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Safety and Tolerability of the Antibacterial Rifaximin in the Treatment of Travellers' Diarrhoea

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Abstract

Although travellers' diarrhoea can sometimes be associated with postinfectious complications, the condition is typically self-limiting. The infectious-diarrhoea guidelines subcommittees of the Infectious Disease Society of America and the American College of Gastroenterology recommend empirical antibacterial therapy for travellers' diarrhoea. Because therapy is directed largely at relieving symptoms and minimising inconvenience, the chosen antibacterial should ideally be both efficacious and pose a low risk of adverse effects.

This review discusses the safety and tolerability of rifaximin in the treatment of travellers' diarrhoea, with a focus on data from controlled clinical trials. Data were obtained from a MEDLINE search using the key word 'rifaximin' with no date limits and from the rifaximin New Drug Application submitted to the US FDA for approval to market rifaximin in the US.

Currently, the antibacterials considered as standard treatment for travellers' diarrhoea are systemically absorbed, carry defined risks of adverse effects, and have many uses other than the treatment of enteric disease. The minimally absorbed (<0.4%) oral antibacterial rifaximin constitutes a nonsystemic approach to antidiarrhoeal therapy that should overcome some of the limitations of current antibacterials used for travellers' diarrhoea. Rifaximin is differentiated from these, and most other antibacterials, by having a tolerability profile comparable with that of placebo and minimal potential for drug interactions. To date, clinically relevant resistance to rifaximin has not been observed. As the first nonabsorb-

able antibacterial to be marketed for travellers' diarrhoea, rifaximin should help to change the management paradigm for travellers' diarrhoea and other gastrointestinal illnesses from a systemic approach to a predictably safer, nonsystemic approach.

Travellers' diarrhoea, most often caused by exposure to food or water containing pathogenic bacteria such as diarrhoeagenic *Escherichia coli*, *Salmonella*, *Shigella* or *Campylobacter* spp., occurs in up to 50% of individuals travelling from developed countries to developing countries.[1-5] Although it is rarely life threatening, travellers' diarrhoea impacts health and well-being over both the short term and the long term. Acute effects of travellers' diarrhoea include abdominal pain and cramps, fatigue, nausea, vomiting, fever and occasionally dehydration, all of which cause functional disability. For example, one in three individuals with travellers' diarrhoea require bed rest, and one in five are confined to bed for 1–2 days.[2,6,7]

In addition to these acute consequences of travellers' diarrhoea, long-term complications including reactive arthritis, Guillain-Barré syndrome, ischaemic colitis and postinfectious irritable bowel syndrome can occur.[8,9] In view of these potential consequences of travellers' diarrhoea and the fact that the majority of cases are bacterial in origin, the infectious-diarrhoea guidelines subcommittees of the Infectious Disease Society of America and the American College of Gastroenterology recommend empirical antibacterial therapy for the syndrome.[10,11] Antibacterial therapy shortens the duration of illness and disability, and arguably minimises the risk of long-term complications.

Despite the potential for postinfectious complications, travellers' diarrhoea is typically self-limiting; therefore, it should not be managed with antibacterials that pose a significant risk of adverse effects. First, in this context, flouroquinolones such as ciprofloxacin, a current standard of antibacterial care for travellers' diarrhoea, have safety risks that preclude their use in pregnant women and, arguably, young children – two subgroups of patients at risk of complications of infectious diarrhoea and therefore likely to benefit from antibacterial therapy.[12,13] Second, flouroquinolones interact with other commonly used chemicals and medications including caffeine, theophylline and warfarin.[12,13] Finally, quinolone use is associated with widespread bacterial resistance that is rapidly increasing worldwide.[14]

Fluoroquinolone resistance is particularly a problem for *Campylobacter jejuni*, a common cause of travellers' diarrhoea in southeast Asia.[15] Bacterial resistance associated with use of the drugs for travellers' diarrhoea or other illnesses caused by common gastrointestinal pathogens may eventually cause the flouroquinolones to go the way of cotrimoxazole (trimethoprim/sulfamethoxazole), which was previously a diarrhoeal standard of care but became suboptimal for travellers' diarrhoea because of widespread bacterial resistance.[16,17]

Azithromycin has been found to be efficacious in *Campylobacter* disease and travellers' diarrhoea.[18] This agent, which can be used in children and adults with infectious diarrhoea, is a consideration for use in areas of the world where fluoroquinolone resistance is a serious or rising problem. However, the primary clinical utility of azithromycin lies in its efficacy against bacterial pathogens that cause respiratory illness.

The oral antibacterial rifaximin, an agent that undergoes negligible systemic absorption (<0.4%),[19] was introduced to the US in 2004 for the treatment of travellers' diarrhoea caused by noninvasive strains of diarrhoeagenic *E. coli*. Rifaximin constitutes an approach to antidiarrhoeal therapy that should overcome some of the limitations of current antibacterials used for this condition. The concept of using a nonsystemic antibacterial to treat travellers' diarrhoea was previously explored with the poorly absorbed antibacterials bicozamycin and aztreonam, which were found to be efficacious in the treatment of a wide range of enteropathogens

causing travellers' diarrhoea.[20,21] However, bicozamycin is not available for human consumption and aztreonam is only available in parenteral form.

This review discusses the safety and tolerability of rifaximin in the treatment of travellers' diarrhoea, with a focus on data from controlled clinical trials. Data on controlled clinical trials were obtained from a MEDLINE search, initially in June 2003 and updated in January 2005, using the key word 'rifaximin' with no date limits, and from the rifaximin New Drug Application submitted to the US FDA for approval to market rifaximin in the US.

1. Overview of Rifaximin

Rifaximin, a derivative of rifamycin, binds to the β-subunit of bacterial DNA-dependent RNA polymerase to suppress RNA synthesis and ultimately to inhibit bacterial protein synthesis. *In vitro*, rifaximin is active against anaerobic, aerobic, Gram-positive and Gram-negative bacteria including typical diarrhoeal pathogens such as *E. coli* (enterotoxigenic and other strains) and *Shigella*.[16,22-25]

In a series of controlled clinical trials in patients with travellers' diarrhoea,[22,23,26,27] rifaximin was significantly more effective than placebo and at least as effective as ciprofloxacin or cotrimoxazole at reducing the duration of diarrhoeal illness, improving symptoms of travellers' diarrhoea and eradicating causative pathogens. Nineteen additional controlled and open-label studies demonstrate rifaximin to be effective for infectious diarrhoea (including travellers' diarrhoea) in paediatric patients, adults and the elderly.[28-39]

Because it is minimally absorbed,[19] rifaximin is active only within the lumen of the gastrointestinal tract. The broad-spectrum efficacy of rifaximin is reflected in the variety of enteric illnesses and diseases, in addition to travellers' or infectious diarrhoea, for which it has been studied and used. Rifaximin is indicated outside the US for acute and chronic intestinal infections caused by Gram-positive or Gram-negative bacteria, diarrhoea, pre- and postoperative prophylaxis of surgery-associated gastrointestinal infections, and hyperammonaemia associated with hepatic encephalopathy. It has been studied in the US and other countries for peptic ulcer disease, diverticular disease, small bowel/intestinal bacterial overgrowth, ulcerative colitis, Crohn's disease and pouchitis.[25,40]

2. Safety and Tolerability of Rifaximin

This review focuses on data from controlled clinical trials. The primary sources of information about the safety and tolerability of rifaximin comprise adverse event data and other safety results from large, well controlled clinical trials,[22,23,25,26] as well as smaller controlled and open-label stud-

Table I. Controlled clinical trials of rifaximin safety and tolerability in travellers' diarrhoea

Study	Design	Treatment duration (days)	Travel destination	Treatments (no. of patients in safety analyses)
DuPont et al.[22]	Randomised, double-blind, parallel-group, active-controlled	3	Mexico, Jamaica	Rifaximin 400mg bid (n = 93) Ciprofloxacin 500mg bid (n = 93)
DuPont et al.[23]	Randomised, double-blind, parallel-group, active-controlled	5	Mexico	Rifaximin 200mg tid (n = 18) Rifaximin 400mg tid (n = 18) Rifaximin 600mg tid (n = 19) Cotrimoxazole [trimethoprim-sulfamethoxazole] (n = 17)
Steffen et al.[26]	Randomised, double-blind, parallel-group, placebo-controlled	3	Mexico, Guatemala, Kenya	Rifaximin 200mg tid (n = 124) Rifaximin 400mg tid (n = 126) Placebo (n = 129)
Data on file[25]	Randomised, double-blind, parallel-group, placebo-controlled, active-controlled	3	India, Guatemala, Mexico, Peru	Rifaximin 200mg tid (n = 197) Ciprofloxacin 500mg bid (n = 101) Placebo (n = 101)

bid = twice daily; **tid** = three times daily.

Table II. Number (%) of patients reporting adverse events in two placebo-controlled studies of rifaximin 600 mg[25,26] (adverse events reported in ≥2% of patients in a group are listed)

Adverse event	Rifaximin 600 mg/d [n = 320] (%)	Placebo [n = 228] (%)
Flatulence	36 (11.3)	45 (19.7)
Headache	31 (9.7)	21 (9.2)
Abdominal pain	23 (7.2)	23 (10.1)
Rectal tenesmus	23 (7.2)	20 (8.8)
Defaecation urgency	19 (5.9)	21 (9.2)
Nausea	17 (5.3)	19 (8.3)
Constipation	12 (3.8)	8 (3.5)
Pyrexia	10 (3.1)	10 (4.4)
Vomiting	7 (2.2)	4 (1.8)

ies[28-39] and reports of adverse events during more than 17 years of postmarketing experience with the drug in countries other than the US.[25] Besides these sources of safety information, studies have been conducted to examine particular issues such as development of resistance or drug interactions.[25]

2.1 Adverse Events in Clinical Trials

The safety and tolerability profiles of rifaximin in travellers' diarrhoea were assessed in 4 controlled clinical trials (table I) in which 597 patients were randomised to treatment with rifaximin ≥600mg daily and 443 patients were randomised to treatment with placebo,[25,26] ciprofloxacin[22,25] or cotrimoxazole.[23] Treatment duration was 3–5 days depending on the study. The primary measure of tolerability was the incidence of adverse events, which was defined as any untoward medical occurrence regardless of its suspected cause.

The results of the placebo-controlled studies showed that the adverse-event profile of rifaximin did not differ from that of placebo.[25,26] All of the most common adverse events reported with either rifaximin or placebo (e.g. flatulence, abdominal pain) are common symptoms of travellers' diarrhoea and are unlikely to have been caused by the study medication (table II).[25,26]

In the active-comparator studies as well as the placebo-controlled studies, symptoms of diarrhoea were the most common adverse events.[22,23,25,26] For example, headache, dizziness and asthenia were among the most common adverse events in the comparator study with ciprofloxacin.[25] Pooled data from three of the clinical trials[22,23,26] revealed no difference in the incidence of specific adverse events between rifaximin-treated patients and patients receiving other treatments including placebo, ciprofloxacin or cotrimoxazole (table III).[25]

The incidence of adverse events with rifaximin did not clinically significantly vary as a function of age, race or sex in these studies.[25] The adverse event profile of rifaximin in 59 additional studies in which approximately 1800 patients received rifaximin 500–1800 mg/day for 3–21 days for the treatment of infectious diarrhoea, hepatic encephalopathy, inflammatory bowel disease, diverticulitis or prophylaxis of surgery-associated infections was quantitatively and qualitatively similar to that in the travellers' diarrhoea studies.[25]

2.2 Clinical Laboratory Tests

Clinical laboratory tests were performed pre- and post-treatment in the four controlled clinical trials of rifaximin.[22,23,25,26] Across the studies, the incidence of clinical laboratory abnormalities was extremely low regardless of which treatment patients received and did not differ between patients receiving rifax-

Table III. Number (%) of patients reporting adverse events in three controlled studies of rifaximin pooled[22,23,25,26] (adverse events occurring in >2% of patients in a group are listed)

Adverse event	Rifaximin ≥600 mg/d [n = 400] (%)	Comparator[a] [n = 241] (%)
Flatulence	70 (17.5)	42 (17.4)
Abdominal pain	51 (12.8)	24 (10.0)
Headache	50 (12.5)	25 (10.4)
Nausea	43 (10.8)	22 (9.1)
Faecal incontinence	37 (9.3)	20 (8.3)
Tenesmus	34 (8.5)	20 (8.3)
Constipation	19 (4.8)	9 (3.7)
Pyrexia	16 (4.0)	12 (5.0)
Fatigue	13 (3.3)	1 (0.4)
Vomiting	12 (3.0)	6 (2.5)
Dizziness	8 (2.0)	9 (3.7)
Diarrhoea	4 (1.0)	8 (3.3)

a Other treatments were placebo, ciprofloxacin or cotrimoxazole (trimethoprim/sulfamethoxazole).

imin and patients receiving other antibacterials or placebo.[22,23,25,26]

2.3 Postmarketing Experience

Rifaximin has been available in Italy, where it was first introduced, since 1987 and is now approved for use in 17 countries. In postmarketing experience during which approximately 500 million rifaximin tablets have been sold, 19 adverse events that occurred in 11 patients have been spontaneously reported.[25] The most common adverse event was rash (five cases of urticaria, one of pruritus and one of allergic dermatitis). Only one event, a case of urticaria, was considered to be serious because it was associated with prolonged hospitalisation.

Although postmarketing surveillance data should be interpreted cautiously because of factors such as incomplete and poorly reported data and selective reporting, these data reflect a very low rate of spontaneously reported adverse events – particularly considering the extent of exposure to rifaximin. The postmarketing data do suggest that the risk of allergic skin reaction with rifaximin cannot be excluded.

2.4 Drug Interactions

Because it is minimally absorbed, rifaximin is not expected to interact systemically during clinical use with other medications. Theoretically, rifaximin might interact or chelate with other agents in the gut lumen and prevent absorption and bioavailability; however, there are no data or precedents to support this concern. In the four controlled clinical trials in patients with travellers' diarrhoea, the incidence of adverse events with rifaximin did not appear to differ between those taking concomitant medications and those not taking concomitant medications.[22,23,25,26] However, as the latter studies were not specifically conducted to assess drug interactions, the data cannot be used to draw definitive conclusions about the potential for drug interactions with rifaximin. *In vivo* drug interaction studies demonstrate that rifaximin (2–200 ng/mL) did not inhibit a range of human hepatic cytochrome P450 (CYP) isozymes.[25] In addition, clinical interaction studies demonstrated no presystemic or systemic interaction between rifaximin and midazolam, a CYP3A4 substrate.[41] Rifaximin also did not affect the presystemic metabolism of an oral contraceptive containing ethinylestradiol and norgestimate in a clinical study.[42]

2.5 Resistance

To date, rifaximin has not been associated with the development of clinically relevant resistance.[43] Across two studies in which patients with travellers' diarrhoea were administered rifaximin for 3–5 days, minimum inhibitory concentrations (MICs) of post-treatment bacterial isolates did not increase relative to pretreatment MICs.[22,23,25] These results show that bacteria remain susceptible to rifaximin even immediately after a course of therapy.

Rifaximin also appears not to induce resistance in enteric flora. The development of rifaximin- and rifampicin-resistant intestinal coliforms was studied in 27 subjects receiving rifaximin by plating stool samples on media containing rifaximin or rifampicin before treatment (day 0), after a 3-day course of rifaximin (day 3) and after an additional 2 days (day 5).[44] The susceptibility of enterococci grown on day 0 and day 3 was also studied in 71 subjects. Significant increases in antimicrobial-resistant coliform flora were not observed in samples from either rifaximin-treated subjects or placebo-treated subjects and enterococci showed similar susceptibilities before, compared with after, a course of rifaximin treatment.

On the basis of data collected to date, rifaximin does not appear to be associated with cross resistance to other members of the rifamycin class.[45]

Considered in aggregate, the data suggest that: (i) use of rifaximin for travellers' diarrhoea does not pose a clinically significant risk of development of resistance; (ii) that resistance, when it does develop, is nonpersistent; and (iii) that the drug is not likely to contribute to the public health threat posed by growing bacterial resistance.

3. Conclusions

Rifaximin, a gut-selective, minimally absorbed (<0.4%) antibacterial indicated for the treatment of

travellers' diarrhoea, has a tolerability profile comparable with that of placebo in clinical trials and minimum potential for drug interactions. To date, clinically relevant resistance has not been observed with rifaximin. Such a profile is especially reassuring for an illness that patients self-treat. The first nonabsorbable antibacterial to be marketed for travellers' diarrhoea, rifaximin may help to change the management paradigm for this and other gastrointestinal illnesses from a systemic approach to a safer, nonsystemic approach.

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