POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF OFLOXACIN IN SOUTH AFRICAN PATIENTS WITH DRUG-RESISTANT TUBERCULOSIS

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Introduction

OFLOXACIN PK:

• Well absorbed (bioavailability ~ 98%)
• Tmax 1-2 h, prolonged by food
• Half life 4-6 h
• Mainly renal elimination with minimal metabolism (about 5%)
• Active tubular secretion and glomerular filtration (Lode et al, 1987)
• 4-8% in faeces
• Scant data on Pharmacokinetics and pharmacodynamics of ofloxacin in patients with MDR-TB
• Best predictor of in vivo efficacy of ofloxacin is fAUC/MIC

\[ R^2 = 0.82 \]

\[ \text{fAUC/MIC should be} > 100^* \]

*Nuermberger and Grosset, 2004
Methods

Patients: 38 from Cape Town
27 from Durban
MIC data available from 23 Durban patients
35/65 were HIV positive

<table>
<thead>
<tr>
<th></th>
<th>Median (2.5, 97.5 percentile)</th>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>55 (39, 80)</td>
</tr>
<tr>
<td>Lean body weight (kg)*</td>
<td>46 (32, 54)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 (1.34, 1.84)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>34 (20, 63)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>19.3 (13.6, 36.4)</td>
</tr>
<tr>
<td>CrCL (mL/min)**</td>
<td>109 (69, 159)</td>
</tr>
</tbody>
</table>

*Janmahasatian et al., Clin Pharmacokinet 2005; 44:1051-65
** Calculated using standard Cockroft-Gault equation
Treatment regimen:

• included ofloxacin, kanamycin, pyrazinamide, terizidone, ethionamide

• Daily dose of ofloxacin 800 mg
  – Durban on empty stomach
  – Cape Town after meal

PK sampling schedule:

• Durban: 0, 1, 2, 4, 8, 11, 24 h after dose
• Cape Town: 0.5, 3.5, 5.5, 7.5, 12 h after dose
POPULATION PK MODEL, using NONMEM

- Differences in PK sampling schedule may potentially influence absorption parameter estimates between Cape Town and Durban
- Hence, simulation-estimation experiment:
  - Durban absorption parameters but Cape Town sampling schedule
  - 200 replicates
  - Estimated bias and precision of mean transit time
Probability of Target Attainment (PTA)* – the probability that a fAUC/MIC >100 is achieved at a certain concentration*

- Final model was used to perform Monte Carlo simulations in 1000 individuals towards dose optimization
  - AUCs for each simulated individual
  - Multiplied by 0.75 because ofloxacin protein binding is reported to be 25%**
  - Proportion of patients with fAUC/MIC above 100, was estimated, using the distribution of MICs in the subset from Durban
    - PTA calculated using MIC distribution of the patients in Durban

*Mouton et al. 2005, **Lode et al. 1987
Results

Ofloxacin MIC distribution in 23 Durban patients
**Ofloxacin Pharmacokinetic Model**

- **DOSE**: 800 mg

**CENTRAL COMPT**
- $V = 48 \text{ L/46kg of LBW}$
- $Ka = 2.9 \text{ h}^{-1}$
- $Q = 53 \text{ L/h/70 kg of TBW}$
- $GFR \text{ CL} = 4.0 \text{ L/h for 68mL/min CrCL}$

**PERIPHERAL COMPT**
- $V = 41 \text{ L/70kg of TBW}$
- $Q = 53 \text{ L/h/70 kg of TBW}$
- Extra $GFR \text{ CL} = 4.1 \text{ L/h/70kg of TBW}$

- **MTT**: 1.7 h for Cape Town patients
- **MTT**: 0.5 h for Durban patients
- **n**: 6.5
Random effects

<table>
<thead>
<tr>
<th>PARAMETER*</th>
<th>ESTIMATE</th>
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</thead>
<tbody>
<tr>
<td>PPV_CL %</td>
<td>26</td>
</tr>
<tr>
<td>PPV_V central %</td>
<td>33</td>
</tr>
<tr>
<td>PPV_KA %</td>
<td>126</td>
</tr>
<tr>
<td>PPV_MTT %</td>
<td>61</td>
</tr>
<tr>
<td>PPV_CL-V correlation</td>
<td>0.71</td>
</tr>
<tr>
<td>Proportional error %</td>
<td>9.5</td>
</tr>
<tr>
<td>Additive error mg/L</td>
<td>0.55</td>
</tr>
</tbody>
</table>

* PPV – population variability
Visual Predictive Check

Ofloxacin concentration mg/L

Time after dose

CAPE TOWN

DURBAN

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Simulation-estimation

- Bias of MTT was -4% and precision (RMSE) was 28%
- Hence effect of food on MTT could be estimated with good certainty
Ofloxacin elimination

- GFR clearance with CrCL as covariate - lean body weight (LBW)*, instead of total body weight, was used for calculation of CrCL
- extra-GFR clearance (tubular secretion, metabolism, faeces) allometrically scaled to Total Body Weight

Probability of Target Attainment (PTA) \( f_{\text{AUC}}:\text{MIC} > 100 \)

**Ofloxacin Daily DOSE mg** | **True PTA expectation**
--- | ---
800 | 0.64
1200 | 0.84
1400 | 0.90
1600 | 0.93

*True PTA expectation in this case will never reach 1 because 1 patient (4%) had MIC of 8. The rest had WHO cut-off of 2mg/L or less.
Discussion

• The elimination of ofloxacin by glomerular filtration and extra-glomerular means has been quantitatively described

• Although most MDR-TB patients had ofloxacin MICs below the WHO threshold of 2 mg/L, the true PTA was estimated to be only 0.64

• Our results show that, assuming linear PK, a daily dose of 1400 mg daily is necessary to achieve a PTA of 0.9

• The safety of increased doses would need to be evaluated
Limitations

- Protein binding may be concentration dependent* hence fAUC estimates must be cautiously interpreted
- Fraction unbound** reported in German healthy volunteers may differ from South African patients with MDR-TB
- Extrapolation to high doses whilst assuming linear kinetics of renal elimination must be approached with caution

*Shandil et al, 2007, **Lode et al, 1987
Conclusions

- The pharmacokinetics of ofloxacin in South African MDR-TB patients have been elucidated, taking into account glomerular filtration and active tubular secretion as the primary elimination pathways.

- Thirty-six percent of patients failed to achieve the minimum free AUC/MIC ratio of 100.

- Higher doses of ofloxacin should be considered (about 1400 mg) if a more effective fluoroquinolone is not available.
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