Application of PK/PD in New Anti-Infective Drug Development: Current Challenges and Future Perspectives

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Outline

• Summarize PK/PD principles for anti-infective drugs: Current application

• Describe potential application of PK/PD in new anti-infective drug development

• Discuss current challenges and future perspectives
Why is PK/PD information important?

Drug class/MOA
PK characteristics
PD behavior
Dose and regimen

INSTANT

Susceptibility
Resistance mechanisms
MIC

Immunocompetence
Comorbidities
Previous treatment
Colonization

HOST
BUG
DRUG
PK/PD index: Determinant of drug response

PK/PD indices are crucial for understanding the efficacy of antibiotics. Key indices include:

- **Cmax/MIC**: The ratio of peak drug concentration (Cmax) to the minimum inhibitory concentration (MIC).
- **AUC/MIC Ratio**: The area under the concentration-time curve (AUC) divided by the MIC.
- **T>MIC**: The time above the MIC.

These indices help in evaluating the potential effectiveness and dosing of antibiotics. The graph illustrates how these indices are influenced by different drug classes:

- **Aminoglycosides**: Include amikacin, gentamicin, streptomycin.
- **Daptomycin**
- **Metronidazole**
- **Quinolones**: Such as ciprofloxacin, levofloxacin.
- **Macrolides**: Include clarithromycin, azithromycin.
- **Linezolid**
- **Tetracyclines**

The diagram also highlights drugs with specific PK/PD characteristics, such as oritavancin, which is noted for its unique PK properties.

Understanding these indices is essential for optimizing antibiotic therapy and improving patient outcomes.
Identifying the PK/PD index that best correlates with efficacy

- In vitro hollow-fiber system
- Animal model of infection
Determination of PK/PD Target

PK/PD target: The magnitude of PK/PD index required for desired efficacy in animal models of infection.

PK/PD target determined from animal models is used as the target for humans.
Current Utility of PK/PD target

Dose selection for clinical studies:

Target $AUC_{24}/MIC$ Ratio = 30

- **500 mg** ⇒ $AUC_{24} = 40 \ \mu g\cdot hr/mL$
- **200 mg** ⇒ $AUC_{24} = 15 \ \mu g\cdot hr/mL$
- **100 mg** ⇒ $AUC_{24} = 8 \ \mu g\cdot hr/mL$

$MIC = 0.5 \ \mu g/mL$
Current Utility of PK/PD target: Probability of Target Attainment (PTA)

PK/PD target & Human (Patients) PK

Target AUC$_{24}$/MIC Ratio = 5  Dose: 100 mg QD

<table>
<thead>
<tr>
<th>AUC (n=1000)</th>
<th>AUC/MIC (n=1000)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MIC=1</td>
</tr>
<tr>
<td>10 (P1)....</td>
<td>10</td>
</tr>
<tr>
<td>20 (P10)....</td>
<td>20</td>
</tr>
<tr>
<td>30 (P25)....</td>
<td>30</td>
</tr>
<tr>
<td>40 (P40)....</td>
<td>40</td>
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<td>.....</td>
<td>.....</td>
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<tr>
<td>200 (P100)</td>
<td>200</td>
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</tbody>
</table>

% PTA

~100% 99% 90% 60%
Probability of Target Attainment

- To determine susceptibility criteria
- To evaluate the clinical dose proposed
Potential Application of PTA as an Evidence of Drug Efficacy

When a clinical efficacy trial is not feasible or is limited for infections or pathogens of low occurrence,

Quality of data for **PK/PD target** and **human PK simulation** are critical.
PTA as an Evidence of Drug Efficacy: Limitations and Challenges

PK/PD target determined in animal model

- PD endpoints vs. Clinical Response: stasis, 1-log kill, 2-log kill, or survival in animals
- Role of immune system: Immunocompromised animals
- Concentrations in infection sites Animals ≤ Human
PTA as an Evidence of Drug Efficacy: Limitations and Challenges

Human PK simulations

- Monte Carlo Simulation: Observed PK variability
- Different variability b/w healthy subjects vs. patients with infection
  
  $35 \pm 8.5 \text{ (HS)} \text{ vs. } 33 \pm 23 \text{ (Pts)}$

- Covariates of Pop. PK: Comorbidities, Infection itself, and etc
PTA as an Evidence of Drug Efficacy: Future Perspective

- Intensive animal studies with better animal models
- PK/PD target using clinical exposure-response data
- PK, MIC, and clinical outcomes from Phase 2 dose-ranging studies
- PK, MIC, and clinical outcomes from Phase 3 studies: To apply to other infection sites
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