Backterial Co-infections

Tribute to Professor D. J. Back

17th HIVHEPPK Workshop

Mohammed Lamorde MRCP PhD
Infectious Diseases Institute
Makerere University College of Health Sciences
Included
- D J Back
- D Back

Excluded
- Other Backs
The reduction of the enterohepatic circulation of norethisterone by antibiotics in the rat

D.J. BACK, A.M. BRECKENRIDGE, K.J. CROSS, M.L.E. ORME, A. PERCIVAL & P.H. ROWE

Department of Pharmacology & Therapeutics and Medical Microbiology, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

Table 1  Percentage excretion of radioactivity in bile, and bacteriological analysis of gut flora, of recipient rats following intracaelal infusion of labelled conjugates of norethisterone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Excretion</th>
<th>Bacteriological comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>42.4 ± 2.6</td>
<td>Suppression of anaerobes; partial suppression of aerobes.</td>
</tr>
<tr>
<td>Ampicillin (200 mg/kg/day for 4 days)</td>
<td>4.2* ± 0.8</td>
<td>Slight suppression of anaerobes; marked suppression of aerobes</td>
</tr>
<tr>
<td>Neomycin (200 mg/kg/day for 4 days)</td>
<td>13.6* ± 3.3</td>
<td>Marked suppression of anaerobes and aerobes</td>
</tr>
<tr>
<td>Neo. + Linco. (100 + 100 mg/kg/day for 4 days)</td>
<td>4.9* ± 0.33</td>
<td>No effect on anaerobes; marked suppression of aerobes.</td>
</tr>
<tr>
<td>Rifampicin (200 mg/kg/day for 1 day)</td>
<td>8.7* ± 2.0</td>
<td>No effect on anaerobes; some rifampicin resistant aerobes.</td>
</tr>
<tr>
<td>Rifampicin (200 mg/kg/day for 2 days)</td>
<td>10.3* ± 1.3</td>
<td>No effect on anaerobes; increased rifampicin resistant aerobes.</td>
</tr>
<tr>
<td>Rifampicin (200 mg/kg/day for 3 days)</td>
<td>22.2* ± 1.8</td>
<td>No effect on anaerobes; marked rifampicin resistant aerobes.</td>
</tr>
<tr>
<td>Rifampicin (200 mg/kg/day for 4 days)</td>
<td>47.5 ± 5.7</td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different from controls, $P < 0.001$. 

Experiments were performed on the 5th day. The percentage recovery of radioactivity in bile in 6 hours is shown in Table 1. Ampicillin, neomycin and neomycin + lincomycin pretreatment all caused a reduction in the biliary excretion of radiolabelled drug. Following treatment with rifampicin (4 days) there was no significant change in excretion. At the termination of each inves-
# Clinical studies

<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Antibiotic</th>
<th>Effect on contraceptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back, 1979</td>
<td>Rifampicin</td>
<td>Lower norethisterone levels</td>
</tr>
<tr>
<td>Back, 1980</td>
<td>Rifampicin</td>
<td>Lower ethynylestradiol (EE) levels</td>
</tr>
<tr>
<td>Back, 1982</td>
<td>Ampicillin</td>
<td>No effect on EE, levonorgestrel</td>
</tr>
<tr>
<td>Grimmer, 1983</td>
<td>Cotrimoxazole</td>
<td>Increased EE</td>
</tr>
</tbody>
</table>

*Note: N < or = 13 all studies, participants used as their own controls*

Contraceptive efficacy: Rifampicin may increase risk for contraceptive failure. Low risk of contraceptive failure with other antibiotics.

Dickinson BD Obstet Gynecol. 2001 Nov;98(5 Pt 1):853-60
Induction of Influx and Efflux Transporters and Cytochrome P450 3A4 in Primary Human Hepatocytes by Rifampin, Rifabutin, and Rifapentine

Beth Williamson,¹ Kelly E. Dooley,¹ Yuan Zhang,¹ David J. Back,¹ Andrew Owen¹

Department of Molecular and Clinical Pharmacology, The University of Liverpool, Liverpool, United Kingdom; ¹Department of Medicine, Divisions of Clinical Pharmacology and Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA¹
Relative gene expression of cytochrome P450 isoenzyme 3A4 and ABCB1 in primary hepatocytes when incubated with rifampin (RIF), rifabutin (RBT), or rifapentine (RPT) at 0, 0.5, 5, and 10 μM.

Relative gene expression of cytochrome P450 isoenzyme 3A4 and ABCB1 in primary hepatocytes when incubated with rifampin (RIF), rifabutin (RBT), or rifapentine (RPT) at 0, 0.5, 5, and 10 μM.

In 2014, TB killed 1.5 million people
- 1.1 million HIV-negative
- 0.4 million HIV-positive

43 million lives saved since 2000

WHO Global Tuberculosis Report, 2015
Key recommendations

- Treat TB/HIV with rifamycins for the full course of TB treatment (5-7 days per week in intensive phase)
- Efavirenz plus 2 NRTIs is preferred when using rifampicin
- When efavirenz cannot be used nevirapine (without a lead-in) may be considered where options are limited
- Use rifabutin 150 mg daily with boosted protease inhibitor
- Double dose of raltegravir when used with rifampicin

Reference: CDC 2013 Managing Drug Interactions in the Treatment of HIV-Related TB

Semvua HH et al. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Ther Drug Monit. 2015 Feb;37(1):22-32

Yapa HM, Boffito M, Pozniak A. What dose of rifabutin is recommended with antiretroviral therapy? JAIDS 2016 Jun 1;72(2):138-52
Key recommendations

• Treat TB/HIV with rifamycins for the full course of TB treatment (5-7 days per week in intensive phase)
• Efavirenz plus 2 NRTIs is preferred when using rifampicin
• When efavirenz cannot be used nevirapine (without a lead-in) may be considered where options are limited
• Use rifabutin 150 mg daily with boosted protease inhibitor
• Double dose of raltegravir when used with rifampicin

Reference: CDC 2013 Managing Drug Interactions in the Treatment of HIV-Related TB

Semvua HH et al. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Ther Drug Monit. 2015 Feb;37(1):22-32

Yapa HM, Boffito M, Pozniak A. What dose of rifabutin is recommended with antiretroviral therapy? JAIDS 2016 Jun 1;72(2):138-52
Nevirapine dose escalation with rifampicin?

Uganda

Day 7 nevirapine C_{12} ng/mL

Mozambique

CARINEMO RCT for TB/HIV Co-infection

Week 48 VL <50 copies/ml
• NVP (no-lead in) 60%
• EFV 68.4%

Bonnet et al. Lancet ID 2013

<table>
<thead>
<tr>
<th>AUC (0-12) (ng.h/mL)</th>
<th>Day 7</th>
<th>Day 14</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose escalation</td>
<td>25 223 (21 978-29 695)</td>
<td>23 668 (18 253-32 218)</td>
<td>0.01</td>
</tr>
<tr>
<td>Full dose</td>
<td>43 195 (35 607-57 035)</td>
<td>44 918 (36 264-62 769)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Lamorde et al. JAC 2011
Key recommendations

- Treat TB/HIV with rifamycins for the full course of TB treatment (5-7 days per week in intensive phase)
- Efavirenz plus 2 NRTIs is preferred when using rifampicin
- When efavirenz cannot be used, nevirapine (without a lead-in) may be considered where options are limited
- Use rifabutin 150 mg daily with boosted protease inhibitor
- Double dose of raltegravir when used with rifampicin

Reference: CDC 2013 Managing Drug Interactions in the Treatment of HIV-Related TB

Semvua HH et al. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Ther Drug Monit. 2015 Feb;37(1):22-32

Yapa HM, Boffito M, Pozniak A. What dose of rifabutin is recommended with antiretroviral therapy? JAIDS 2016 Jun 1;72(2):138-52
GM steady-state raltegravir plasma concentrations for (a) 400 mg of raltegravir twice daily (day 5), (b) 400 mg of raltegravir twice daily with thrice weekly rifampicin (day 33) and (c) 800 mg of raltegravir twice daily with thrice weekly rifampicin (day 38).

Raltegravir $C_{\text{max}}$ and $\text{AUC}_{0-12}$ significantly higher with rifampicin when dosed at 800 mg twice daily (76% and 84%, respectively) but this dose was well tolerated.
<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Antibiotic</th>
<th>Effect on antimalarial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karbwang, 1990</td>
<td>Ampicillin</td>
<td>Mefloquine AUC N/S increased</td>
</tr>
<tr>
<td>Karbwang, 1992</td>
<td>Tetracycline</td>
<td>Mefloquine AUC N/S increased</td>
</tr>
</tbody>
</table>
**Artemether-lumefantrine and rifampicin**

Artemisinin-combination therapy recommended by WHO for uncomplicated malaria, and parenteral artemisinins for severe malaria

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether</td>
<td>89%</td>
</tr>
<tr>
<td>DHA</td>
<td>85%</td>
</tr>
<tr>
<td>Day 7 lumefantrine</td>
<td>89%</td>
</tr>
</tbody>
</table>

**Conclusion:** Artemether-lumefantrine should not be administered during rifampicin-based TB treatment


Manufacturer included a label change for artemether-lumefantrine to include this contraindication

**NO EVIDENCE-BASED OPTIONS FOR MALARIA TREATMENT WITH ARTEMISININ-COMBINATION THERAPY AMONG PATIENTS ON RIFAMPICIN**
ARTEM-TB Project

Objectives:

- **Group 1 (DHA-PIPERAQUINE):** To investigate the single dose pharmacokinetics (PK) of dihydroartemisinin (DHA) and piperaquine among patients receiving rifampicin and in the same patients after stopping rifampicin intake.

- **Group 2 (ARTESUNATE-AMODIAQUINE):** To investigate the single dose PK of artesunate, DHA and desethylamodiaquine (DEAQ) among patients receiving rifampicin and in the same patients after stopping rifampicin intake.

- **Group 3 (IV ARTESUNATE):** To investigate the single dose PK of intravenous artesunate among patients receiving rifampicin and in the same patients after stopping rifampicin intake.

Clinical Trials Registration: PACTR201302000483287
The potential for interactions between antimalarial and antiretroviral drugs

Saye Khoo, David Back and Peter Winstanley

David, Thank You
Acknowledgements
Ceppie Merry
Kim Scarsi
Catriona Waitt
Jonathan Mayito
Lillian Nabukeera
Mairin Ryan
Marta Boffito
Mohammed Lamorde
Paul Waako
Pauline Byakika-Kibwika
Saye Khoo

Collaborating Institutions
Haughton Institute; Dublin and Trinity College Dublin
University of Liverpool
Mahidol University Thailand

Funding
European and Developing Countries Clinical Trials Partnership
WHO Tropical Diseases Research
Health Research Board, Ireland
Janssen Pharmaceutica
Gilead Foundation
University of Liverpool
HIV Research Trust