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A Proposal of a Pharmacokinetic/pharmacodynamic (PK/PD) Index Map for Selecting an Optimal PK/PD Index from Conventional Indices (AUC/MIC, \( C_{\text{max}}/\text{MIC} \), and TAM) for Antibiotics

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Summary: A pharmacokinetic/pharmacodynamic (PK/PD) analysis is important in antibiotic chemotherapy. Basically, the \textit{in vivo} efficacy of antibiotics that exert concentration-dependent effects can be predicted using conventional PK/PD indices such as the ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC) and/or the ratio of the maximum plasma concentration to MIC (\( C_{\text{max}}/\text{MIC} \)), whereas that of antibiotics with time-dependent effects can be determined using the period of time for which the drug concentration exceeds the MIC (time above MIC [TAM]). However, an optimal PK/PD index remains to be established for some antibiotics. Thus, a PK/PD model which describes the PK profile and effect of an antibiotic was developed, and the results obtained from this model were interpreted to form a PK/PD index map to assess the optimal PK/PD index for the antibiotic. The findings from the map were generally consistent with clinical outcomes even for the antibiotics which proved to be exceptions to the conventional classification. For example, AUC/MIC was an optimal index for azithromycin despite its time-dependent bactericidal activity, and \( C_{\text{max}}/\text{MIC} \) was a poor index for arbekacin despite its concentration-dependent profile. Thus, the map would be useful for selecting the appropriate PK/PD index for an antibiotic.

Keywords: pharmacokinetics and pharmacodynamics; antibiotics; AUC/MIC; \( C_{\text{max}}/\text{MIC} \); time above MIC

Introduction

For decades, the importance of pharmacokinetic/pharmacodynamic (PK/PD) analysis has been increasing in antibiotic chemotherapy. Understanding the PK/PD relationship, an estimate of \textit{in vivo} efficacy on the basis of plasma concentration, is essential for determining the dosing regimen in clinical use. Historically, the minimum inhibitory concentration (MIC) was considered the principal PD parameter to determine \textit{in vivo} efficacy. However, since antibiotics with the same MIC value can have different bactericidal characteristics, \(^1\) MIC alone cannot predict \textit{in vivo} efficacy.

Antibiotics are generally classified into two groups according to the shape of the time–kill curve. Concentration-dependent drugs exhibit a linear relationship between drug concentration and the killing rate after the administration of a clinically approved dose. Time-dependent drugs have a low maximum killing rate, and the bactericidal activity is independent of drug concentration above the MIC; rather, the exposure time predominantly determines the bactericidal activity. These classifications evolved into the following three PK/PD indices: the \textit{in vivo} effect of concentration-dependent drugs is associated with the ratio of the area under the curve (AUC) to MIC (AUC/MIC) and/or the ratio of the maximum plasma concentration to MIC (\( C_{\text{max}}/\text{MIC} \)), whereas the \textit{in vivo} effect of time-dependent drugs is associated with the time above MIC (TAM). \(^2\) Antibiotics have been conventionally classified into these three categories, usually according to their class.

However, for some antibiotics, the correlation between the identified PK/PD index and the actual clinical efficacy is controversial. For example, for arbekacin, a concentration-dependent aminoglycoside, AUC/MIC data were considered a good predictor, \(^2\) whereas \( C_{\text{max}}/\text{MIC} \) was concluded to be the best index in some studies. \(^3\) For vancomycin, a time-dependent drug, both concentration and the TAM were regarded as predictive indices; \(^7\) conversely, Moise-Broder \textit{et al}. showed that AUC/MIC was the most predictive index. \(^8\) These discrepancies cannot be resolved easily because they necessitate extensive clinical studies.

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To describe and predict the in vivo antibacterial activity more accurately than the conventional approach, the concept of model-based PK/PD analysis has been proposed, in which the time course of the plasma concentration is considered. According to this approach, in addition to MIC, in vitro parameters that are necessary to distinguish between concentration-dependent and time-dependent drugs are incorporated to describe the bactericidal characteristics more precisely. Although the predictability of this model is assumed superior to that of the conventional approach, this model requires modeling and simulation capabilities that may preclude its use from general use. Thus, the goal of this study was to develop a method for this model-based analysis without the use of advanced PK/PD modeling and computer simulation. Here, the PK/PD index map was presented to assess the predictability of conventional PK/PD indices by using the model-based analysis. The PK/PD index map enables the selection of the optimal PK/PD index, requiring only a few parameters, such as the elimination rate constant (ke) and in vitro bactericidal characteristics (ε, γ, and λ). The dosing schedule map was also developed to determine whether once-daily dosing is more effective than divided dosing. These maps were developed with regard to efficacy only; the occurrence of adverse events and the emergence of resistant strains were not considered.

Methods

PK/PD modeling: The PK/PD model consists of 2 units (Fig. 1). The pharmacokinetic unit is a typical 1-compartment model with a gut compartment. The bacterial unit—the time profile of the number of bacteria at the infection site—is essentially identical to the “enhanced-death constant-replication” model described by Czock et al.3 These units are related to each other under the assumption that the free plasma concentration at a certain point in time determines the kill rate of bacteria at the same time.

\[
\frac{dX_1}{dt} = -k_sX_1 \tag{1}
\]

\[
\frac{dX_2}{dt} = k_sX_1 - k_eX_2 \tag{2}
\]

\[
C_{\text{free}} = \frac{f_pX_2}{V_d} \tag{3}
\]

\[
\frac{dN}{dt} = \left(\lambda - \varepsilon \frac{C_{\text{free}}^\gamma}{C_{\text{free}}^\gamma + EC_{50}^\gamma}\right)N \tag{4}
\]

\[
\text{MIC} = \left(\frac{\lambda}{\varepsilon - \lambda}\right)^{\frac{1}{\gamma}} EC_{50} \tag{5}
\]

where kc is the absorption rate constant from the gut compartment to the central compartment; ke is the elimination rate constant from the central compartment; X1 is the amount of drug in the gut compartment; X2 is the amount of drug in the central compartment; Vd is the distribution volume; fp is the free fraction in plasma; Cfree is the plasma concentration of free drug; N is the number of bacteria; λ is the growth rate of bacteria without drug; ε is the maximum kill rate constant; γ is the Hill coefficient, EC50 is the concentration of drug at which 50% of the maximum effect is obtained, and MIC is the minimum inhibitory concentration, which is equal to Cfree when dN/dt = 0.

PK/PD simulation under steady state after repeated dosing: The PK profile of an antibiotic in vivo and the number of bacteria were calculated at steady state from 0 to 24 h in 4 different dosing schedules—one-daily dosing at time 0, twice-daily dosing at times 0 and 12 h, 4 times daily dosing every 6 h, and 8 times daily dosing every 3 h—by numerical integration using the ode23s function of MATLAB (The MathWorks Inc., Natick, MA), which is based on a modified Rosenbrock formula of order 2.4 Initial conditions for the numerical integration were given as follows (Supplemental material 1):

\[
X_1(0) = F \cdot D \cdot \frac{1}{1 - \exp(-k_s\tau)} \tag{6}
\]

\[
X_2(0) = F \cdot D \cdot \frac{k_s}{k_d - k_e} \left\{\frac{\exp(-k_s\tau)}{1 - \exp(-k_e\tau)} - \frac{\exp(-k_e\tau)}{1 - \exp(-k_e\tau)}\right\} \quad (k_a \neq k_e) \tag{7-1}
\]

\[
X_2(0) = F \cdot D \cdot k \cdot \frac{\tau \cdot \exp(-k_r\tau)}{1 - \exp(-k_r\tau)} \quad (k_a = k = k_e) \tag{7-2}
\]

\[N(0) = N_0 \tag{8}\]

where F is the oral bioavailability, D is the oral dose, τ is the dosing interval, and N0 is the number of bacteria at 0 h. X1(0) and X2(0) represent steady-state trough concentrations in the gut compartment and the central compartment, respectively. In most cases, X1(0) was calculated using Eq. (7-1). However, when ke is equal to ka, the denominator of Eq. (7-1) becomes 0, which means that X1(0) cannot be calculated. In such cases, Eq. (7-2) was used instead.

PK/PD index mapping: The dose at which the number of bacteria at 24 h is equal to that at 0 h was determined using the fminbnd function of MATLAB, which is based on golden section search and parabolic interpolation. This dose was defined as the static dose (Dose\text{static,}i), where n is the daily dosing frequency. For each static dose (Dose\text{static,}1, Dose\text{static,}2, Dose\text{static,}4, and Dose\text{static,}8), AUC/MIC was calculated using fixed parameters F, Vd, fp, k_s, k_e, ε, γ, λ, and EC50. Then, AUC/MIC values corresponding to each of the four different dosing schedules were obtained. The ratio of the maximum to minimum among the four values was defined as the index ratio (AUC/MIC) for the parameters F, Vd, fp, k_s, k_e, ε, γ, λ, and EC50. The same calculation was used to determine the index ratios for C\text{max}/MIC and TAM.

Index ratio (AUC/MIC) = \frac{\text{maximum AUC/MIC among the four dosing schedules}}{\text{minimum AUC/MIC among the four dosing schedules}} \tag{9-1}
PK/PD Index Map for Selecting the Best Predictor

Index ratio \( (C_{\text{max}}/\text{MIC}) \)

\[
\frac{\text{maximum } C_{\text{max}}/\text{MIC among the four dosing schedules}}{\text{minimum } C_{\text{max}}/\text{MIC among the four dosing schedules}}
\]

(9–2)

Index ratio (TAM)

\[
\frac{\text{maximum TAM among the four dosing schedules}}{\text{minimum TAM among the four dosing schedules}}
\]

(9–3)

When the index ratio of a PK/PD index approximates 1, the PK/PD index can be regarded as robust, regardless of the dosing schedule. The PK/PD index map was developed by determining the index ratios after varying two selected parameters as described below.

*Effect of varying \( k_a \) and \( k_e \)*

PK/PD index maps were generated by varying \( k_a \) (from 0.1 to 6 h\(^{-1}\)) and \( k_e \) (from 0.05 to 1 h\(^{-1}\)) at 4 different \( \varepsilon - \gamma \) pairs (\( \varepsilon = 3 \text{ h}^{-1} \), \( \gamma = 1 \); \( \varepsilon = 3 \text{ h}^{-1} \), \( \gamma = 3 \); \( \varepsilon = 10 \text{ h}^{-1} \), \( \gamma = 1 \); and \( \varepsilon = 10 \text{ h}^{-1} \), \( \gamma = 3 \)). Other parameters were fixed at the following values: \( F = 1, V_d = 1 \text{ L/kg}, f_p = 1, \lambda = 1 \text{ h}^{-1}, \) and \( EC_{50} = 1 \mu g/\text{mL} \).

*Effect of varying \( \varepsilon \) and \( \gamma \)*

PK/PD index maps were generated by varying \( \varepsilon \) (from 1.5 to 15 h\(^{-1}\)) and \( \gamma \) (from 0.5 to 10) at 4 different \( k_e \) values (0.1, 0.2, 0.5, and 1 h\(^{-1}\)). Other parameters were fixed at the following values: \( F = 1, V_d = 1 \text{ L/kg}, f_p = 1, \lambda = 1 \text{ h}^{-1}, \) and \( EC_{50} = 1 \mu g/\text{mL} \).

**Dosing schedule mapping:** For the static doses of once-daily (\( \text{Dose}_{\text{static,1}} \)) and 4 times daily dosing (\( \text{Dose}_{\text{static,4}} \)), the total daily dose amounts required to achieve the same antibacterial outcome were calculated, and their ratio (\( 1 \times \text{Dose}_{\text{static,1}}/4 \times \text{Dose}_{\text{static,4}} \)) was defined as the dose ratio. When the dose ratio is <1, once-daily dosing requires a smaller amount of antibiotic than 4 times daily dosing to exert the same antibacterial effect, suggesting that a single dose is better than multiple dosing; a ratio >1 suggests that 4 times daily dosing is better. The dosing schedule map was developed by calculating the dose ratios after varying \( \varepsilon \) (from 1.5 to 15 h\(^{-1}\)) and \( \gamma \) (from 0.5 to 10) at 4 different \( k_e \) values (0.1, 0.2, 0.5, and 1 h\(^{-1}\)). Other parameters were fixed at the following values: \( F = 1, V_d = 1 \text{ L/kg}, f_p = 1, \lambda = 1 \text{ h}^{-1}, k_e = 1 \text{ h}^{-1}, \) and \( EC_{50} = 1 \mu g/\text{mL} \).

*Effect of MIC on the calculation of TAM:*

The static dose of each dosing schedule was calculated at 4 different \( k_e \) values (0.1, 0.2, 0.5, and 1 h\(^{-1}\)) under the following conditions: \( F = 1, V_d = 1 \text{ L/kg}, f_p = 1, k_a = 1 \text{ h}^{-1}, \varepsilon = 3 \text{ h}^{-1}, \gamma = 1, \lambda = 1 \text{ h}^{-1}, \) and \( EC_{50} = 1 \mu g/\text{mL} \). MIC was theoretically determined to be 0.5 \( \mu g/\text{mL} \) from the given parameters by using Eq. (5). To investigate the impact of the accuracy of MIC on the calculation of TAM, TAM values at the static doses were calculated using 2 different MIC values around the theoretical value (0.4 and 0.6 \( \mu g/\text{mL} \)).

**Actual data collection:** The plasma concentration of 6 antibiotics on the market (arbekacin, cepditoren, levofloxacin, teipenem, vancomycin, and azithromycin) belonging to different classes (aminoglycoside, cephem, fluoroquinolone, carbapenem, glycopeptide, and macrolide, respectively) were obtained from the package inserts (Package insert of Habekacin® Injections 7th ed. Tokyo, Japan, Meiji Seika Pharma Co., Ltd.; 2011; Package insert of Meiac MS® Tablets 5th ed. Tokyo, Japan, Meiji Seika Pharma Co., Ltd.; 2011; Package insert of Cravit® Tablets 7th ed. Tokyo, Japan, Daiichi Sankyo Company, Limited; 2011; Package insert of Orapenem® Fine Granules 5th ed. Tokyo, Japan, Meiji Seika Pharma, Co., Ltd.; 2011; Package insert of Vancomycin 12th ed. Osaka, Japan, Shionogi & Co., Ltd.; 2009; Package insert of Zithromax® Tablets 18th ed. Tokyo, Japan, Pfizer Japan Inc.; 2013). The elimination rate constant (\( k_k \)) was obtained by fitting the plasma concentration to a 1-compartment model (weight: 1/\( \text{concentration}^2 \)). Parameter optimization was performed using the computer program WinNonlin (version 6.3; Certara, Saint Louis, MO).

In the case of azithromycin, only the data up to 24 h were used because the plasma concentrations up to 72 h did not align well with a 1-compartment model.

**In vitro** antibiotic parameters for arbekacin, cepditoren, levofloxacin, teipenem, and vancomycin were obtained from the literature.\(^{10}\) For azithromycin, the killing profile derived by Den Hollander et al.\(^{11}\) was converted to a time–kill curve. The number of bacteria was transformed to its natural logarithm, and the initial slope of the time–kill curve was plotted against the drug concentration (C). The growth rate of bacteria (\( \lambda \)) was determined from the slope in the absence of drug. Other \( \text{in vitro} \) antibiotic parameters (\( \varepsilon, \gamma, \) and \( EC_{50} \)) were determined by fitting these plots to the following equation.

\[
slope = \lambda - \frac{C}{C^* + EC_{50}}
\]

(10)

**Results**

**PK/PD index mapping:**

*Effect of varying \( k_a \) and \( k_e \) on the index ratio*

The PK/PD index map is shown in Figure 2. According to the flip-flop phenomenon in pharmacokinetics, the \( k_a \) and the \( k_e \) are essentially interchangeable in this pharmacokinetic model analysis. The analysis regarding the case of \( k_e < k_e \) (shown in gray triangles in Fig. 2) can be substituted for the equivalent case by alternating \( k_a \) and \( k_e \) to one another. For each \( \varepsilon - \gamma \) pair, \( k_e \) had a significant effect on the index ratio, whereas \( k_e \) had a marginal influence on the index ratio when \( k_e > k_e \).

*Effect of varying \( \varepsilon \) and \( \gamma \) on the index ratio*

The PK/PD index value is dependent on \( \varepsilon/\lambda \), not their absolute values (Supplemental material 2). Small \( \varepsilon/\lambda \) corresponds to drugs that demonstrated time-dependent antibacterial activity, where saturation of the killing rate occurred at low multiples of the MIC—usually around four to five times the MIC.\(^{12}\) Concentrations above these values did not kill the organisms any faster. Large \( \varepsilon/\lambda \) corresponds to those drugs that demonstrated concentration-dependent characteristics, where bactericidal activity increased with increased concentrations of the antibiotic, across a wide range of concentrations. The PK/PD index can be regarded as a good predictor when the index ratio approximates 1 (shown in red), and a poor predictor when its index ratio is large (shown in pale blue) (Fig. 3). The map suggests that the best PK/PD index is dependent on both \( \varepsilon/\lambda \) and \( \gamma \). The map appeared different with different \( k_e \) values, showing that \( k_e \) is another important factor. This is consistent with the observation from the \( k_e - k_e \) maps in Figure 2. For time-dependent drugs (i.e., small \( \varepsilon/\lambda \)), TAM was always a good predictor, regardless of \( \gamma \) and \( k_e \); if \( k_e \) was low, AUC/MIC was also a good predictor. For concentration-dependent drugs (i.e., large \( \varepsilon/\lambda \)), the predictability of AUC/MIC and \( C_{\text{max}}/\text{MIC} \) was dependent on \( \gamma \) and \( k_e \). Generally, AUC/MIC was a good predictor if \( \gamma \) was small; \( C_{\text{max}}/\text{MIC} \) was a good predictor if \( \gamma \) was large. If \( k_e \) was large, both AUC/MIC and \( C_{\text{max}}/\text{MIC} \) were poor predictors at \( \gamma = 3–4 \).
Fig. 2. Pharmacokinetic/pharmacodynamic (PK/PD) index map (k₀–kₑ plot)
The PK/PD index maps with regard to AUC/MIC, Cmax/MIC, and TAM are depicted, varying k₀ (from 0.1 to 6 h⁻¹) and kₑ (from 0.05 to 1 h⁻¹) at 4 different ε–γ pairs (ε = 3 h⁻¹, γ = 1; ε = 3 h⁻¹, γ = 3; ε = 10 h⁻¹, γ = 1; and ε = 10 h⁻¹, γ = 3). Other parameters were fixed at the following values: F = 1, Vd = 1 L/kg, fₚ = 1, λ = 1 h⁻¹, and EC₅₀ = 1 µg/mL. According to the flip-flop phenomenon of pharmacokinetics, k₀ and kₑ are essentially interchangeable in this pharmacokinetic model analysis. The analysis regarding the case of k₂ < kₚ (shown by the gray triangles) can be substituted for the equivalent case, replacing k₀ and kₑ with one another.

Fig. 3. Pharmacokinetic/pharmacodynamic (PK/PD) index map (ε/λ–γ plot)
The PK/PD index maps with regard to AUC/MIC, Cmax/MIC, and TAM are depicted, varying ε (from 1.5 to 15 h⁻¹) and γ (from 0.5 to 10) at 4 different λ values (0.2, 0.5, and 1 h⁻¹). Other parameters were fixed at following values: F = 1, Vd = 1 L/kg, fₚ = 1, λ = 1 h⁻¹, k₀ = 1 h⁻¹, and EC₅₀ = 1 µg/mL. The parameters of actual antibiotic drugs are from Tables 1 and 2. TAM is not suitable for practical use for a drug with low kₑ (surrounded by the gray rectangle).

Fig. 4. Dosing schedule map (ε/λ–γ plot)
Static daily dose was determined for once-daily and 4 times daily dosing; the ratio was defined as dose ratio. The dose ratios were plotted, varying ε (from 1.5 to 15 h⁻¹) and γ (from 0.5 to 10) at 4 different λ values (0.1, 0.2, 0.5, and 1 h⁻¹) to generate the dosing schedule map. Other parameters were fixed at following values: F = 1, Vd = 1 L/kg, fₚ = 1, λ = 1 h⁻¹, k₀ = 1 h⁻¹, and EC₅₀ = 1 µg/mL. The parameters of actual antibiotic drugs are from Tables 1 and 2.

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PK/PD Index Map for Selecting the Best Predictor

Dosing schedule mapping: The dosing schedule map was developed by plotting the dose ratio. According to the dosing schedule map, the dose regimen was very important for antibiotics with large \( k_e \) (Fig. 4). For time-dependent drugs, divided dosing was strongly recommended. For concentration-dependent drugs, single dosing was preferred if \( k_e \) was large. In contrast, for antibiotics with small \( k_e \), the selection of the dose regimen exerted only a slight influence on the treatment effectiveness.

Effect of MIC on the calculation of PK/PD indices: Small differences in MIC strongly affected the calculated TAM values when \( k_e \) was low and the compound was administered multiple times per day (Fig. 5). For example, if \( k_e = 0.1 \) h\(^{-1} \), the theoretical TAM value (MIC = 0.5 \( \mu \)g/mL) at the static dose for a drug administered 4 times daily (Dose\(_{\text{static,4}}\)) was 54%; the calculated TAM values at Dose\(_{\text{static,4}}\) was 100% and 0% with MIC values of 0.4 and 0.6 \( \mu \)g/mL, respectively. However, if \( k_e = 1 \) h\(^{-1} \) and the drug was administered 4 times daily, the theoretical TAM value (MIC = 0.5 \( \mu \)g/mL) at Dose\(_{\text{static,4}}\) was 50%, and the calculated TAM values were 58% and 46% with MIC values of 0.4 and 0.6 \( \mu \)g/mL, respectively. Conversely, variability in AUC/MIC and C\(_{\text{max}}\)/MIC was always inversely proportional to the variability in MIC.

Comparison between prediction and actual data: Actual antibiotic and pharmacokinetic parameters of 6 antibiotics from different classes are summarized in Tables 1 and 2, and plotted on the PK/PD index maps and the dosing schedule maps. Because maps are provided only for \( k_e \) (Fig. 3 and 4). The PK/PD index map shows that the in vivo effects of cefditoren and tebipenem are associated with TAM, because these compounds lie in the area of good predictor (red color) on the TAM map, and in the area of a poor predictor (blue pale color) on the AUC/MIC and the C\(_{\text{max}}\)/MIC maps (Fig. 3). Similarly, the in vivo effects of arbekacin, levofloxacin, and azithromycin are associated with AUC/MIC. According to the dosing schedule map, divided dosing was better than once daily dosing for cefditoren, tebipenem, and vancomycin (Fig. 4). For arbekacin, the dosing schedule map predicts that divided dosing might have a slightly better outcome. Conversely, administration frequency has only limited influence on the in vivo effectiveness of levofloxacin and azithromycin.

Table 1. In vitro antibiotic parameters

<table>
<thead>
<tr>
<th>Class</th>
<th>Bacterial species</th>
<th>( \kappa A )</th>
<th>( \gamma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbekacin</td>
<td>methicillin-resistant Staphylococcus aureus</td>
<td>2.4–65</td>
<td>0.47–1.14</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>MRSA</td>
<td>2.2, 2.3</td>
<td>2.31, 10.4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>S. pneumoniae</td>
<td>3.1, 3.1</td>
<td>2.61, 2.63</td>
</tr>
<tr>
<td>Tebipenem</td>
<td>S. pneumoniae</td>
<td>2.5, 3.0</td>
<td>2.13, 3.27</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>MRSA</td>
<td>1.3–1.6</td>
<td>0.37–14.0</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>S. pneumoniae</td>
<td>2.58</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Table 2. In vivo pharmacokinetic parameters in humans

<table>
<thead>
<tr>
<th>Dosing amount and route</th>
<th>( k_e ) (h(^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbekacin</td>
<td>200 mg, iv infusion (1 h)</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>200 mg, po</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg, po</td>
</tr>
<tr>
<td>Tebipenem</td>
<td>250 mg, po</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>500 mg, iv infusion (1 h)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg, po</td>
</tr>
</tbody>
</table>

The plasma concentration was obtained from package inserts (Package insert of Habekacin® Injections 7th ed. Tokyo, Japan, Meiji Seika Pharma Co., Ltd.; 2011; Package insert of Meizact MS® Tablets 5th ed. Tokyo, Japan, Meiji Seika Pharma Co., Ltd.; 2011; Package insert of Cravit® Tablets 7h ed. Tokyo, Japan, Daiichi Sankyo Company, Limited; 2011; Package insert of Orapenem® Fine Granules 5th ed. Tokyo, Japan, Meiji Seika Pharma Co., Ltd.; 2011; Package insert of Vancomycin 12th ed. Osaka, Japan, Shinogi & Co., Ltd.; 2009; Package insert of Zithromax® Tablets 18th ed. Tokyo, Japan, Pfizer Japan Inc.; 2013). The elimination rate constant (\( k_e \)) was obtained by fitting the plasma concentration to a 1-compartment model using WinNonlin. For azithromycin, plasma concentrations up to 24 h were used for the calculation.

Discussion

A PK/PD index map was devised to assess the optimal PK/PD index for a given antibiotic with the use of a model-based PK/PD analysis. The map suggests that the elimination rate constant (\( k_e \)) is an important in vivo PK parameter for selecting the relevant PK/PD index; the absorption rate constant (\( k_a \)) also plays a marginal role. Selection of the optimal PK/PD index was also dependent on...
in vitro characteristics, including the ratio of the maximum kill rate constant to the growth rate of bacteria without drug (β/λ) and the Hill coefficient (γ) of the concentration–kill rate curve. The PK/PD classifications by the map were mostly in agreement with convention; TAM is a good index for the in vivo effects of time-dependent drugs, and Cmax/MIC and AUC/MIC are good indices for concentration-dependent drugs. The selection of Cmax/MIC versus AUC/MIC was predominantly dependent on γ.

Our results suggest that indices incorporating MIC must consider the error in the measured value inherent in the method used to derive it, i.e. 2-fold dilution concentration series. Errors in AUC/MIC and Cmax/MIC are always inversely proportional to the error in MIC, irrespective of ke. Conversely, small errors in MIC are amplified in the calculation of TAM when ke is low (Fig. 5). For example, the calculated AUC/MIC and Cmax/MIC always decrease by 33% when the MIC changed from 0.4 to 0.6 µg/mL, irrespective of the dosing frequency and ke. Our simulation demonstrated that the calculated TAM values at Dosestat:4 for a drug with small ke (0.1 h⁻¹) decreased dramatically from 100% to 0% when the MIC changed from 0.4 to 0.6 µg/mL, whereas the reduction was only 12% (from 58% to 46%) for a drug with large ke (1 h⁻¹). Thus, our results suggest that TAM should not be used for a drug with a ke less than 0.2 h⁻¹, even if the drug belongs to the time-dependent category.

The PK/PD index map suggests that the in vivo effects of cefditoren and tebipenem are related more closely with TAM, whereas those of arbekacin, levofloxacin, and azithromycin are associated with AUC/MIC (Fig. 3). These predictions by the map are largely in good agreement with the clinical results, suggesting that the map is fairly reliable (Table 3). Regarding azithromycin, the ke estimated using WinNonlin (0.094 h⁻¹) was quite different from that calculated from the half-life on the package insert (0.011 h⁻¹). This difference can be explained by the different data used to estimate the parameter. The index ratio of AUC/MIC always decreases with a decreasing ke when the values of β/λ and γ are fixed (Fig. 2). According to the PK/PD index map of ke = 0.1 h⁻¹, AUC/MIC is a good predictor for azithromycin (Fig. 3), because the ke of azithromycin is smaller than 0.1 h⁻¹ in either case. There has been some difference between the clinically observed effect and the conventional classification of the antibacterial effect. For example, aminoglycosides have generally been classified in the Cmax/MIC or the AUC/MIC category because they exhibit an obvious concentration-dependent antibiotic profile (large e). However, this is inconsistent with many clinical studies in which in vivo antibacterial effects were similar regardless of the dosing frequency within the same total daily dose, suggesting that the Cmax/MIC is a poor index for aminoglycosides. The PK/PD index map (Fig. 3) indicates that the Cmax/MIC is a poor index for arbekacin, an aminoglycoside, despite its concentration-dependent characteristic. For azithromycin, a time-dependent drug, convention dictates that the in vivo efficacy is dependent on TAM; however the clinical observation shows that the AUC/MIC is a good index. Generally this inconsistency has been attributed to factors like post antibiotic effect (PAE) or sub-MIC effect (SME). However, the PK/PD index map would suggest that AUC/MIC is a good index for a time-dependent drug such as azithromycin, without employing additional factors. These observations suggest that the PK/PD index map can be a better predictor of the antibacterial effect than the conventional classification. Regarding vancomycin, although AUC/MIC and TAM have been identified as predictive indices, the PK/PD index map showed that none of the conventional PK/PD indices seemed to be useful. Since the ke is 0.16 h⁻¹, the TAM cannot be appropriate for practical use as mentioned above. The Cmax/MIC appeared to be a poor index and the AUC/MIC would be of only limited use. Thus, the PK/PD index map deduced that none of conventional PK/PD indices is predictable and the clinical regimen should be decided by a model-based PK/PD analysis on a case-by-case basis.

The PK/PD index map shows that the selection of the PK/PD index is dependent on the ke of antibiotics. It is known that pharmacokinetic parameters show inter-individual variability in humans for various reasons. Drug-drug interactions can also change the pharmacokinetics of antibiotics; for example, concomitant probenecid administration decreases the ke of some cephalosporin antibiotics, primarily by reducing their renal clearance. Renal impairment also accounts for the decreased renal clearance of antibiotics such as ciprofloxacin and levofloxacin. Single nucleotide polymorphisms on the genes encoding metabolic enzymes and transporters may affect the metabolism and excretion of some antibiotics. Pediatric patients may exhibit different pharmacokinetic properties compared to adults. In such cases, a different PK/PD index might have a better correlation with the therapeutic efficacy due to an individual difference in the ke. Since the ke can also have some species differences between experimental animals and humans, a PK/PD index identified in an animal study would not be always applicable to the clinical prediction.

In addition to the PK/PD index map, the dosing schedule map was developed to predict the relative effectiveness of once-daily versus divided dosing (Fig. 4). According to the dosing schedule map, the selection of the dosing regimen has little effect on the clinical outcome for drugs with low ke, such as levofloxacin and azithromycin. In contrast, for drugs with large ke, the dosing regimen exerts a greater influence. The map suggests that divided dosing is better for time-dependent drugs such as cefditoren, tebipenem, and vancomycin. Contrary to convention, divided dosing might be better for a concentration-dependent drug when it has very low γ and high ke. A comparison between the recommendation by the dosing schedule map and the clinical usage is summarized in Table 4. Most of the clinical dosing regimens were consistent with those suggested by the dosing schedule map, supporting the validity of the map.

One limitation of this study is that we only considered the
in vivo effect of antibiotics. Risks such as the occurrence of adverse events and the evolution of resistant strains were beyond our scope because incorporating the quantitative analysis of these risk factors is overly complicated. However, benefits and risks of a drug are considered simultaneously in deciding the clinical dosages and dose regimen. For example, aminoglycosides are known to cause nephrotoxicity.25 Because the trough concentration is associated with the frequency of toxicity, an extended dosing interval is often recommended. Another example is the QT interval prolongation caused by fluoroquinolones,26 in which Cmax is associated with the risk of torsade de pointes in clinical use.27 Antibiotic resistance is also a significant issue posed by antibiotic treatment. The concept of the mutant selection window (MSW) was introduced to optimize the dosing regimens.28 Since drug resistance is acquired within the MSW, the drug concentration should exceed the MSW for a particular duration of the dosing interval.

Another limitation is that these maps are only applicable for antibiotics that induce cell death, because the PK/PD simulation for a particular duration of the dosing interval. Preparation of a PK/PD index map and a dosing schedule map based on different PD models would be beneficial to expand the concept of these maps for a wide variety of drugs.

In summary, a PK/PD index map was proposed to assess the predictability of in vivo efficacy of each PK/PD index. The underlying assumption in deriving the index map was that the bactericidal activity of a drug in vitro is identical to that in vivo. The fact that most of the clinical results show good agreement with the predictions obtained from the map suggests this model analysis is reliable. The map also suggests that the appropriate PK/PD index for each antibiotic is dependent on both in vitro (α and γ) and in vivo PK (k) parameters. Moreover, a dosing schedule map was generated using this model-based analysis to predict whether once-daily or divided dosing is more effective. The PK/PD index map and the dosing schedule map are expected to be a practical guide for optimizing antibiotic therapy, by exploiting the advantages of the model-based analysis without the need for advanced PK/PD modeling and computer simulation.

References

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