Understanding and Interpreting Pharmacokinetic (PK) and Pharmacodynamic (PD) Targets for Antimicrobial Dosing

Back to Basics – a reminder of PK/PD

**PK** describes the movement of drug through the body over time - influenced by its absorption, distribution, metabolism and excretion.

- Physiological factors which can influence this include gastrointestinal conditions, drug/food interactions, renal function, volume of distribution and the site of infection
- Drug factors which can influence this include lipophilicity of the drug, bioavailability and protein binding

**PD** is the study of effect (efficacy and toxicity) once the drug has reached a specified site of action. In the case of antimicrobials this is the ability to kill or inhibit antimicrobial growth once at the site of action.

**Time-dependent versus Concentration-dependent activity**

Different antimicrobials have different mechanisms of action and bactericidal activity characteristics. The efficacy of an antimicrobial is determined by a range of factors including activity and duration of effect at the site of infection (known as the PK-PD indice) and MIC as outlined below.

The PK-PD indices associated with antibacterial activity

- **Time (%T) > MIC** = Time-dependent antimicrobials
  - Effect depends on duration the unbound drug is at concentrations above the MIC
  - Increasing the frequency of dosing or giving via continuous infusion will increase %T > MIC
  - Increasing dose to achieve higher concentrations does not result in greater efficacy once it is above the MIC

- **AUC:MIC** = Concentration-dependent antimicrobials with time dependence
  - Effect is related to the AUC of the unbound drug from 0-24 hours and the MIC

- **Cmax:MIC** = Concentration-dependent antimicrobials
  - Greater killing achieved as the ratio of drug concentration (Cmax) to MIC increases within the therapeutic range
  - Changing the dose will mainly alter the Cmax:MIC and AUC:MIC ratio
  - Larger doses, less frequently improve chances of success
Pharmacodynamic index correlated with maximal efficacy of selected antimicrobials:

<table>
<thead>
<tr>
<th>Antimicrobial / Class</th>
<th>Effect</th>
<th>Distribution</th>
<th>Excretion</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams (includes Carbapenems)</td>
<td>Bactericidal</td>
<td>Low protein binding + hydrophilic</td>
<td>Renal</td>
<td>Time &gt; MIC</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Bactericidal</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>Cmax:MIC &amp; AUC:MIC</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Bactericidal</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>AUC:MIC</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Bacteriostatic</td>
<td>Lipophilic wide distribution</td>
<td>Renal / Non-renal</td>
<td>AUC:MIC</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Bacteriostatic</td>
<td>Lipophilic wide distribution</td>
<td>Hepatobiliary</td>
<td>AUC:MIC</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Bactericidal</td>
<td>Highly protein bound (weak, reversible) + hydrophilic</td>
<td>Renal</td>
<td>Cmax:MIC &amp; AUC:MIC</td>
</tr>
<tr>
<td>Fluoroquinolones (e.g. ciprofloxacin)</td>
<td>Bactericidal</td>
<td>Lipophilic wide distribution</td>
<td>Renal &amp; hepatobiliary</td>
<td>Cmax:MIC &amp; AUC:MIC</td>
</tr>
</tbody>
</table>

Where should we be considering PK/PD?

**Hypoalbuminaemia**
- Leads to more unbound drug available causing temporarily higher drug concentrations
- Is usually associated with ↑ Vd & drug clearance of highly protein bound hydrophilic drugs so free drug is diluted through total body water and rapidly cleared
- Patients may need higher loading & maintenance doses of these antimicrobials

**Renal Function**
- Especially important for hydrophilic antimicrobials which are almost entirely renally cleared
- Vd increased in patients with moderate to severe CKD due to reduced protein binding, increased tissue binding +/or fluid overload
- Impact of dialysis on PK/PD depends on type of dialysis, molecular weight, protein binding and Vd of the drug

**CNS Infections**
- Penetration into CSF determined by molecular size, lipophilicity and protein binding
- ↑ in permeability of blood-CSF/blood brain barrier and ↓ in CSF flow leading to ↑ drug concentrations during inflammation

**Critical Illness**
- Multi-organ failure changes absorption, distribution, metabolism and excretion of drugs
- Changes to pH, protein binding and interstitial fluid shifts affects drug distributions especially of mainly hydrophilic drugs with low Vd

**Obesity**
- This will be covered in a future issue

**Burns**
- Area and depth of burn, presence of sepsis, dehydration & time since injury all affect PK
- Hypometabolic state in first 48hrs post burn due to reduced cardiac output & tissue perfusion & therefore decreased metabolism/clearance of drugs
- Hypermetabolic state after 48hrs resulting in ↑ cardiac output & tissue perfusion hence increased metabolism/clearance of drugs

**References / Further reading:**

Produced by the Central Adelaide Local Health Network (CALHN) Antimicrobial Stewardship Committee

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