Pharmacokinetics of Rifampicin in African Children
Evaluation of the new WHO dosing guidelines

Paolo Denti, Carmen Gonzalez-Martinez, Jana Winckler,
Adrie Bekker, Heather Zar, Gerry Davies,
Annelies van Rie, Helen McIlrnon
Rifampicin

Mainstay of 1-st line TB treatment

Pharmacokinetics:

• Metabolised to desacetyl-rifampicin - which has with lower activity
• Excreted in the bile (unchanged or as desacetyl-rifampicin)

Saturable pharmacokinetics:

Increasing dose yields more than proportional increase in exposure

Promising results from the Panacea studies suggest benefits in significantly increasing the dose beyond the current 10 mg/kg in adults
Simulated AUC for RIFAMPICIN in children given daily 10 mg/kg doses, compared to AUC estimates in adults treated according to current WHO guidelines (8-12 mg/kg doses). New (2010) WHO guidelines:

- RIFAMPICIN +50%: 15 (10-20) mg/kg
Study design and population

n=169 children
3 study sites (2 South Africa + Malawi)
Dosed daily 15 mg/kg (range 10-20)
Samples at 0, 1, 2, 4, 6, 8, 10 hours after dose

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>11 (3.2 - 29)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>2.0 (0.22 - 12)</td>
</tr>
<tr>
<td>HIV+</td>
<td>17 (10%)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>97/72</td>
</tr>
</tbody>
</table>

Two “liquid” formulations used to implement WHO guidelines
  1. Powder to reconstitute in water
  2. Suspension

Youngest children were dosed using a naso-gastric tube
Some early results – Low exposures

Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Recommended Treatment Guidelines

A. Bekker, H. S. Schaaf, H. R. Draper, L. van der Laa, WHO

Department of Clinical Research, Global Alliance
University of Cape Town, Cape Town

Bioavailability of two licensed paediatric rifampicin suspensions: implications for quality control programmes


Division of Clinical Pharmacology, Department of Medicine, and Clinical Research Centre, Health Sciences Faculty, University of Cape Town, Cape Town; Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town; Department of Paediatrics and Child Health, and Medical Research Council Unit on Child and Adolescent Health, University of Cape Town, Cape Town; Red Cross War Memorial Children’s Hospital, Cape Town, South Africa; Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; International Health Unit, Epidemiology and Social Medicine, Faculty of Medicine, University of Antwerp, Antwerp, Belgium
Rifampicin PK model

1 cmpt parent + 1 cmpt metabolite
- Liver hepatic extraction
- Saturable excretion of parent and metabolite
- Non-saturable clearance forming the metabolite
Competitive substrates saturable elimination - Michaelis-Menten

Both RIF and DES-RIF compete for the same transporters for excretion, so both their concentrations drive the saturation.

Using formula for competitive substrates

Type equation here.

Single substrate (concentration is $C_{RIF}$):

$$R_{el}^{RIF} = \frac{V_{max} \cdot C_{RIF}}{K_{m}^{RIF} + C_{RIF}}$$

Two substrates ($C_{RIF}$, $C_{D-RIF}$):

$$R_{el}^{RIF} = \frac{V_{max}^{RIF} \cdot C_{RIF}}{K_{m}^{RIF} \cdot \left(1 + \frac{C_{D-RIF}}{K_{m}^{D-RIF}}\right) + C_{RIF}}$$

The concentration of $C_{DRIF}$, adjusted by its $K_m$ (affinity) changes the $K_m$ of $a$. 
Main results - Rifampicin PK model

• Allometric scaling to adjust for body size
  • using with fat-free mass

• Age on clearance (maturation)

• Age on bioavailability (~75% at birth, increasing up to 3 yrs)

• Suspension formulation with low bioavailability (~35%)

• High correlation between excretion clearance for parent and metabolite, higher affinity for the metabolite

• Strong correlation between error terms of parent and metabolite
Model Fit - Visual Predictive Check

Desacetyl-rifampicin

Rifampicin

Good formulation

Bad formulation

Age > 1 yr

Age < 1 yr

Age > 1 yr

Age < 1 yr

Age > 1 yr

Age < 1 yr

Time after dose [h]
Model Fit

Rifampicin, only reference formulation

Age > 1 yr

Age < 1 yr

Time after dose (h)

Rifampicin (mg/L)
Maturation of excretion and esterase (rate of metabolism)
Effect of Age on bioavailability

Lower bioavailability in infants <3 years

Is due to naso-gastric tube? Is it age per se? Is it due to the formulations used?
Simulated $C_{\text{max}}$ with current WHO doses

$C_{\text{max}}$ target 8 mg/L, Peloquin et al.
Simulated AUC with current WHO doses

Median AUC from meta-analysis in adults ~39 mg·h/L, Stott et al.
Dose escalation in children

Predicted in children

Conclusions

• Improved exposure with new WHO guidelines

• Exposure in younger children still low, reasons unclear
  • Poor absorption?
  • Possibly due to use of NGT and liquid formulations?
  • Or Higher pH in the stomach of younger children?

• Bioequivalence of formulations in children must be ensured
Acknowledgements

Study sites
Anneke Hesseling, Heather Zar, Gerry Davies

UCT clinical pharmacology and Lab:
Maxwell Chirehwa, Lubbe Wiesner, Jennifer Norman, Marilyn Solomons

Pharmacometrics Group at Uppsala University:
Mats Karlsson

Funding:
NIH R01HD069175

Supporting funds: NIH UM1 AI068634, UM1 AI068636, UM1 AI106701, U01 AI068632; AI068632; TB Alliance S003410.