Ototoxicity is associated with exposure to Kanamycin & Capreomycin in the treatment of MDR TB

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Background

- MDR and XDR TB burden: cost & mortality
- Aminoglycosides are part of the treatment of drug-resistant tuberculosis
- Concentration-dependent killing
- Adversely affect auditory, vestibular, and renal function
Background

• Risk of ototoxicity of *streptomycin, kanamycin,* and *amikacin* was associated with older age and larger cumulative dose received, but not the size of dose or the frequency.

• Cumulative days of therapy and AUC of *amikacin*: primary predictors of hearing loss.

• *Amikacin/kanamycin*: no correlation with dose (per kg / cumulative), duration, gender, age, BMI, weight, AUC$_{0-24}$, weighted C$_{max}$
  ○ At 8000 Hz: dose correlated with hearing loss
Methods

- Prospective cohort study *(ongoing)*
- Sites: Tanzania, Bangladesh, Russian Federation
- *Inclusion*: MDR TB, receiving capreomycin / kanamycin
- *Exclusion*: pregnant, unable to undergo sample collection / consent / return or contacted for follow up
Methods

- Subjects were enrolled in the hospital and followed for up to 96 weeks
Methods

- Hearing testing:
  - Baseline, 1, 2, and 6 months after initiation of treatment
- Threshold measurements:
  - via air conduction at 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz.
  - via bone conduction at 500, 1000, 2000, and 4000 Hz.

- Ototoxicity: pure tone threshold change (loss) ≥20dB compared to baseline at any frequency.
Methods

• PK samples:

  Weeks 1 2 3 4 5 6 7 8

  1,2,6,12 hr 2,6 hr 2,6 hr

• UF Infectious Disease Pharmacokinetics Lab

• Phoenix WinNonlin v7.0: NCA highest $\text{AUC}_{0-12}$ with corresponding $C_{\text{max}}$ and $t_{1/2}$
Methods

• Pretreatment sputum samples:
  • MIC testing and culture

• Statistical analysis:
  • JMP v13
## Results

- Tanzania data only

<table>
<thead>
<tr>
<th>Baseline characteristics&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N=31 (225 serum samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.6 (20-68)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>52 (31-81)</td>
</tr>
<tr>
<td>Treatment received, n&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>30</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>10</td>
</tr>
<tr>
<td>Total duration of treatment prior to ototoxicity or audit, weeks</td>
<td>24 (2-32)</td>
</tr>
<tr>
<td>MIC, mcg/mL</td>
<td></td>
</tr>
<tr>
<td>Kanamycin&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2 (0.3-10.0)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>0.6 (0.3-2.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> data presented as medians and ranges unless specified; <sup>b</sup> the total exceeds 31 as some patients were switched from one treatment to the other; <sup>c</sup> two patients had MIC of 10 mcg/mL for kanamycin
Results

• Gender vs. Ototoxicity

2 females (22%) vs. 11 males (50%)

p>0.05
Results

• Age\textsuperscript{a} vs. Ototoxicity

no ototoxicity: 33 years (20-48)

ototoxicity: 45 years (27-68)

\[ p = 0.01 \]

\textsuperscript{a} Data presented as median and range
Results

• Weight\textsuperscript{a} vs. Ototoxicity

no ototoxicity: 51 kg (36-81)

ototoxicity: 57.5 kg (31-73)

p>0.05

\textsuperscript{a} Data presented as median and range
Results

• Duration of therapy\textsuperscript{a} vs. Ototoxicity

  no ototoxicity: 24 weeks (2-32)
  ototoxicity: 24 weeks (8-32)

  \( p > 0.05 \)

\textsuperscript{a} Data presented as median and range
Results

- **Capreomycin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Ototoxicity</th>
<th>Ototoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mcg/mL)</td>
<td>24.9</td>
<td>25.7 (8.8-43.5)</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (hr)</td>
<td>2.4</td>
<td>2.7 (2.5-4.2)</td>
</tr>
</tbody>
</table>

  $p > 0.05$

a) Data presented as median and range
Results

- **Capreomycin**

  $\text{AUC}_{0-12} (\text{hr.mcg/mL})$
  - no ototoxicity: 121.2
  - ototoxicity: 197.5 (119.4-227.2)

  $p > 0.05$ (small $N$)

  a) Data presented as median and range
Results

• Kanamycin

\[ \text{Cmax (mcg/mL)} \]
  no ototoxicity: \( 27.8 \ (15.7-65.1) \)
  ototoxicity: \( 36.9 \ (23.9-50.5) \)

\[ \text{t}_{1/2} (\text{hr}) \]
  no ototoxicity: \( 2.4 \ (1.3-5.5) \)
  ototoxicity: \( 2.4 \ (1.6-7.3) \)

\( p>0.05 \)

a) Data presented as median and range
Results

• Kanamycin\textsuperscript{a}

\textbf{AUC}_{0-12} (hr.mcg/mL)

no ototoxicity: 153.5 (72.9-250.6)

ototoxicity: 228.8 (111-334.9)

p=0.03

\textsuperscript{a) Data presented as median and range}
Conclusions

• KM and CM ototoxicity were associated with older age and higher $AUC_{0-12}$

• $C_{\text{max}}$/MIC and $AUC$/MIC: dosing with lower exposure and toxicity

• Ongoing study: target enrollment of 125 MDR each from Tanzania (current N=72), Bangladesh (current N=68), Russia (current N=51)
  • more exposure and toxicity data: better assess other determinants or confounders
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