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

Note: See also under AUC, below. For unbound fraction of the drug, use *fAUBC*.

Dimensions: No dimensions.

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 derived from the area under the bactericidal curve.⁴ It was originally used as the area under the curve of the reciprocal values of the serum inhibitory titre (SIT) versus time⁵ and some authors still use that definition.^{6,7} 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,⁸ and a few years later yet the AUIC was defined as the total AUC divided by the MIC.^{9,10} To avoid further confusion, 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. For unbound fraction of the drug, use *f* **AUC**.

Dimensions: No dimensions.

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, providing appropriate sampling, 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 µg/mL).

Peak/MIC (C_{max}/MIC) (ratio)

Definition: The peak level divided by the MIC.

Note: There are no dimensions, as the units cancel. For unbound fraction of the drug, use *f* **Peak/MIC** or *f* **C_{max}/MIC** .

Dimensions: No dimensions.

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

Definition: The cumulative percentage of 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. For unbound fraction of the drug, use *f* **$T_{>MIC}$** .

Dimensions: %.

E_{max} model or Hill equation

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.

$$E = E_{max} \times C^s / (C^s + EC_{50}^s)$$

where E_{max} is the maximum effect, C is the concentration, EC_{50} is the concentration where 50% of

the maximum effect is measured, and 's' is the Hill or sigmoidicity coefficient.

Note: When referred to it should be mentioned that 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 can also 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, by using the term EI_{50} , where I stands for PK/PD index.

Static dose; static PK/PD index

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 or otherwise stated.

Note: The net static effect is the dose or exposure resulting in the measure of effect being unchanged from baseline to the time of evaluation [e.g. the number of cfu at $t=0$ h (baseline, start of treatment) and $t=24$ h (time of sampling)]. The use of the term static expressly does not imply that no changes have occurred during the period of reference; indeed kill and regrowth may have occurred (repeatedly) during this period. 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); dimension of PK/PD index.

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 µg/mL).

50% Effective dose (ED_{50}); 50% effective PK/PD index (EI_{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); dimension of PK/PD

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index. If body weight is not used, the weight of the experimental group should be stated.

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 which can be measured are the same, but there is an essential difference.

Minimum effect

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

Note: Theoretically, there is no minimum effect during exposure, only a question whether the effect can be detected. This in turn depends on the variance of the parameters, the statistical evaluation and the methods used. In any expression, the limits of detection should be noted.

Expressions in modelling

Growth rate

Definition: The rate at which organisms (bacteria, viruses, etc.) grow over (a certain period of) time.

Note: See remarks under maximum kill rate.

Dimensions: Units/time (e.g. cfu/h).

Growth rate constant (k_0)

Definition: The first-order rate constant that describes growth.

Note: In general, the growth rate constant is independent of the investigated drug. See remarks under maximum kill rate.

Dimensions: 1/time (e.g. h^{-1}).

Kill rate

Definition: The rate at which organisms (bacteria, viruses, etc.) are killed over (a certain period of) time.

Note: See remarks under maximum kill rate.

Dimensions: Units/time (e.g. cfu/h).

Kill rate constant

Definition: The first-order rate constant that describes the kill rate.

Note: See remarks under maximum kill rate.

Dimensions: 1/time (e.g. h^{-1}).

Maximum kill rate (MKR)

Definition: Maximum rate at which organisms are killed.

Note: The MKR is usually obtained from *in vitro* time–kill experiments and the estimated value is therefore dependent on a number of experimental (technical) factors. These include: (i) The time over which the maximum kill rate is measured. The time points included in the regression analysis to determine the MKR should include at least two points above the detection limit. (ii) For some antimicrobials, there is a lag-time before the kill rate is maximal; in those cases, a maximum kill rate should not be determined from time = 0 h or at least be interpreted with caution. (iii) For drugs with a concentration-dependent effect over a wide concentration range, special care should be taken for carry-over drug effects at high concentrations (e.g. killing by quinolones may be so fast when carrying out time–kill experiments for some microorganisms that significant kill is observed during sampling and plating). (iv) The maximum kill rate may be very high for a very short period of time and much slower when measured over a longer period (two-phase kill). If the MKR is reported, this should be taken into consideration. (v) Although some bacteria may be killed during a certain period of time, growth may still occur. Depending on the model used to explain the data, the MKR can therefore have two different values or interpretations: the observed MKR (MKR_o) as directly determined from the kill curves or the intrinsic MKR (MKR_i) as determined from models taking the growth rate into account. The MKR_o in that case is the MKR_i –growth rate. It should be clearly stated which MKR is being used.

Dimensions: Units/time (e.g. cfu/h).

Maximum kill rate constant (k_{max})

Definition: The rate constant that describes the maximum kill rate.

Note: See remarks under maximum kill rate. Likewise, if a mathematical model is used that includes growth as a separate parameter, one should distinguish between the maximum kill rate constant that is actually observed or determined directly from experiments ($k_{max,o}$) and the intrinsic kill rate constant ($k_{max,i}$). The latter can be obtained by correcting for the growth rate constant. The two constants are indicated by the two

suffixes o (for observed) and i (for intrinsic). Thus, $k_{\max,o} = k_{\max,i} - k_0$.

Dimensions: 1/time (e.g. h^{-1}).

Stationary concentration

Definition: The concentration of antimicrobial at which growth equals kill, i.e. no net growth or kill.

Note: This value has been referred to in the past by different names. The value itself was introduced and first derived by Bouvier d'Yvoire and Maire¹¹ and they named it the ZMIC. Using a slightly different approach Mouton and Vinks¹² came to a similar value based on the E_{\max} model with a variable slope to describe the kill kinetics and named it the stationary concentration to indicate no net growth/kill at a certain point in time but still indicate the dynamics at that time point. It differs from the static dose or static PK/PD index because the latter includes a time span, whereas the stationary concentration does not.

Dimensions: Concentration (e.g. mg/L).

Post-exposure effects

The nomenclature of post-exposure effects has been confusing because of the various experimental conditions in which these effects have been measured. Post-exposure effects include both exposure to an antimicrobial at high concentrations and subsequently removing the antibiotic by artificial means as well as effects that are observed *in vivo* after concentrations have declined to values below the MIC. It has to be emphasized that the experimental circumstances during which an *in vitro* post-antibiotic effect (PAE) is determined are markedly different from those *in vivo* and should be interpreted with the greatest caution.

In vitro PAE

Definition: The PAE *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 $\text{PAE} = T - C$ 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.¹³

Dimensions: time (e.g. h).

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.

Dimensions: Time (e.g. h).

Sub-MIC 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 or another parameter. Details of the procedure have to be described exactly.

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 (if dilutions are used to remove antibiotic), time points measured, and calculation method. The PA SME is calculated as $T_{\text{pa}} - C$, 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.¹⁴

Dimensions: Time (e.g. h).

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, the infection site or an *in vitro* pharmacokinetic model fall below the MIC. The PME thus includes the effects of sub-MIC concentrations and includes the *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.

Dimensions: Time (e.g. h).

Terms used in Monte Carlo simulations

Probability of target attainment (PTA)

Definition: In Monte Carlo simulations, the probability that at least a specific value of a pharmacodynamic index (e.g. 30% $fT_{>MIC}$; $fAUC/MIC$ of 100) is achieved at a certain (minimum inhibitory) concentration.

Note: Different terms have been used conveying different meanings, target attainment rate (TAR) being one of them. However, TAR has been used now for several different purposes and the meaning is therefore not clear, nor does the term describe what actually is obtained. The term PTA includes 'probability' to unambiguously indicate its meaning. When a PTA is mentioned, it should always be used in conjunction with the PDI value corresponding to the target value of the PDI; the PDI target value should also be motivated (e.g. the PDI target corresponding to a stasis of the initial inoculum at 24 h, a 3 \log_{10} kill, or a 90% maximal killing effect).

Dimensions: None.

Cumulative fraction of response (CFR)

Definition: The expected population probability of target attainment for a specific drug dose and a specific population of microorganisms.

Note: The CFR is an estimate of the proportion of the population achieving a certain PDI value, given the Monte Carlo simulation and the MIC distribution of the target microorganism(s). It is calculated as

$$\sum_{i=1}^n PTA_i \times F_i$$

The subscript i indicates the MIC category ranked from lowest to highest MIC value of a population of microorganisms, PTA_i is the PTA of each MIC category and F is the fraction of the population of microorganisms at each MIC category.¹⁵ The (group of) microorganisms should be specified.

Dimensions: Proportion (e.g. %).

Terms under consideration

The terms mutation prevention concentration and mutant selection window are increasingly being used. Although the concept has not been proven, these terms are included here to at least standardize their use.

Mutation prevention concentration (MPC)

Definition: Concentration preventing growth at a high ($> 10^9$) inoculum using agar dilution methodology.

Note: The method to determine the MPC is essentially similar to an agar dilution assay but with a high inocu-

lum. Thus, this concentration is usually higher than the MIC because the bacterial population tested encompasses a larger tail of the MIC distribution, and thus will depend on the shape and extent of that tail. In addition, because of the higher inoculum, there will be a greater probability of selecting mutants at concentrations higher than the MIC but lower than the MPC. This is dependent on the nature of expected mutations and the rate thereof. The clinical significance of the MPC needs further study.

Dimensions: Concentration (e.g. mg/L).

Mutant selection window (MSW)

Definition: Difference between MIC and MPC for a given microorganism.

Note: It is proposed that exposure of a growing inoculum of bacteria to drug concentrations between the MIC and MPC may increase the selection of resistant mutants. The probability of mutants emerging is increased in this window based on the MPC concept and that the time concentrations fall within this window should be minimized.¹⁶

Dimensions: Concentration (e.g. mg/L).

Time interval within mutant selection window (tMSW)

Definition: In settings where bacteria are exposed to changing concentrations of drug over time, tMSW represents the time during which concentrations stay within the MSW.

Note: Unbound fraction of the drug should be used in calculations.

Dimensions: Time (e.g. h).

Mutation prevention index (MPI)

Definition: The ratio between MPC and MIC.

Note: None.

Dimensions: None.

Drug interaction effects

Definition: Any effect of a combination of antimicrobials, or a combined effect of drugs. For the definitions of synergy, additivity and other terms of interaction, see the paper by Greco *et al.*¹⁷

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

Dimensions: None.

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