AUC/MIC: a PK/PD index for antibiotics with a time dimension or simply a dimensionless scoring factor?

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A previous article on standardization of pharmacokinetic/pharmacodynamic terminology for anti-infective drugs recommended deletion of the units of the AUC/MIC ratio (actually h). We express here the difficulties presented by this proposal and we propose expressing AUC/MIC as a scaling factor corresponding to the current index divided now by 24 h. This is the scaling factor without units by which the targeted MIC should be multiplied to estimate the average in vivo plasma concentration to be achieved. Associated with this proposal, we address the specific issue of veterinary drug products for which steady conditions are seldom achieved. To accommodate the need for dose prediction during these novel therapeutic situations, we propose a general approach that is based on the targeted time interval over which some desired average concentration should be maintained.

Keywords: terminology, standardization, PK/PD index, time dimension

In their article entitled ‘Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update’, Mouton et al.1 encouraged readers to submit proposals or suggestions for future evaluation and description. In this short article, we address the proposal to delete the units of the AUC/MIC ratio, a PK/PD index actually possessing a time dimension (h). We express the difficulties inherent in this proposal and offer an alternative that meets the requirements motivating the aforementioned proposal while remaining formally correct in terms of dimensional analysis. In addition, we believe that the proposed definition of this PK/PD index should be universal and therefore applicable regardless of dosing regimen. Our particular interest arises as a result of the varied kinds of dosing regimens associated with numerous veterinary pharmaceutical formulations. In many cases, these products are not designed to achieve steady-state conditions. Further discussion of this issue is provided below.

To begin with, we acknowledge that the actual ‘time dimension’ of the AUC/MIC ratio, i.e. hours, is more confusing than informative and that the implication of a statement such as ‘the MIC is measured after 18–24 h of incubation and Cmax/MIC is obtained appropriately, expressed as a dimensionless ratio. Therefore, if the argument for the 18–24 h holds for AUC/MIC, Cmax/MIC should now have a dimension of 1/hour.

Apart from the target PK/PD information that the AUC/MIC ratio is expected to convey, this ratio may be used to compute a dose using the following equation (Eqn 1):

\[
\text{Dose (per day)} = \frac{\text{Clearance (per hour)} \times (\text{AUC/MIC})_{\text{breakpoint}} \times \text{MIC}_{\text{90}}}{\text{fu} \times F}
\]

where dose (per day) is the daily maintenance dose at steady state; clearance is the plasma clearance expressed as L/h, as is the custom in most PK manuscripts; (AUC/MIC)_{breakpoint} the targeted AUC/MIC value (e.g. 125 h); MIC_{90} the 90th percentile of the MIC distribution; fu (from 0 to 1) the free (unbound) fraction, thereby accounting for the fact that only the free antibiotic plasma concentration is a relevant plasma surrogate of the free antibiotic concentration at the biophase level; and F the absolute bioavailability (from 0 to 1).

To be applied, such an equation needs to be consistent from a dimensional perspective. It is because the (AUC/MIC)_{breakpoint} has a dimension of hours that the plasma clearance is also

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expressed in hours (and not in days) when computing a daily dose. Furthermore, forgetting the actual dimension of AUC/MIC may lead to gross errors that are difficult to detect (e.g. when the results are published without units by investigators who have forgotten that the numerical value of the AUC/MIC needs to be computed in a way consistent with the dimension of hours). In addition, in cases where daily steady-state concentrations are not achieved, this can be particularly problematic. Therefore, we believe that the numerical value should still be reported in some manner consistent with the appropriate units of time.

We recognize that convention is moving away from the reporting of AUC/MIC with its time unit of hours. Nevertheless, we believe that a straightforward solution exists that is both consistent in terms of dimensional analysis and that facilitates capture of the biological information conveyed by the AUC/MIC ratio. Indeed, according to the current recommendation, AUC/MIC should be computed over a 24 h period at steady state and it should be realized that the operational dimension of AUC/MIC is not hours but rather ‘hours over a 24 h period’. Thus, if AUC is directly computed using day (rather than hours) as the time unit, the ratio AUC/MIC (now day per day) then becomes naturally dimensionless. Instead of reporting an AUC/MIC of 120 h (per day) when the AUC is computed in mg x h/L, the equivalent would be to report a ratio of 5 if the AUC is directly computed in mg x day/L. Alternatively, AUC/MIC may be expressed in hour per hour, rather than per 24 h, and this would simply imply dividing the current 24 h AUC/MIC of 120 h by 24 h. From an operational point of view, both approaches lead to the same scalar with a numerical value of 5.

These approaches have two advantages. First, they permit the assessment of a truly dimensionless ratio (e.g. 5 rather than 120 h) to be obtained. Secondly, the computed numerical value has direct clinical interpretation. Indeed, this ratio is the scaling factor by which the targeted MIC (population MIC90 or other MICs) should be multiplied to estimate the average in vivo plasma concentration we need to achieve under steady-state conditions, e.g. if a clinical cure requires an AUC/MIC of 120 h, it can equivalently be said that the average steady-state plasma concentration should be five times the MIC in question to predict a clinical cure. When expressed in this manner, the two possible indices for concentration-dependent PK/PD relationships can easily be contrasted, i.e. the maximal plasma concentration being 10 times the MIC (with Cmax/MIC typically equal to 10) and the average plasma concentration being 5 times the MIC (with AUC/MIC having a typical value of 5). In doing so, it is also far more informative with regard to the relationship between drug effects and the PK of that compound in the targeted patient population.

Using this proposed factor, the computation of a maintenance dose is straightforward (Eqn 2) and reflects only a minor modification of Eqn 1:

\[
\text{Dose (per day)} = \frac{\text{Clearance (per day)} \times \text{factor} \times \text{MIC90}}{\text{fu} \times F}
\]

(2)

Plasma clearance is now expressed in L/day (consistently with the dose) and not as L/h (as per Eqn 1). The factor is the dimensionless numerical value of AUC/MIC. Upon inspection of Eqn 2, one can readily discern the biological meaning of the AUC/MIC ratio (i.e. the scaling factor by which the targeted MIC needs to be multiplied to estimate the targeted average steady-state plasma concentration).

By stipulating time as a component of the AUC/MIC assessment, we can better accommodate those situations for which the AUC/MIC (as currently defined by Mouton et al.\(^3\)) is poorly suited. For example, AUC/MIC is not well suited to the kinds of dosing regimens for which steady-state conditions are not achieved. This is the case with food-producing animals in which single-dose regimens are promoted to minimize animal handling, thereby reducing the cost of administration and animal stress. Examples of the unique dosing regimens associated with food-producing animals include danofloxacin, a fluoroquinolone manufactured by Pfizer Animal Health, which is administered at a dose of 6 mg/kg every other day, for a total of two administrations\(^3\) and several US-approved long-acting oxytetracycline formulations that can be administered either once or daily, depending on dose and indication.\(^4\) For these dosage regimens, if the targeted AUC/MIC ratio is expressed using the AUC extrapolated to time infinity (which is equal to steady-state AUC values over a single dosing day at steady state), we obtain a PK/PD index that markedly exaggerates the average drug concentrations to which the animal will actually be exposed. In contrast, the duration of a treatment may be difficult to qualify in veterinary medicine. Although for humans it is equated to the number of daily administrations, the duration of treatment for a single-dose injection of a long-acting parenteral formulation is more difficult to express.

A possible solution to these various challenges is to adopt the concept of a dimensionless factor corresponding to the AUC/MIC scaled by some selected time interval. In our discussion up to this point, the time interval was hours 0–24 at steady state. With long-acting antimicrobial products, the time interval could reflect any of the various time segments of interest. For example, with danofloxacin, the approved dosage is 6 mg/kg once every 48 h for a maximum of two doses. Our time segment of interest may be AUC0–24, AUC24–48 or AUC0–48. It should be noted that as this product is associated with a t\(_{1/2}\) of ~5.3 h (Freedom of Information Summary NADA 141–207), AUC0–48 would be equivalent to AUC0–inf. Alternatively, there are long-acting parenteral products that are approved for a single administration. In this case, we may wish to identify a specific partial area as the target to achieve for a dose determination. This point is exemplified by the simulated oxytetracycline concentration–time profile provided in Figure 1.

Using this example, if we divide any partial AUC/MIC value by the corresponding time interval of interest (0–24, 0–48, 24–48 h or other), we will obtain a scalar that expresses the actual ratio of the average blood concentrations relative to the targeted MIC. This provides a flexible index that is applicable regardless of the dosing regimen and whether or not steady state is achieved.

With regard to dose estimation, the challenge is that because we are no longer dealing with steady-state AUC values, we need to modify Eqn 1 to allow for dose estimation based on some targeted partial areas. Assuming that we can apply an equation for an intravenous (iv) one-compartment body model to estimate dose (amount), the resulting equation is provided below (Eqns 3–7):

\[
\text{Dose} \times (\text{FR}_{\text{time1}} - \text{FR}_{\text{time2}}) = \text{CL} \times AUC_{\text{partial}}
\]
Figure 1. Long-acting oxytetracycline concentrations in calves following intramuscular injection. Simulated values based upon PK parameter values reported by Kumar and Malik, i.e. \( V = 0.9 \text{L/kg}; \lambda = 0.028875 \text{h}^{-1} \) and \( F = 0.9 \).

Therefore,

\[
\text{FR}_{\text{time1}} - \text{FR}_{\text{time2}} = \exp(-\lambda \times \text{time1}) - \exp(-\lambda \times \text{time2})
\]  

(5)

Substituting Eqn 4 and Eqn 5 into Eqn 3, we can now solve for dose (Eqn 6):

\[
\text{Dose} = \frac{\frac{V \times \lambda \times \text{AUC}_{\text{partial}}}{\exp(-\lambda \times \text{time1}) - \exp(-\lambda \times \text{time2})}}{\frac{\text{FR}_{\text{time1}} - \text{FR}_{\text{time2}}}{\exp(-\lambda \times \text{time1}) - \exp(-\lambda \times \text{time2})}}
\]  

(6)

The targeted \( \text{AUC}_{\text{partial}} \) is determined as the desired average serum concentration we wish to achieve relative to the MIC (e.g. \( 4 \times \text{MIC} \); where \( 4 \) is termed the “factor”) and the duration of time over which this average concentration needs to be maintained (defined as \( \text{time2} - \text{time1} \)).

To achieve a particular average ratio of serum-free drug concentration versus MIC during the time interval in question for a product associated with bioavailability, \( F \), we can solve for dose (as contrasted to the estimate of dose per day in Eqn 2), using Eqn 7:

\[
\text{Dose} = \frac{\frac{V \times \lambda \times \text{factor} \times \text{MIC} \times (\text{time2} - \text{time1})}{\frac{\text{FR}_{\text{time1}} - \text{FR}_{\text{time2}}}{\exp(-\lambda \times \text{time1}) - \exp(-\lambda \times \text{time2})}}}{}
\]  

(7)

With our example in Figure 1 and for an MIC = 1 mg/L, a volume of 900 mL/kg, \( F = 0.9 \), \( \lambda = 0.028875 \text{h}^{-1} \) and \( \text{fu} = 1.0 \), we estimated the doses required to achieve various potential partial areas of interest for a scaling factor of 1 to achieve an average plasma concentration equal to the MIC of interest over the selected time interval \( (\text{Time2} - \text{Time1}) \) and to achieve an average plasma concentration equal to five times the MIC of interest over \( \text{Time2} - \text{Time1} \). These are provided in Table 1.

Thus, depending on the average concentration we wish to achieve over a particular time segment, we can use Eqn 7 to estimate the single dose required to meet this target.

Table 1. Oxytetracycline dose computed for various targeted partial AUC and scaling factor (1 or 5) for a pathogen having an MIC of 1 mg/L [the terminal half-life was 24 h (slope = 0.028875 h\(^{-1}\)], \( \text{V/F} = 1 \) and \( \text{fu} = 1 \)]

<table>
<thead>
<tr>
<th>Targeted partial area (h)</th>
<th>Dose (mg/kg) for a given scaling factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>0–24</td>
<td>1.39</td>
</tr>
<tr>
<td>24–48</td>
<td>2.77</td>
</tr>
<tr>
<td>48–72</td>
<td>5.54</td>
</tr>
<tr>
<td>72–96</td>
<td>11.08</td>
</tr>
<tr>
<td>96–120</td>
<td>22.17</td>
</tr>
</tbody>
</table>

For example, if the goal is to achieve an average plasma concentration equal to five times the MIC between 48 and 72 h, the dose should be 27.72 mg/kg. Currently, the recommended dose for a long-acting formulation of oxytetracycline is 20 mg/kg. From this table, it can be deduced that the duration of the action of such a formulation is \( \sim 5 \) days (120 h) if the goal is to achieve a bacteriostatic plasma concentration (scaling factor of 1) over the last 24 h of the claimed duration of action.
We acknowledge that Eqn 7 has been derived for an iv mono-compartmental model and therefore may not be appropriate for drugs whose PKs are best described using a multi-exponential equation. Nevertheless, this equation may serve as a tool for obtaining an initial estimate of the doses needed to assure efficacy based on the average blood concentrations over a specified timeframe.

Once the targeted average concentration over partial areas has been determined, the duration of a treatment for a single-dose administration may be defined as the last 24 h partial area giving some critical value for the scalar. In our example mentioned earlier, we may wish to conclude that for whatever dose is selected, the targeted treatment effect has terminated at the last day for which the scalar is still above 1 (i.e. the last day for which the average daily plasma concentration is at least equal to the MIC). This approach, which enables investigators to consider exposure within some discrete time period, may also be of importance for rapidly reproducing organisms or for drugs associated with rapid killing properties. Depending on the drug and the targeted pathogen, partial AUCs may provide a better pathogen-specific prognostic than a fixed 24 h AUC. In addition, these results can be directly compared with data represented by in vitro kill curves, with the duration of partial AUC adjusted to accommodate the timeframe of the in vitro test.

In conclusion by dividing the AUC/MIC by the time interval of interest, a more universal metric is obtained that can be used not only as a scoring figure (as proposed by Mouton et al.) but also for computation of different doses or alternatively to assess duration of treatment. Most importantly, by using this alternative definition, the same metric can be applied to nearly any dosing regimen that may be used in either human (often targeting steady-state condition) or in veterinary medicine (seldom targeting steady-state condition).

**Transparency declarations**

None to declare.

**References**


