Does Rifaximin Chemoprophylaxis Prevent Campylobacteriosis in the Human Challenge Model?

Clayton D. Harro1, Joanna E. Rimmer2,3,4, David A. Sack1, Kawser R. Talata1, Ramiro L. Gutierrez2, Barbara DeNearing1, Chad K. Porter2, Jessica Brubaker1, Alexander C. Maue2, Renee M. Laird2, Frédéric Poly2, Patricia Guerry2, Kayla Jaep2, Ashley Alcala2, David R. Tribble2 and Mark S. Riddle3

1Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 2Enteric Diseases Department, Naval Medical Research Center, Silver Spring, MD, 3School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom, 4Academic Department of Military Medicine, Royal Centre for Defence Medicine (Academia and Research), Medical Directorate, Joint Medical Command, ICT Centre, Birmingham Research Park, B15 2QO Birmingham, UK; 5Infectious Disease Clinical Research Program (IDCRP), Uniformed Services University of the Health Sciences, Bethesda, MD

Conclusion
This study showed no significant difference in the development of the primary endpoint, Campylobacteriosis, between subjects treated with rifaximin or placebo. However, the difference in mean total loose stool output (mL) is significantly reduced in the rifaximin group, and within this group a reduction in the maximum volume of loose stools in 24 hours was also observed. Therefore, whilst rifaximin does not protect against Campylobacteriosis, this objective data relating to stool volume suggests that fluid loss is reduced, and therefore should be considered when evaluating the efficacy of rifaximin in reducing the severity of the burden of disease in all cause bacterial travelers’ diarrhea. Based on the high diarrhea attack rates noted in this human challenge model, the efficacy of rifaximin chemoprophylaxis against campylobacteriosis in a field setting requires further evaluation.

Background
Travelers’ diarrhea (TD) is common; the growing concern regarding post-infectious chronic health sequelae raises the need to consider strategies for primary prevention. Studies have demonstrated field efficacy of rifaximin prophylaxis in prevention of travelers’ diarrhea where diarrheagenic Escherichia coli predominates, as well as in a Shigella human challenge model1. The efficacy of rifaximin as prophylaxis against other invasive pathogens, such as Campylobacter jejuni, remains in question.

Methods
• Design: double-blind, placebo-controlled, randomized (1:1)
• Clinical site: Johns Hopkins Center for Immunization Research
• Primary objective: estimate the efficacy of rifaximin in preventing campylobacteriosis in an experimental C. jejuni infection
• Primary endpoint: campylobacteriosis in 144 hours post-challenge
  • Moderate to severe diarrhea (max 24 hr loose stool output)
  • Severe: > 6 loose stools or > 800 g
  • Moderate: 4-5 loose stools or 401-800 g
  • Fever without diarrhea, with an associated symptom
• Prophylactic treatment (Days -1, 0, 1, 2)
  • Rifaximin (550 mg) BID
  • Placebo BID
• Challenge (Day 0): 1.8×10⁷ C. jejuni, strain CG8421
• Sample size:
  • 28 subjects (1:1) challenged
• Antibiotic treatment:
  • Azithromycin 500 mg daily and Ciprofloxacin 500 mg BID for 5 days
• Discharge: Day 10 (earlier if infection cleared & symptoms resolved)
• Outpatient follow-up: Days 14, 21, 28, 35, 56, 84, 180

Results
• Study population: 28 subjects challenged
  • 71% male
  • 93% African-American
  • Median age: 30
  • 100% of Subjects had C. jejuni CG8421 positive stool
• No difference in campylobacteriosis rate, or the incidence of other clinical signs or symptoms, across study groups (Table 1)
• Lower maximum 24 hour volume and total output by volume of loose stool in the rifaximin group (Table 2, Figures 1 and 2)
• 68% met criteria for early antibiotic treatment
• 18% microbial recrudescence
• Rifaximin: 13.1%
• Placebo: 23.1%

Discussion
The results of this study suggest that Rifaximin does not protect against moderate-severe Campylobacter disease in the human challenge model using C. jejuni strain CG8421 (despite susceptibility to rifamycins, data not shown).

• Zanger et al. found relatively less efficacy in a TD trial among participants to SE Asia where Campylobacter and Salmonella are known to be common pathogens2.
• Rifaximin, a bile soluble antibiotic, is known to have less activity in the colon; the site of infection for this pathogen. Alternative forms, rifamycin SV MMX, may have more activity at this site and may be more effective against colonic infections.
• Given the increasing recognition of post-infectious complications of TD, consideration of a safe and effective chemoprophylactic may be of value in reducing the overall burden of disease.
• More studies on safety (including microbiome and ESBL-PE carriage), and efficacy (against acute disease and chronic consequences) are needed.

Table 1. Symptoms experienced, by group (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n = 13)</th>
<th>Rifaximin (n = 15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacteriosis</td>
<td>84.6</td>
<td>86.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Dysentery</td>
<td>30.8</td>
<td>26.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Abdominal Pain/ Cramps</td>
<td>69.2</td>
<td>73.3</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>38.5</td>
<td>40.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.0</td>
<td>20.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Fever</td>
<td>46.2</td>
<td>46.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 2. Loosen stool output data, by group

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n = 13)</th>
<th>Rifaximin (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number loose stools</td>
<td>18 (11, 23)</td>
<td>12 (7, 18)</td>
<td>0.13</td>
</tr>
<tr>
<td>Max number loose stools/24 hrs</td>
<td>9 (8, 11)</td>
<td>7 (3, 12)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total volume loose stools (mL)</td>
<td>1505 (377, 3833)</td>
<td>1437 (531, 2213)</td>
<td>0.05</td>
</tr>
<tr>
<td>Max volume loose stools/24 hrs (mL)</td>
<td>1063 (946, 1490)</td>
<td>704 (476, 1056)</td>
<td>0.07</td>
</tr>
<tr>
<td>Time to first loose stools</td>
<td>34.0</td>
<td>44.5</td>
<td>0.34</td>
</tr>
<tr>
<td>(hrs)</td>
<td>(24.5, 49.3)</td>
<td>(33.1, 56.4)</td>
<td></td>
</tr>
<tr>
<td>Duration of diarrheal episode</td>
<td>100.4</td>
<td>75.2</td>
<td>0.36</td>
</tr>
<tr>
<td>(days)</td>
<td>(83.5, 113.2)</td>
<td>(71.2, 113.6)</td>
<td></td>
</tr>
</tbody>
</table>

References