Challenges of therapeutic drug monitoring in paediatrics

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Overview

• Outline of the challenges
• Efficient TDM
• TDM in children: why and when?
Challenge #1

A paediatric case

Another paediatric case
Other challenges

- Children don’t like needles &/or are difficult to bleed
- In neonates repeated blood sampling leads to need for blood transfusions
- Ensuring safe dosing for children
  - Using a linear model to extrapolate drug doses from those used in adults doesn’t always work
  - Influence of co-morbidities on drug disposition
  - Inter and intra individual variability in drug disposition
- Inappropriate antibiotic assays are wasteful of resources
EFFICIENT TDM

• Needle avoidance
• Minimise sampling
• Minimise sample size
Children don’t like needles
Solution: don’t use needles?

• Can blood be collected through central venous catheters?
  – Various techniques used
  – None of these have been adequately researched
### Children don’t like needles

**Accuracy of CVC sampling**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>Antibiotic(s)</th>
<th>Method evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al</td>
<td>43 Febrile neutropenia</td>
<td>Gentamicin</td>
<td>Push-pull (repeated aspiration &amp; reinjection)</td>
<td>88% agreement</td>
</tr>
<tr>
<td>Mogayzel et al</td>
<td>28 CF patients</td>
<td>Tobramycin</td>
<td>3 mL saline flush</td>
<td>57% agreement</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10-20 mL saline flush</td>
<td>87% agreement</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>50 CF patients</td>
<td>Vancomycin, Tobramycin</td>
<td>5mL flush + discard</td>
<td>97% concordance</td>
</tr>
</tbody>
</table>
Children don’t like needles
Solution: Minimise number of blood samples

- Review of 104,586 paediatric patients in 40 US hospitals concluded that:

(Vancomycin) Monitoring practices are highly variable in children admitted to pediatric hospitals

- 46% of patients had no monitoring
- No correlation with length of therapy

Monitoring practices in the UK are also highly variable

• Gentamicin (43 NNUs)
  – 10 obtained blood before the second dose
  – 17 obtained blood before the third dose
  – 4 obtained blood before the 2\textsuperscript{nd} or 3\textsuperscript{rd} dose
  – 12 had no policy

• Vancomycin (29 NNUs)
  – 17 different dose/TDM regimens

Source: Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units
Minimising sample volumes

• Commercially available immunoassays have different sample volume requirements
• Insufficient sample size/quality is a problem
  – Compromises accuracy
  – May require repeat venepuncture
  – Delay in result availability
• Little sign that miniaturisation of lab testing (e.g. lab-on-a-chip) is being developed for antibiotic assays
TDM IN CHILDREN: WHY & WHEN?

• Why?
• When?
  o Antibacterials
  o Antifungals
  o Antivirals
Why: inter and intra individual variability in drug disposition

- Volume of distribution often larger in children than in adults: slows clearance of many drugs
- Excretion & elimination may also be altered in children (especially the very young): can change rapidly in the very young &/or a very sick child who is recovering
- Effect of comorbidities on drug disposition and clearance:
  - Cystic fibrosis
  - Burns
  - Parenteral nutrition
  - Cancer
When: antibacterials

• For the β-lactam antibiotics this is less important, because:
  – Lots of experience
  – Wide therapeutic window

• For the aminoglycosides and chloramphenicol TDM is recognised as being important, because of the narrow therapeutic window

• For vancomycin TDM is now recognised as important mainly to ensure that adequate serum concentrations are achieved
Growing problems with antibiotic resistance mean that paediatric formularies now need to include antibiotics for which there are few good PK data on which to base standardised doses:

- Teicoplanin
- Colistin
- Ciproflxacin
When: antifungals

- **Itraconazole**: highly variable absorption
- **Voriconazole**: paediatric patients have a higher capacity for elimination per kilogram of body weight than do adult healthy volunteers
- **Micafungin**: younger children have lower peak plasma concentrations and lower overall exposure. Infants demonstrate even higher micafungin clearance
- **Caspofungin**: dosing by body surface area appears adequate in most cases
When: antivirals

- Aciclovir: PKs may be significantly altered in the very sick
- Ganciclovir: subtherapeutic concentrations are commoner in children than in adults
  - TDM definitely indicated where virological response is poor.
### Do I need to assay?

<table>
<thead>
<tr>
<th>Age of child</th>
<th>Severity of infection</th>
<th>Closeness of MIC to expected tissue/serum concentrations</th>
<th>Risk of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSIDER</td>
<td>ALWAYS</td>
<td>RARELY</td>
<td>CONSIDER</td>
</tr>
</tbody>
</table>
When to assay

• Careful planning is required to ensure that treatment monitoring is optimised
  – Risk of suboptimal treatment whilst awaiting assays must be mitigated against
  – For drug assays that are not commercially available, or only infrequently required, they may not be available locally.
  – Consider how long it takes to reach steady state concentrations
    • Colistin: at least 4 doses
    • Voriconazole: 5 days
Summary

• Insufficient evidence to recommend sampling through CVCs
• Develop and audit local policies for TDM for aminoglycosides and vancomycin
• Careful planning to ensure that other assays are timed correctly
• Ensure that treatment is not interrupted inappropriately whilst awaiting antibiotic assay results