The Systemic Pharmacokinetics of Rifaximin in Volunteers with Shigellosis

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ABSTRACT

Rifaximin is an oral antibiotic indicated for travelers’ diarrhea. Rifaximin pharmacokinetics were evaluated in individuals challenged with *Shigella flexneri*. Peak plasma rifaximin concentrations were low after 9 consecutive doses, and no accumulation was observed. Rifaximin serum levels were minimal and similar to those previously reported in studies of healthy volunteers.

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Rifaximin (Xifaxan®, Salix Pharmaceuticals, Inc., Morrisville, NC) is an oral antibiotic with broad spectrum antimicrobial activity that exerts its effect by inhibiting bacterial RNA synthesis (1). Rifaximin is currently approved in the United States for the treatment of travelers’ diarrhea caused by noninvasive strains of *Escherichia coli* at a recommended dose of 200 mg three times daily for 3 days (1). Studies have indicated that <0.4% of rifaximin is systemically absorbed following oral administration (1, 2, 7).

Evaluation of the systemic pharmacokinetics of a single, oral 400-mg dose of ^14^C-rifaximin in 3 healthy male volunteers demonstrated that the majority of radiolabeled drug was recovered unchanged in the feces (97%) and that only a trace amount was excreted in the urine (0.32%) (1). Additional studies in patients with gastrointestinal conditions further support the lack of systemic absorption of rifaximin (4-6). The objective of the present study was to evaluate the pharmacokinetics of rifaximin in individuals challenged with the invasive bacterium *Shigella flexneri* and to determine whether gastrointestinal inflammation in the colon, in response to a microbial pathogen, would have an impact on the pharmacokinetic profile of rifaximin.

This phase 1, single-site, open-label, pharmacokinetic study enrolled healthy male and female volunteers aged 18 to 45 years with no significant medical conditions at screening and no history of abnormal bowel habits or stool patterns. Eligible individuals were admitted to the General Clinical Research Center at Johns Hopkins Hospital on day 0. On day 1, volunteers were challenged with approximately 1500 colony-forming units of *S. flexneri* 2a strain 2457T given orally in sodium bicarbonate buffer (2 g/dose in a total of 150 ml). *S. flexneri* was supplied from a master cell bank fermented and vialed under GMP conditions by the Bioproduction Facility of the Walter
Reed Army Institute of Research. The protocol for this study was approved by the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health and Salix Pharmaceuticals of Morrisville, NC. The trial was carried out in full compliance with Good Clinical Practices guidelines.

At the onset of illness (i.e., diarrhea plus ≥1 enteric symptom), oral rifaximin 200 mg was administered every 8 hours for 3 days for a total of 9 doses. Volunteers remained in the inpatient research facility at least through day 7 to be monitored for signs and symptoms of shigellosis and other adverse events. During rifaximin treatment, volunteers were administered a 3-day course of oral ciprofloxacin 500 mg twice daily to eradicate *S. flexneri* if an individual developed shigellosis and did not respond to 3 doses of rifaximin. Individuals who began ciprofloxacin therapy completed the full 9-dose course of rifaximin. Volunteers were discharged after ciprofloxacin treatment was initiated, clinical assessments were complete, and 2 negative stool cultures for *S. flexneri* were obtained.

Blood samples for evaluation of rifaximin pharmacokinetics were collected on day 1 (pre-challenge); immediately before the 3rd, 5th, 7th, and 9th rifaximin doses; serially at 0.5, 1, 1.5, 2, 4, 6, and 8 hours after the 3rd and 9th doses; and additionally at 12, 16, 20, and 24 hours after the 9th dose. Plasma concentrations of rifaximin were measured by reverse-phase high performance liquid chromatography with tandem quadrupole mass spectrometric detection, with a lower limit of quantitation of 0.5 ng/ml. Subjects were eligible for pharmacokinetic evaluation if they developed shigellosis, they received 9 consecutive doses of rifaximin, and sufficient plasma concentration data were
obtained to determine maximum plasma concentration (C\text{max}) and area under the concentration-time curve from zero to the last measurable time point (AUC\text{0-last}).

Pharmacokinetic parameters were calculated by the model independent approach (noncompartmental analysis) (3) using the WinNonlin Pro software program, version 4.0 (Pharsight Corporation, Mountain View, CA). Both C\text{max} and time to maximum observed plasma concentration (T\text{max}) were calculated, and AUC\text{0-last} was determined using a combination of linear and logarithmic trapezoidal rules. Data summaries and statistical models were generated using SAS version 8.2 for Windows (SAS Institute Inc., Cary, NC). As the AUC\text{0-\infty} and half-life (T\text{1/2}) could not be accurately determined (AUC\text{0-\infty} extrapolated was >40%) for rifaximin, they were not included as part of the statistical analyses.

Fifteen healthy volunteers were enrolled in the study and challenged with S. flexneri. Thirteen individuals met criteria for rifaximin treatment (i.e., developed shigellosis), received at least 1 dose of study medication, and were included in the pharmacokinetic and safety populations: 12 received all 9 doses of rifaximin and 1 received 8 doses. Of the 13 volunteers who received rifaximin, 9 were male (69%) and 4 were female (31%). The mean age of volunteers was 32.5 years (range, 18 to 45 years). All 13 individuals developed \geq 1 symptom of shigellosis; the predominant symptoms were abdominal pain (100%), headache (85%), and diarrhea (77%). Eight volunteers received rescue therapy with ciprofloxacin.

Rifaximin administration did not result in any clinically relevant changes in pharmacokinetic parameters (Table 1 and Fig. 1). After repeated administration of oral rifaximin 200 mg, the mean C\text{max} values for rifaximin were 1.63 ± 0.86 ng/ml on day 1 (3
doses) and 1.23 ± 0.52 ng/ml on day 3 (9 doses). Similarly, no differences were observed on day 1 and day 3 for mean $T_{\text{max}}$ values (2.77 ± 2.24 and 2.11 ± 1.58 h, respectively) or mean $\text{AUC}_{0-\text{last}}$ values (6.95 ± 5.15 and 7.83 ± 4.94 ng • h/ml, respectively), indicating no accumulation of rifaximin. The range of peak plasma rifaximin concentrations was comparable after 3 and 9 consecutive rifaximin doses (0.81 to 3.40 ng/ml and 0.68 to 2.26 ng/ml, respectively), and there were no differences in mean rifaximin plasma concentrations after repeated dosing (Fig. 1A and 1B).

Clinical pharmacokinetic studies conducted in healthy volunteers and in patients with travelers’ diarrhea caused by noninvasive $E. coli$ indicate that rifaximin is poorly absorbed from the gastrointestinal tract and that most of the drug is excreted unchanged in the feces (1, 2). The goal of the current study was to evaluate the potential impact of colonic inflammation caused by a microbial pathogen on the pharmacokinetics of rifaximin. Oral rifaximin administered with the same dosing regimen indicated for travelers’ diarrhea (200 mg three times daily) effectively prevented shigellosis (8). Plasma concentrations and systemic exposure of rifaximin were low during the study. The $C_{\text{max}}$ and $T_{\text{max}}$ values were comparable, indicating no substantial accumulation of drug following repeated administration. Overall, results from the current study demonstrate a lack of systemic absorption of rifaximin in individuals with mucosal inflammation in the colon, findings consistent with published reports demonstrating minimal rifaximin plasma concentrations and lack of drug accumulation (4, 5, 7). There was no apparent difference in rifaximin’s pharmacokinetic profile in this study compared with data from other studies, which further supports a lack of systemic absorption of rifaximin.
Data from this study were presented in abstract form (Trapnell CB, Taylor DN, Montgomery C, Bettenhausen D, Haake R, Pentikis HS. Systemic pharmacokinetics of rifaximin [RFX] in subjects with shigellosis. American Society for Clinical Pharmacology and Therapeutics Annual Meeting, March 2-5, 2005). We thank Dr. T. Larry Hale of WRAIR for providing the challenge strain; Arlene Bloom for coordinating the study; and Gail Kropf, Ruval Comendador, Sabrina Weaver-Drayton, LaNisha Burke, Felipe Troncoso, George Gomes, and the nursing staff of the Johns Hopkins University Hospital General Clinical Research Center for their assistance in conducting this research study.

**Potential conflicts of interest:** Authors R Haake and DN Taylor are employed by Salix Pharmaceuticals, Inc., the marketer of rifaximin in the United States. The research described in this manuscript was funded in part by Salix Pharmaceuticals, Inc., and the National Institutes of Health grant RR-00052. Salix Pharmaceuticals, Inc., also participated in the data analysis through a third party. All other authors have no conflict.
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1. 2007. Xifaxan prescribing information Salix Pharmaceuticals, Inc. Morrisville, NC.


FIGURE LEGEND

FIG. 1. Mean rifaximin concentration-time profiles for the 3rd (A) and 9th (B) consecutive rifaximin doses in 13 healthy volunteers challenged with *S. flexneri*. Upon diagnosis of a case definition of diarrhea, patients were administered oral rifaximin 200 mg every 8 hours for 3 days for a total of 9 doses.
### TABLE 1. Pharmacokinetics of rifaximin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifaximin 200 mg</th>
<th>Rifaximin 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 3</td>
<td>Dose 9</td>
</tr>
<tr>
<td></td>
<td>$n = 12^a$</td>
<td>$n = 13$</td>
</tr>
<tr>
<td>$C_{\text{max}}^b$ (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.63 ± 0.86</td>
<td>1.23 ± 0.52</td>
</tr>
<tr>
<td>Range</td>
<td>0.81–3.40</td>
<td>0.68–2.26</td>
</tr>
<tr>
<td>Median</td>
<td>1.16</td>
<td>1.06</td>
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<tr>
<td>% CV</td>
<td>53.02</td>
<td>42.76</td>
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<tr>
<td>$T_{\text{max}}^d$ (h)</td>
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<tr>
<td>Mean ± SD</td>
<td>2.77 ± 2.24</td>
<td>2.11 ± 1.58</td>
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<tr>
<td>Range</td>
<td>0.50–8.33</td>
<td>0.55–6.00</td>
</tr>
<tr>
<td>Median</td>
<td>1.85</td>
<td>1.52</td>
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<tr>
<td>% CV</td>
<td>80.96</td>
<td>74.84</td>
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<tr>
<td>$\text{AUC}_{0-\text{last}}^e$ (ng · h/ml)</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>6.95 ± 5.15</td>
<td>7.83 ± 4.94</td>
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<tr>
<td>Range</td>
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<td>1.09–19.76</td>
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<tr>
<td>Median</td>
<td>5.69</td>
<td>6.98</td>
</tr>
<tr>
<td>% CV</td>
<td>74.10</td>
<td>63.10</td>
</tr>
</tbody>
</table>

$^a$ Rifaximin concentrations below assay limit of quantitation in 1 individual.
$C_{\text{max}}$, maximum concentration of drug in serum.

$\% \text{ CV}$, percent coefficient of variation.

d$T_{\text{max}}$, time to maximum concentration of drug in serum.

e$\text{AUC}_{0-\text{last}}$, area under the concentration-time curve from 0 to the last measurable time point.
A.

![Graph showing concentration (ng/mL) over time (h) with error bars.](http://aac.asm.org/)