Balancing efficacy and reduction in renal function to optimize gentamicin dosing in children with cancer

Carolina Llanos-Paez, Christine Staatz, Stefanie Hennig
Childhood cancer

Every year,

175,000 children are diagnosed with cancer worldwide.

950 children are diagnosed with cancer in Australia.

Every week,

1800 children die from cancer worldwide.

3 children die from cancer in Australia.

https://www.stbaldricks.org

1. Introduction
2. Aims
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Childhood cancer and gentamicin

Infections 85%

Causes of death in patients with ALL during therapy

- Haemorrhage 11%
- Chemotherapy toxicity 4%

Asim. JPMA 2011
Current dosing and clinical exposure targets for gentamicin

- Current initial dose recommendation:
  - Patients < 10 years: 7.5 mg/kg/24 hours
  - Patients ≥ 10 years: 6 mg/kg/24 hours

- Current exposure institution guideline targets:
  - $C_{\text{max}}$ of 25 – 40 mg/L
  - $\text{AUC}_{24}$ of 70 – 90 mg*h/L
Difficulties in dosing gentamicin in paediatric oncology patients

54% of patients do not achieve exposure targets, even after several dose adjustment

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**Introduction**

**Aims**

**Methods**

**Results**

**Summary**

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## Patient demographics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Values (n=475)</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body weight (kg)</td>
<td>25.6</td>
<td>(24.0 – 27.3)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>19.4</td>
<td>(18.3 – 20.5)</td>
</tr>
<tr>
<td>Post-natal age (years)</td>
<td>6.47</td>
<td>(6.38 – 6.56)</td>
</tr>
<tr>
<td>Post-menstrual age (weeks)</td>
<td>376.4</td>
<td>(355.2 – 397.6)</td>
</tr>
<tr>
<td>(GFR_{\text{mat}}) (mL/min)</td>
<td>40.8</td>
<td>(39.1 – 42.6)</td>
</tr>
</tbody>
</table>

\(GFR_{\text{mat}}\): maturation of glomerular filtration rate calculated using equation developed by Rhodin et al.

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**Rhodin Pediatr nephrol 2009**
Population PK model and renal compartment

Dose rate

Peripheral compartment

Q

Central compartment (C)

V_max

K_reabs

Renal compartment (R)

CL

Semi-mechanistic PD model to explore bacterial killing over time

Initial dose

Exposure targets for efficacy

Reduction in renal function

Gentamicin renal accumulation

C_max/MIC = 10

AUC_24/MIC = 100

icacy targets were equally weighted
Exposure targets for efficacy

Figure from Moore et al. and adapted by Standing et al.

MIC = 1 mg/L

Probability of efficacy ($\Psi_{EFF}$) (%)

$C_{max}/MIC$

$AUC_{24}/MIC$

Figure from Kashuba et al.

Standing In PAGE meeting Athens 2011
Moore J infect Dis 1987
Kashuba Antimicrob Agents Chemother 1999


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Gentamicin accumulation in the renal cortex

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Llanos-Paez Antimicrob Agents Chemother, 2017
Gentamicin accumulation in the renal cortex

\[ A_R(t) = -K_{\text{reabs}} \times A_R + V_{\text{max}} \times \frac{C_c}{K_m + C_c} \]
Effect of gentamicin renal accumulation

\[ A_R(t) = -K_{\text{reabs}} \times A_R + V_{\text{max}} \times \frac{C_c}{K_m + C_c} \]

If \( A_R \) (mg) < 42.5 mg \( E_{GFR}(t) = 0 \)

If \( A_R \) (mg) > 42.5 mg \( E_{GFR}(t) = E_{\text{max}} \times \frac{A_R^\gamma}{A_{R50}^\gamma + A_R^\gamma} \)

Llanos-Paez Antimicrob Agents Chemother, 2017

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Reduction in renal function

\[ GFR_{\text{new}}(\text{mL/min}) = GFR_0 - (GFR_{\text{max}} \times \frac{E_{GFR}^\delta}{E_{GFR50}^\delta + E_{GFR}^\delta}) \]

Relative reduction in renal function

Relative change in GFR (rΔGFR) = \[ \frac{(GFR_0 - GFR_{\text{new}})}{GFR_0} \]

Population PK model and renal compartment

Semi-mechanistic PD model to explore bacterial killing over time

Exposure targets for efficacy

Reduction in renal function

\[
\frac{C_{\text{max}}}{\text{MIC}} = 10 \\
\frac{\text{AUC}_{24}}{\text{MIC}} = 100
\]

Gentamicin renal accumulation

Initial dose

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Estimation of an optimal initial gentamicin dose for different microorganism’s MICs using a logit function in NONMEM®

\[
\text{logit}(\Psi_{\text{EFF}}) = \log(\Psi_{\text{EFF}}) - \log(1 - \Psi_{\text{EFF}})
\]

\[
\text{logit}(r\Delta GFR) = \log(r\Delta GFR) - \log(1 - r\Delta GFR)
\]

\[
\mathcal{U}(x, \theta) = \text{logit}(\Psi_{\text{EFF}}(x, \theta)) - \text{logit}(r\Delta GFR(x, \theta))
\]
Semi-mechanistic PD model to explore bacterial killing over time

Population PK model and renal compartment

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Semi-mechanistic PD model to explore bacterial killing over time

Mohamed Antimicrob Agents Chemother 2012
### Results

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Dose (mg/kg)</th>
<th>( \Psi_{\text{EFF}} ) (%) Mean</th>
<th>rΔGFR (%) Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>7.0</td>
<td>91.2</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>8.1</td>
<td>84.0</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>8.4</td>
<td>76.8</td>
<td>1.7</td>
</tr>
<tr>
<td>4</td>
<td>11.2</td>
<td>75.9</td>
<td>3.8</td>
</tr>
</tbody>
</table>

MIC: minimum inhibitory concentration; \( \Psi_{\text{EFF}} \): probability of efficacy; rΔGFR: relative change in renal function
Doses estimated and probability of efficacy

Probability of efficacy ($\Psi_{\text{EFF}}$) (%)

$C_{\text{max}}$/MIC = 10
$AUC_{24}$/MIC = 100

MIC (mg/L)

7.0 mg/kg
8.1 mg/kg
8.4 mg/kg
11.2 mg/kg
Gentamicin renal accumulation

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Simulation from semi-mechanistic PD model

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Summary

- An utility function estimated optimal initial dose of gentamicin balancing probability of efficacy and reduction in renal function.

- An initial dose of 7.0 mg/kg, commonly administered in clinical practice, may not achieve adequate efficacy for microorganisms with a MIC of > 0.5 mg/L.
Acknowledgments

Dr Christine Staatz
Dr Stefanie Hennig
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