Rifaximin therapy for metronidazole-unresponsive *Clostridium difficile* infection: a prospective pilot trial

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Abstract:

Background: *Clostridium difficile* infection (CDI) is a recent epidemic in the United States, particularly in the hospital setting. Oral metronidazole is standard therapy for *C. difficile* infection, but resistance to metronidazole is becoming a clinical challenge.

Methods: We evaluated the efficacy of the nonsystemic oral antibiotic rifaximin for the treatment of metronidazole-resistant *C. difficile* infection. Twenty-five patients with *C. difficile* infection were enrolled in the study. All had mild-to-moderate *C. difficile* infection (5–10 bowel movements a day without sepsis) unresponsive to metronidazole (i.e. stools positive for toxins A and B after oral metronidazole 500 mg three times daily [t.i.d.] for 5 days). After discontinuation of metronidazole, rifaximin 400 mg t.i.d. for 14 days was prescribed. Patients were followed for 56 days and stool was tested for *C. difficile* using polymerase chain reaction (PCR) to assess the effect of treatment. A negative PCR test result was interpreted as a favorable response to rifaximin.

Results: Sixteen of 22 patients (73%) were eligible for study inclusion and completed rifaximin therapy experienced eradication of infection (stool negative for *C. difficile*) immediately after rifaximin therapy and 56 days post-treatment. Three patients (12%) discontinued therapy because of abdominal distention. Rifaximin was generally well tolerated.

Conclusions: In conclusion, rifaximin may be considered for treatment of mild-to-moderate *C. difficile* infection that is resistant to metronidazole. Larger randomized trials are needed to confirm these positive findings.

Keywords: *Clostridium difficile* infection, metronidazole, resistant, rifaximin

Introduction

Clostridium difficile infection (CDI) is the most common cause of hospital-acquired diarrhea and is responsible for approximately 15–30% of all cases of antibiotic-associated diarrhea [Muto *et al.* 2005]. The incidence [McFarland *et al.* 2007; Muto *et al.* 2005; Pépin *et al.* 2004] and severity [McFarland *et al.* 2007; Muto *et al.* 2005; Pépin *et al.* 2004] of nosocomial CDI has been increasing in recent years despite rigorous infection control guidelines in hospitals [McFarland *et al.* 2007]. Increased frequency of CDI has been reported in US veterans administration facilities, with approximately 5.1 CDIs occurring per 1000 discharges in 1994 compared with 13.5 cases per 1000 discharges in 2004 [McFarland *et al.* 2007]. The incidence of *C. difficile* infection

is also increasing in Canada, with 35.6 cases reported per 100,000 people in 1991 compared with 156.3 cases per 100,000 in 2003 [Pépin *et al.* 2004]. In addition to incidence, the severity of CDI is escalating. CDI with severe outcomes increased from 5.6% in 1999 to 8.8% in 2000–2001 at a US tertiary-care teaching hospital [Muto *et al.* 2005]. The cause of the increased incidence and severity of CDI remains unknown; however, possible sources include suboptimal infection control practices, emergence of a hyper-virulent strain of *C. difficile* (such as the BI/NAP1/027 strain), and poor response to standard treatment [McFarland *et al.* 2007].

Standard therapy for initial and recurrent CDI is metronidazole 1500 mg/day for 10–14 days

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[Mylonakis *et al.* 2001]. Unfortunately, the frequency of metronidazole treatment failure has increased in recent years. In a study of 908 patients diagnosed with CDI between 1982 and 1991, only 2% of patients were unresponsive to metronidazole [Olson *et al.* 1994]. This is in contrast to a report demonstrating resistance to metronidazole in 22% of 207 patients with CDI diagnosed between 2003 and 2004 [Musher *et al.* 2005]. Although the cause of increased metronidazole treatment failure remains unknown, possibilities include increased severity of disease, poor immune response of patients, or resistance to antibiotics [Musher *et al.* 2005]. Currently, antibiotics that elicit marginal bacterial antibiotic resistance, such as rifaximin, are being examined for use in patients with recurrent CDI.

Rifaximin is a nonsystemic gut-selective antibiotic that displays minimal clinically relevant antibiotic resistance when used as directed [Scarpignato and Pelosini, 2006]. It has a placebo-like tolerability profile [Scarpignato and Pelosini, 2006] and high *in vitro* activity against *C. difficile* [Hecht *et al.* 2007; Marchese *et al.* 2000]. Encouraging clinical results with rifaximin for CDI have been reported in a small randomized study, in which 9 of 10 patients who received rifaximin had resolution of diarrheal symptoms [Boero *et al.* 1990], as well as in three small nonrandomized studies [Garey *et al.* 2008; Johnson *et al.* 2009, 2007]. The current study examined the use of rifaximin 400 mg three times daily (t.i.d.) for 14 days in the eradication of recurrent CDI in patients unresponsive to metronidazole therapy.

Materials and methods

Patient population

This prospective, open-label study was conducted in consecutive patients ≥ 18 years of age who presented at a hospital in Queens, New York, with mild-to-moderate CDI (5–10 bowel movements per day without sepsis) between June 2007 and August 2008. All patients were unresponsive (i.e. had a stool sample positive for toxins A and B, as analyzed by polymerase chain reaction [PCR] after discontinuation of metronidazole treatment) to metronidazole 500 mg t.i.d. for 5 days. Patients were excluded from the study if they had sepsis, abdominal distention, white blood cell count $>20,000$ cells/mm³, human immunodeficiency virus infection, multiorgan failure, renal failure, a recent organ transplant, or exposure to vancomycin or

rifampicin within 6 weeks before study initiation or if they were receiving chemotherapy. The study protocol, all protocol amendments, and the informed consent form were approved by the institutional review board of New York Hospital Queens.

Study assessments

All patients received oral rifaximin 400 mg t.i.d. for 14 days immediately after termination of metronidazole because of nonresponse. Patients were periodically visited for 56 days after the end of rifaximin therapy to obtain stool samples and assess patient compliance.

Stool samples were collected via rectal swab from all participants at the end of rifaximin treatment and on a final follow-up visit 56 days after cessation of rifaximin therapy; all samples were evaluated for the presence of *C. difficile* toxin B gene using qualitative real-time PCR techniques (Quest Diagnostics, Teterboro, NJ). A favorable response to rifaximin was defined as possession of a stool sample negative for *C. difficile* toxin B gene.

The intent-to-treat (ITT) population comprised all patients who were screened, met all inclusion criteria, and did not qualify for exclusion. The per-protocol population encompassed all patients within the ITT population who completed rifaximin therapy. Data from both populations were analyzed to ascertain the efficacy of rifaximin on CDI.

Results

Of the 85 patients screened, 25 met criteria for inclusion in the study (ITT population; Table 1). Thirteen patients acquired CDI from the community, and 12 patients had onset of CDI during a stay at a nursing home. All patients had prior exposure to antibiotics for CDI within 3 months preceding the study, and 18 patients (72%) had taken proton-pump inhibitors (PPIs) within 3 months before study initiation. Of the 25 patients recruited, 22 (88%) completed rifaximin therapy and were included in the per-protocol population. Patients had resolution of diarrhea within an average of 12 days (range, 8–16 days) after initiation of rifaximin therapy. After 14 days of rifaximin treatment, 16 of 25 patients (64%) in the ITT population and 16 of 22 (73%) patients in the per-protocol population had stool samples negative for *C. difficile* (Figure 1). This response was maintained in all patients at the final

Table 1. Patient demographics and characteristics.

Parameter	Rifaximin 1200 mg/day (N = 25)
Mean age (range), years	59 (48–65)
Male:female ratio	13:12
Race, n (%)	
White	13 (52)
Black	8 (32)
Hispanic	2 (8)
Asian	2 (8)
CDI acquisition, n (%)	
Community (out-patient)	13 (52)
Nursing home (in-patient)	12 (48)
Mean white blood cell count (range), cells/mm ³	14,000 (6000–18,000)
Hospitalization within 3 months before study initiation, n (%)	12 (48)
Mean creatinine level (range), mg/dL	0.9 (0.2–1.3)
Exposure to PPIs within 3 months of study initiation, n (%)	18 (72)
Antibiotics taken within 3 months of study initiation, n (%)	
Metronidazole	25 (100)
Cephalosporins	3 (12)
Isoxazolyl penicillin	7 (28)
Comorbid conditions, n (%)	
Hypertension	15 (60)
Diabetes mellitus type 2	9 (36)
COPD	3 (12)
Peripheral vascular disease	2 (8)
Aortic aneurysm	1 (4)

CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; PPIs, proton-pump inhibitors.

Figure 1. Percentage of patients with stool samples negative for *Clostridium difficile* immediately after rifaximin 1200 mg/day for 14 days and at a follow up 56 days post-treatment. ITT, intent-to-treat; PP, per protocol.

follow-up visit 56 days after treatment cessation (Figure 1).

In general, oral rifaximin was well tolerated, with few reported adverse events (Table 2). However, 3 of 25 patients (12%) who initiated rifaximin therapy discontinued the medication due to abdominal distention. In addition, headache (three patients, 12%) and belching (three

Table 2. Adverse events reported in the intent-to-treat population.

Adverse event	Rifaximin 1200 mg/day (N = 25)
During rifaximin treatment, n (%)	
Headache	3 (12)
Belching	3 (12)
Abdominal distention	3 (12)
During 56-day post-treatment, n (%)	
Constipation	2 (8)

patients, 12%) were reported by patients in the ITT population (12%) but these were not severe enough to cause discontinuation.

Discussion

Metronidazole is considered first-line therapy for CDI; however, recent evidence suggests that efficacy of this antibiotic may be declining. A study of 207 patients with CDI at the Houston Veterans Administration Medical Center from 2003 to 2004 demonstrated that 46 patients (22%) were unresponsive to metronidazole and 58 patients (28%) initially responsive to

metronidazole experienced symptom recurrence within 90 days post-treatment [Musher *et al.* 2005]. Similarly, 243 of 845 patients (29%) treated with metronidazole for CDI in Quebec displayed recurrence of symptoms within 60 days of treatment cessation [Pépin *et al.* 2005]. Although the underlying factors perpetuating a lack of response to metronidazole are unknown, bacterial antibiotic resistance is a potential culprit.

Rifaximin is indicated in the United States for treatment of travelers' diarrhea and the reduction of risk of overt hepatic encephalopathy recurrence [XIFAXAN (package insert), 2010] and is currently being investigated for use in other gastrointestinal diseases, including CDI. In an *in vitro* study of 93 *C. difficile* isolates, rifaximin showed good antibacterial activity against *C. difficile*, with 74% of isolates being susceptible to rifaximin and only rare development of resistant clones [Marchese *et al.* 2000]. In another study of 6000 *C. difficile* isolates from the United States and Europe, rifaximin demonstrated lower minimum inhibitory concentrations than metronidazole, suggesting that doses of rifaximin lower than those commonly used for metronidazole may provide equivalent antimicrobial efficacy [Hecht *et al.* 2007].

In addition to *in vitro* analysis, three small studies ($N = 6-8$) of patients with CDI treated with rifaximin support its clinical use. Two studies of six to eight patients with recurrent CDI who received rifaximin 400 to 800 mg/day for 2 weeks as follow-up therapy after resolution of symptoms with vancomycin showed that 67-88% of patients remained symptom free during a follow-up period of 75-780 days [Johnson *et al.* 2009, 2007]. Another study of six patients with active CDI unresponsive to standard treatments (vancomycin, metronidazole, nitazoxanide) found that five of six patients (83%) achieved complete resolution of diarrhea after treatment with rifaximin 400 mg t.i.d. for 14 days followed by rifaximin 200 mg t.i.d. for 14 days [Garey *et al.* 2008]. This response was sustained during a 54- to 398-day follow-up period [Garey *et al.* 2008]. The present work extends these observations by demonstrating that rifaximin 400 mg t.i.d. for 14 days successfully eradicated *C. difficile* in 64-73% of patients unresponsive to metronidazole. Symptoms of *C. difficile* did not recur during a 56-day follow-up period in any of these patients. Thus, it

appears that rifaximin may reduce symptoms of CDI via elimination of the aberrant organism. Recurrence of CDI may also be prevented because rifaximin initiates minimal changes in fecal flora (coliforms) [DuPont *et al.* 2005], which may deter *C. difficile* colonization.

Rifaximin was well tolerated in the current study, with only three patients discontinuing treatment because of adverse events (abdominal distention). Larger studies (~80 patients) examining use of rifaximin 1200 mg/day in patients with gastrointestinal disorders (irritable bowel syndrome [Scarpellini *et al.* 2007] and small intestinal bacteria overgrowth [Pimentel *et al.* 2006]) similarly reported abdominal pain and dyspepsia in patients receiving rifaximin; however, these events were reported to be mild [Scarpellini *et al.* 2007] and rare [Pimentel *et al.* 2006].

The present prospective clinical trial evaluated the efficacy of rifaximin 1200 mg/day in eradicating CDI in patients unresponsive to metronidazole. The majority of patients responded to rifaximin therapy and sustained CDI resolution as ascertained by stool samples negative for the organism up to 56 days post-treatment. This suggests that rifaximin may be useful in patients with recurrent CDI, although one study has suggested that the use of rifaximin be contraindicated in patients with prior exposure to rifamycin derivatives (i.e. rifampin) because of the possibility of bacterial antibiotic resistance [Johnson *et al.* 2009]. The correlation between rifaximin and rifampin resistance, however, remains unclear in *in vitro* studies [Jiang *et al.* 2010; O'Connor *et al.* 2008] and in a susceptibility study of isolates from patients who were unresponsive to rifaximin [Johnson *et al.* 2007]. Additional investigations into the possibility of bacterial antibiotic resistance in patients who receive rifaximin for CDI are essential to provide insight into which patient population would be the most responsive to rifaximin therapy. Taken together, these data suggest that rifaximin should be considered as a potential alternative therapy in some patients with CDI that is unresponsive to metronidazole therapy.

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Conflict of interest statement

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