Challenging breakpoints with supranormal dosing: Where is the limit in terms of side effects with higher dosing, and can toxicodynamics help?

Jason A Roberts  B Pharm (Hons), PhD, FSHP
Professor of Medicine and Pharmacy
UQ Centre for Clinical Research & Centre for Translational Anti-infective Pharmacodynamics, The University of Queensland, Australia
Royal Brisbane and Women’s Hospital, Australia
j.roberts2@uq.edu.au
@jasonroberts_pk
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Contents

1. Introduction (PK/PD and dosing)
2. MIC Breakpoints
3. Supranormal dosing?
4. Toxicodynamics
5. How to achieve supranormal exposures
6. Conclusions
Introduction

• Antibiotics: clear exposure:effect relationship
  • Defined by PK/PD

PK-PD Relationship

- dose → concentration → effect

- Optimal PK/PD ratio consistent regardless of MIC
Do PK/PD targets change with increasing MIC?
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Importance of MIC for PK/PD

- Decreased susceptibility of organisms corresponds with an elevated MIC
- Common PK/PD indices:
  - T>MIC
  - Cmax/MIC
  - AUC/MIC
- Standard doses assume low/normal MICs and PK
- Where decreased susceptibility or resistance present, increased doses needed to achieve PK/PD targets
Relevance of MIC

The aim of susceptibility testing and MIC measurement is to predict the likely treatment success or failure of a chosen therapy.

MICs are used to measure the susceptibility of a pathogen to a possible antimicrobial therapy *in vitro*.
- A low MIC indicates higher susceptibility to the antimicrobial.
- A high MIC indicates lower susceptibility and potential resistance to the antimicrobial.

Assumes ‘standard’ dosing regimen.
What are clinical MIC breakpoints?

Clinical Breakpoints:

- Separates strains with MICs from those likely to succeed in treatment from those that are likely to fail
- Takes into account likely drug concentrations/dosing
- **What if we used bigger doses so we could obtain adequate PK/PD against higher MICs?**
Relevance of MIC?

- MICs use a fixed drug concentration to work out susceptibility
- What are the limitations of this? Sources of variation?
  - 2-fold dilution series
  - Visual minimum
  - Assay affected by:
    - Inoculum concentration
    - Incubation time

http://vet360.vetlink.co.za/training/cpd-article-antibiotic-stewardship/
Limitations of accuracy MIC

- Overall bacterial response
- High standard deviation
- Inter-strain Variability
- Biological Variation
**Figure 1.** Schematic MIC distributions. White area, MICs with a WT phenotype as defined by EUCAST; striped area, MICs with a low-level resistance phenotype; black area, MICs with a high-level resistance phenotype. (a) ECOFF = 0.25 mg/L, resistance rare. (b) ECOFF = 0.5 mg/L, resistance common.
This is our big problem with supranormal dosing:

Can we believe the MIC we are targeting?

Table 1. Suggested interpretation of the MIC for target attainment under various conditions

<table>
<thead>
<tr>
<th>MIC found</th>
<th>Interpretation for target attainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within WT, ≤ECOFF</td>
<td>ECOFF</td>
</tr>
</tbody>
</table>
| >ECOFF | MIC + two 2-fold dilutions

*Number of dilutions could be higher or lower than two depending on the proficiency of the lab and the drug–species distribution.
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Drug dosing studies aren’t done in high MIC cases

PK/PD can propose answers to the remaining questions

Titrating to clinical effect won’t work…
Spectrum of organ function

Need for supranormal dose depends on PK and MIC of pathogen
Where might supranormal doses be needed?

- Where PK/PD obtained in registration trials can’t be achieved with standard dosing
- Low PK/PD numerator:
  - Augmented renal clearance
  - Obesity
  - Burns
  - Cystic fibrosis
  - Transplant
  - Extracorporeal circuits etc…
- High PK/PD denominator: High MIC
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Therapeutic window

Different MIC scenarios

![Diagram showing the therapeutic window with concentration on the y-axis and time on the x-axis. The diagram includes areas for toxic concentration, therapeutic concentration, and sub-therapeutic concentration.]
Therapeutic window

Different MIC scenarios

Concentration

Toxic concentration

MIC c

Therapeutic concentration

MIC b

Sub-therapeutic concentration

MIC a

Time
Safety thresholds for various antibiotics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Example toxic thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>AUC &gt;120 mg.h/L</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Cmin &gt;26 mg/L</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>Cefepime (Cmin &gt;20 or &gt;70 mg/L)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Cmin &gt;6 mg/L</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Cmin &gt;6 mg/L</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>AUC &gt; 50 mg.h/L</td>
</tr>
</tbody>
</table>

Toxicity is not likely to be all or nothing above and beyond a defined exposure → problem with regression tree analyses
Toxicity? High doses or high concentrations?

- N=93 ICU patients
- Retrospective analysis of licensed (group A) vs ‘higher-than-licensed’ doses (group B)
- Group B had 40% higher daily doses
- No differences for liver transaminases, cholestatic enzymes, need for CRRT, seizures, thrombocytenemia or neutropenia
- High doses not associated with greater beta-lactam toxicity
High beta-lactam concentrations → neurotoxicity?

- N=199 ICU patients
- Meropenem, Pip/Tazo and Cefepime
- No differences in neurology between antibiotics
- Increased Cmin/MIC associated with worse neurology for meropenem (p<0.01) and pip (p<0.05)
- Cmin/MIC vs altered neurology OR 1.12 (1.04-1.20)

Unclear why MIC was included in exposure in this study?
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<th>PK/PD Target</th>
<th>Preclinical Studies</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentration-dependent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC 80-100, C&lt;sub&gt;90&lt;/sub&gt;/MIC 10-30</td>
</tr>
<tr>
<td><strong>Time-dependent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Maximum killing, resistance suppression</td>
<td>40% T&lt;sub&gt;IBC&lt;/sub&gt;, 16 x MIC C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 6.2</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Maximum killing, resistance suppression</td>
<td>60-70% T&lt;sub&gt;IBC&lt;/sub&gt;</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Maximum killing, resistance suppression</td>
<td>40-50% T&lt;sub&gt;IBC&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Concentration-dependent and time-dependent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 30-100</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 160; AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MPC &gt; 22</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 200</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Maximum killing, resistance suppression</td>
<td>50% T&lt;sub&gt;IBC&lt;/sub&gt;</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 38-442; AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 200</td>
</tr>
<tr>
<td>Colistin</td>
<td>Maximum killing, resistance suppression</td>
<td>AUC&lt;sub&gt;C&lt;sub&gt;90&lt;/sub&gt;/MIC &gt; 7-23</td>
</tr>
</tbody>
</table>

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Table 1: Studies reporting pharmacokinetic/pharmacodynamic indices from preclinical and clinical assessments, by antibiotic class
Achieving higher exposures

• Depends on antibiotic PK/PD
• Depends on drug safety profile
• Higher doses – YES
• More frequent, longer infusions – MAYBE
• Suggested approaches:
  • Dosing nomograms (e.g. meropenem)
  • TDM (+++)
  • Local administration of drug
  • Use of RRT (e.g. aminoglycosides)
Achieving higher exposures

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Nebulised therapy

- Insufficient evidence for VAT or VAP

- Advantages
  - Smaller dose
  - Higher local tissue concentrations
  - Minimum systemic side-effects
  - Rapid onset of action

- Disadvantages
  - Adverse reaction
  - Cost
  - Drug resistance
Serum, ELF and ETA PK post aerosolisation

- New amikacin formulation-device combination
- Pulmonary drug delivery system (PDDDS) – breath synchronised vibrating mesh nebuliser
  - 40-50% dose (droplets) reaches lungs
- Describes serum, ELF and ETA amikacin concentrations post 400mg q12h dose
ELF and ETA amikacin concentrations post aerosolisation

Day 3 amikacin concentration in the alveolar epithelial lining fluid (ELF) of the 28 assessable patients. The dotted line corresponds to 128 μg/mL, which is 10-fold the critical 90% minimum inhibitory concentration (MIC₉₀) for Pseudomonas aeruginosa. T-bars represent the 10th and 90th percentiles; the horizontal line in the box is the median; the lower and upper limits of the box represent the 25th and 75th percentiles, respectively. Circles represent outliers.

Day 3 amikacin concentration in the tracheal aspirates of the 19 assessable patients. H1 to H6 corresponds to the first six hours following the first aerosol, H7 to H12 to the next six hours (before the second aerosol of the day), H13 to H18 to the six hours following the second nebulization, and H19 to H24 to the last six hours of the day, before next aerosol. T-bars represent the 10th and 90th percentiles; the horizontal line in the box is the median; the lower and upper limits of the box represent the 25th and 75th percentiles, respectively. Circles represent outliers.
CSF PK of antimicrobials

- Pathophysiology of meningitis vs ventriculitis
- Penicillin penetration 10-fold higher in meningitis (2% vs 20%)
- Meropenem penetration 4-8-fold higher in meningitis (5% vs 21-39%)
- Vancomycin and daptomycin penetration low,
- Linezolid highly variable
- Fluoroquinolones, tigecycline and metronidazole ‘good’
Intraventricular administration of antimicrobials?

• Low evidence base

• Doses:
  • Vancomycin 50mg daily
  • Tobra/Gentamicin 4-10mg daily
  • Amikacin 5-50mg daily

• TDM of antimicrobial concentrations reported in CSF to confirm target site exposure
Use of RRT for MDR infections?

- 15 ICU patients
- CRRT used to reduce AUC and troughs of amikacin
- Amikacin MIC range 4-16 mg/L
- Max doses 13-67 mg/kg (n=5 >50mg/kg)
Conclusions

• PK/PD determines success of treatment
• In some high MIC cases, supranormal dosing can help, but need to consider:
  • Safety profile of antibiotic
  • PK/PD of antibiotic
  • Can local administration be used
  • Is TDM available to support dosing?
  • What toxicity monitoring should be in place?