Experiences with MIC-based PK/PD indices in the dose selection of antimicrobial drugs

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Disclaimer

Views presented are those of the speaker and do not reflect official FDA, DHHS or other government opinion or policy.
Outline

• General workflow using MIC-based PK/PD indices
• Implications of MIC-based PK/PD indices
• Concerns and caveats
• Limitations of MIC-based PK/PD indices
  – Pharmacological Consideration
• Potential solutions
• Summary
General Workflow Using MIC-based PK/PD Indices

Identify an appropriate PK/PD index in dose fractionation studies

Determine a PK/PD target value in animal infection models

PTA analysis, select a dose that can cover a target MIC
Implication of MIC-based PK/PD Indices

- Limited supportive evidence for clinical efficacy at high MICs in clinical trials

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Year Approved</th>
<th>Indication</th>
<th>Proposed Target MIC (mcg/mL) by PTA Prediction</th>
<th>Clinical Efficacy at the Proposed Target MIC, n/N (cure/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem and Vaborbactam</td>
<td>2017</td>
<td>cUTI</td>
<td>8</td>
<td>Enterobacteriaceae: 1/1*</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>2017</td>
<td>ABSSSI</td>
<td>0.5</td>
<td>S. aureus, 2/4</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>2015</td>
<td>cIAI/cUTI</td>
<td>8</td>
<td>Escherichia Coli, 0</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>2014</td>
<td>ABSSSI</td>
<td>0.25</td>
<td>S. aureus, 2/2</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>2014</td>
<td>ABSSSI</td>
<td>0.25</td>
<td>S. aureus, 13/17</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>2014</td>
<td>ABSSSI</td>
<td>0.5</td>
<td>S. aureus, 54/55</td>
</tr>
<tr>
<td>Ceftolozane/Tazobactam</td>
<td>2014</td>
<td>cIAI/cUTI</td>
<td>8</td>
<td>P. aeruginosa: 3/4 Enterobacteriaceae: 16/29</td>
</tr>
<tr>
<td>Telavancin</td>
<td>2013</td>
<td>cSSSI, HABP/VABP</td>
<td>2</td>
<td>S. aureus, 0</td>
</tr>
</tbody>
</table>

* Data from MIC=32 mcg/mL

Source: Drugs@FDA
Concerns and Caveats
(current MIC-based PK/PD indices to support dose selection)

• PK components
  – PK from healthy subjects, assuming similar PK;
  – Literature PK values and/or inflated PK variation from the same drug class in the target patient population, e.g., cIAI, cUTI, HABP, VABP.

- fAUC/MIC
- fCmax/MIC
- %fT>MIC

• Body size (obese patients)
• Systemic inflammation
• Critical illness
• Fluid support

- Age
- Disease (cancer patients)
- Chronic renal impairment
- Augmented renal clearance
- Hepatic impairment

- Determined in vitro
- Critical illness
- Hepatic impairment
- Burns
Concerns and Caveats
(current MIC-based PK/PD indices to support dose selection)

• “PD” component
  – MIC, a categorical/ordinal variable

    – MIC value has no correlation with infectious disease severity

    – Variability of MIC assays
      • 2-fold differences in a standard microbiological assay

    – Uncertainty of MIC range that should be included in an animal study.
Concerns and Caveats
(current PK/PD approach to support dose selection)

• Identification of an appropriate PK/PD index is most important.

• Bacterial killing,
  – Net stasis, 1-log reduction, or 2-log reduction
  – Relationship with clinical effectiveness is not clearly known.

• PTA analysis,
  – The PK/PD target value is a single number
    • Confident with median/mean?
    • Same target value for all indications?
  – Is confidence interval on PTA curve helpful for interpretation?

Limitations of MIC-based PK/PD Indices
(Pharmacological Consideration- Case 1)

- Bacterial killing in humans is a combination of drug effect and host immunologic reaction
  - Drug effect and immune response may be additive.
  - Drug action may require the presence of neutrophils.

Limitations of MIC-based PK/PD Indices
(Pharmacological Consideration- Case 2)

• Biofilm formation in chronic infections (e.g., cystic fibrosis, chronic wound infections)

https://microbewiki.kenyon.edu

Antimicrob Agents Chemother 2012 May; 56(5): 2683–2690
Potential Solutions
(Robust PK/PD studies in vitro or in animals)

• Dose fractionation and animal efficacy studies
  – Choose appropriate animal infection models
  – Include a sufficient number of isolates, with some around MIC90

• PTA analysis
  – Identification of PK/PD index
    • If both AUC/MIC and T>MIC are relevant, use both to support each other.
    • Don’t limit evaluation to the traditional indices; try something different/innovative (e.g., AUC/MIC/tau, AUMC/MIC).
  – The PK/PD target value
    • Median (mean), 75th percentile, 95th percentile, from multiple isolates of EACH pathogen.
Potential Solutions
(if PK/PD indices do not work)

• Explore some other PK-PD modeling approaches
  – Mechanism-based PK-PD modeling
    • Meropenem on *Pseudomonas aeruginosa*
  – Semi-mechanistic PK-PD modeling
    • Imipenem/Relebactam on *Pseudomonas aeruginosa*
Sailing with PTA

A- “Let’s just agree they are dolphins, not sharks...”
B- “I will not jump....”

Knowledge to distinguish the fins of sharks and dolphins would save you.

More understanding of your drug could save you.
Always keep in mind:

What you are looking for is the robust evidence to support your dose selection, no matter what PK-PD approach is being used.
Summary

• Value of PK/PD indices has been well recognized in many successful drug development programs.
• In some cases, traditional MIC-based PK/PD indices are not very informative.
• Concerns and caveats should be considered, when PK/PD indices are used.
• ANY reasonable PK-PD modeling approach to support drug development is encouraged.
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