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Rifaximin—a novel antimicrobial for enteric infections☆

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Summary Rifaximin is a poorly absorbed rifamycin antimicrobial drug with in vitro activity against Gram-positive, Gram-negative and anaerobic bacteria. The minimal concentration that inhibits 90% of strains of bacterial pathogens (MIC_{90}) ranges between 32 and 64 μg/ml. Less than 1% of the drug is absorbed after oral administration. After three days of therapy, the average fecal level of this drug is 8000 μg/g of stool. Selection of resistant mutants, a problem with the related rifampin, appears to be unusual with rifaximin. Rifaximin shortens the duration of travelers' diarrhea and non-dysenteric diarrheal illness due to enterotoxigenic, enteroaggregative *E. coli* and *Shigella sonnei* without major alteration of aerobic fecal flora and without important side effects. The drug has been successfully used in preliminary studies of small bowel bacterial overgrowth syndrome and hepatic encephalopathy. To explain the beneficial effect of the drug on bacterial diarrhea without change in colonic flora or high rates of pathogen eradication, rifaximin may be more active against pathogens in the small bowel rather than the colon and/or the drug may alter the virulence of enteric pathogens in addition to organism inhibition.

Travelers' diarrhea

Diarrhea is the most common illness among persons traveling from industrialized to developing countries. Among persons venturing into high-risk areas, 40% will contract travelers' diarrhea due to exposure of enteropathogen-contaminated food or less commonly contaminated water. The most common definable causes of travelers' diarrhea in all tropical and semitropical areas are pathogenic bacteria such as diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli* and enteroaggregative *E. coli*), *Shigella* spp., *Salmonella* spp. and *Campylobacter* spp., accounting for more than half of the illness and possibly up to 80% of cases.[1–3]

While travelers' diarrhea is not fatal, the consequences of travelers' diarrhea are important and include impaired functional ability with decreased quality of life of the traveler as a result of physical distress and disruption of scheduled activities.[4] The illness results in financial cost to the

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traveler and lost income for the host countries because of failed business and pleasure travel because of the well known threat of illness to travelers.[5,6] It is now recognized that persistent diarrhea follows a bout of travelers' diarrhea in at least 2% of cases.[7] Irritable bowel syndrome (IBS) is increasingly being recognized with post-infectious diarrhea and occurs in 4–10% of travelers who earlier developed acute diarrhea in the country of risk.[8,9] Other chronic complications of travelers' diarrhea occasionally may occur as with other forms of bacterial diarrhea, such as reactive arthritis with *Salmonella*[10] and Guillain–Barré Syndrome from *Campylobacter* infection.[11]

From the United States, practice guidelines from the American College of Gastroenterology and the Infectious Diseases Society of America (IDSA) have indicated that persons traveling from industrialized to developing countries should carry antibacterial drugs for self-treatment because of the high likelihood of a bacterial cause of travelers' diarrhea and the value of the drugs in shortening illness.[12,13]

With the emergence of widespread bacterial resistance, antimicrobials with previous value now have a limited role as effective therapy of travelers' diarrhea.[14,15] Ampicillin and trimethoprim-sulfamethoxazole are no longer effective in treating bacterial diarrhea and resistance to ciprofloxacin, the most commonly employed fluoroquinolone for bacterial diarrhea, is occurring among bacterial pathogens, especially *Campylobacter*.[15,16] Ciprofloxacin-resistance is particularly common in Thailand among prevalent strains of *Campylobacter* spp., making treatment recommendations more complicated for illness occurring in this country.[15] In the case of ciprofloxacin-resistant *Campylobacter* spp., azithromycin, an azalide antibiotic related to the macrolides, has been shown to be an effective agent for the management of diarrhea in US servicemen stationed in Thailand.[15,17] Also, in a recent clinical trial, azithromycin 1000 mg per day has shown to be equivalent to levofloxacin 500 mg per day administered for 1–3 days in shortening the duration of travelers' diarrhea.[18] Macrolide resistance in *Campylobacter* strains isolated in Thailand and Europe has been reported and may increase with the use of this class of drugs as well as the azalides. With increasing resistance by commonly used drugs, new agents are needed for treatment of the more severe cases of illness among international travelers. An ideal therapeutic agent for the treatment of travelers' diarrhea and other localized bacterial enteric infections include being: (1) a poorly absorbed drug with little value outside enteric infections which would limit general use; (2) active against a broad range of bacterial enteropathogens; and (3) safe for use in young children and pregnant women.[19] An effective, poorly absorbed drug, while likely to be active against gastrointestinal pathogens, would pose a limited public health problem if widespread use encouraged resistance, since the drug would be without value for important extra-intestinal infections.

A promising antimicrobial that best meets the three criteria for an ideal therapeutic agent for the treatment of travelers' diarrhea and enteric bacterial infections is the oral antimicrobial rifaximin.[20] In this review, we discuss the recent advances of rifaximin, in vitro activity against bacterial enteropathogens, the pharmacokinetics, clinical trials, and indications and safety with the use of rifaximin in enteric infections including travelers' diarrhea.

Drug class and mechanism of action

Rifaximin was first available in Italy in 1987 and since has been approved for use in 13 countries. Rifaximin is a semisynthetic derivative of rifamycin with trade names in various countries that include Xifaxan, Normix, Flonorm, Redactiv, Zaxine, Rifacol and Spiraxin. Unlike other rifamycin agents, rifaximin possesses an additional pyridoimidazole ring (Fig. 1), which makes it minimally absorbable. Of the rifamycin class, rifampin is the best known where the drug is used together with other drugs in the therapy of tuberculosis and Gram-positive bacterial infections. Rifampin and rifaximin both have the same mechanism of action by binding the beta subunit of the bacterial DNA-dependent RNA polymerase to suppress the initiation of chain formation in RNA synthesis.

In vitro activity against enteric bacterial pathogens

Traditionally, minimal inhibitory concentration (MIC) breakpoints to determine bacterial pathogen susceptibility to antibacterial drugs have been defined in reference to the concentration of drug in plasma. For rifaximin, an unabsorbed drug, clinically relevant and bioavailable gut concentrations of drug achieved should be more relevant where serum levels will be undetectable. While rifaximin achieves very high fecal levels of drug after oral administration, the non-absorbable and reduced aqueous solubility of the drug affect pharmacokinetics and bioavailability.