Scaling Renal Function in Neonates and Infants to Describe the Pharmacodynamics of Antibiotic Nephrotoxicity

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Outline

• What does Scaling of Pharmacodynamics mean?

• What is GAVamycin?

• Creatinine Production Rate
• Glomerular Filtration Rate
• Renal Function
  • Disease Progression
  • PD of Gavamycin
Scaling, Maturation, Disease Progression

• Scaling
  • Body mass used to predict body structure and body function differences
  • Allometric theory

• Maturation
  • Describing maturation of structure and function using biological age
  • Applied with allometric theory to account for body mass

• Disease Progression
  • Description of changes in disease status with time
  • Pharmacodynamics may change disease progress
Pharmacodynamic Scaling and Maturation

• Effect Scale (Emax, Slope)

No scaling possible when effect is not related to size
e.g. EEG effects, analgesia, antibiotic action, anti-depressant effect, ..

• Receptor Affinity (C50)
  • Maturation using biological age to young adult values
  • Ageing changes in older adults (probably no real change in affinity – changes more likely related to age associated changes in body function)
GAVamycin

- Gentamicin
- Amikacin
- Vancomycin

- Three similar antibiotics
- Eliminated primarily by the renal route
- Used extensively in neonates and adults
- Standard size and maturation model approach


Data and Key Question

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Location</th>
<th>Principal Investigator</th>
<th>Patients</th>
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<tbody>
<tr>
<td>ALL</td>
<td>Pooled gentamicin, amikacin, vancomycin, GFR</td>
<td>International</td>
<td>Holford &amp; Sherwin</td>
<td>6055</td>
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<td>STDY4</td>
<td>Glomerular filtration rate</td>
<td>International</td>
<td>Rhodin et al. (2009)</td>
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<td>Gentamicin</td>
<td>Salt Lake City</td>
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<td>STDY16</td>
<td>Amikacin</td>
<td>Salt Lake City</td>
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Can this large data set be used to demonstrate adverse pharmacodynamics effects of these antibiotics on renal function?
Renal Function

\[ \text{GFR} = FCLcr \times CLcr = FCLcr \times \frac{CPR}{Scr} \] ; Actual GFR but FCLcr unknown

\[ \text{aGFR} = \frac{aCPR}{Scr} \] ; Apparent GFR with FCLcr=1

\[ \text{GFR} = STDGFR \times FSZ_{GFR} \times FMAT_{GFR} \] ; Normal GFR Size and maturation

Renal function (RF) defined as ratio of apparent GFR to normal GFR

\[ RF = \frac{\text{aGFR}}{GFR} \]

\[ aCPR = \text{apparent creatinine production rate estimated by assuming } CLcr = GFR \]

\[ STDGFR = 6.8 \text{ L/h (119 mL/min) from Rhodin et al (2009) updated with neonatal and child FFM predicted using data from Sumpter & Holford (2012)} \]
Computational Methods

• NONMEM 7.4.1

• gfortran 64 bit

• Wings for NONMEM 742

• R to create WFN VPC
Creatinine Production Rate Size
Creatinine Production Rate Maturation

[Graphs showing the relationship between creatinine production rate and post-menstrual age.]
Glomerular Filtration Rate Size
Glomerular Filtration Rate Maturation
Results CPR and GFR

• **Creatinine Production Rate**
  
  • Allometric size exponent=1, Ffat=0 (size fat free mass).
  
  • Constant up to 44 weeks PMA then linear maturation to 20 years using data of Rhodin et al (2009).

• **Glomerular Filtration Rate**
  
  • Update of Rhodin et al (2009) with better prediction of fat free mass in neonates, infants and children.
  
  • GFR predicted best by fat free mass. No effect of fat mass.

PMA=Post Menstrual Age (estimate of post conception age)
Renal Function Size and Maturation

Graphs showing the relationship between renal function, weight, and post-menstrual age.
Neonatal Renal Function Maturation by Drug

Gentamicin

\[ \text{CPRMAT} = \text{CPR20} + (1 - \text{CPR20}) \times (1 - \exp(-\text{T2CPR} \times (\text{PMA} - 20))) \]

Vancomycin

\[ \text{RF} = \frac{\text{RFDRUG}}{\text{CPRMAT}} \]
Results Renal Function

• Renal Function
  • Renal function (median) close to 1 from infancy to adult (30 y).
  • Unexpectedly high renal function in premature neonates can be explained by adding an additional maturation function for CPR.

• Disease Progress
  • No systematic change in renal function with time.

• Pharmacodynamics
  • No slope effect of exposure (Dose/CL) on progression.
  • No offset effect of exposure relative to baseline renal function.
Conclusion

• Creatinine production rate from premature neonates up to young adults can be calculated using fat free mass and post-menstrual age.

• Maturation of CPR increases rapidly in premature neonates approaching an asymptote at 44 weeks PMA then increases linearly to young adulthood.

• Renal function in patients treated with vancomycin, amikacin or gentamicin is close to 100% at all ages.

• No pharmacodynamic effect of antibiotic exposure (AUC) on renal function progression was detectable.

• Current clinical practice is not associated with a population trend for nephrotoxicity.