Potential Use of Fosfomycin-Tromethamine for Treatment of Recurrent Campylobacter Species Enteritis

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We report 2 cases of recurrent Campylobacter coli enteritis caused by macrolide- and fluoroquinolone-resistant strains in 2 patients with hypogammaglobulinemia, successfully treated with a prolonged course of fosfomycin-tromethamine with no side effects. Fosfomycin-tromethamine may be a feasible alternative therapy for recurrent enteritis caused by Campylobacter species resistant to first-line drugs.

Campylobacter jejuni and Campylobacter coli, among other Campylobacter species, are frequent causes of foodborne enteric infection. Macrolides are the drug of choice for treatment, reducing the duration of the illness and bacterial shedding, and fluoroquinolones are the most commonly used alternative therapy (1). Since the 1990s, a significant increase in the prevalence of fluoroquinolone resistance in Campylobacter spp. has been reported in Asian and European countries (1, 2). Increased macrolide resistance has also been described, particularly in developing countries (3). It has also been noted that C. coli isolates are more frequently resistant to antibiotics than C. jejuni isolates (3, 4). Most cases of Campylobacter species enteritis are mild and self-limited; nevertheless, some episodes follow a relapsing course with repeated treatment failures, particularly in patients with predisposing conditions like impaired humoral immunity (5).

Fosfomycin-tromethamine (FT) is an antimicrobial agent active against various Gram-positive and Gram-negative bacteria. It is generally safe and well tolerated and is currently approved for the treatment of uncomplicated urinary infection. A previous study demonstrated that most fluoroquinolone-resistant C. jejuni strains are susceptible to fosfomycin (6). However, reports on its use in acute Campylobacter species enteritis are scarce, outdated, and limited (7, 8).

We report 2 cases of relapsing C. coli enteritis successfully treated with oral FT.

Case 1. A 64-year-old woman was admitted for persistent diarrhea. She had been diagnosed with common variable immunodeficiency many years before and had a history of recurrent respiratory tract infections, bronchiectasis, and chronic diarrhea with numerous exacerbations and repeated isolation of C. jejuni in stool cultures. The patient’s gastroenterologist had undertaken an extensive study of her chronic diarrhea, and other possible causes had been excluded. Her usual medications included intravenous gamma globulin every 3 weeks, bronchodilators, and nebulized colistin. She had received several courses of azithromycin treatment for respiratory and gastrointestinal infections over the last 5 years.

Over the previous 7 days her diarrhea had markedly worsened (up to 10 stool passages a day), and she experienced abdominal pain and hypovolemic shock. She was admitted to the intensive care unit. Blood cultures were sterile; stool cultures were positive for C. coli, which was resistant to erythromycin (MIC of >256 mg/liter), ciprofloxacin (MIC of >32 mg/liter), and tetracycline, as tested by Etest (bioMérieux, Marcy l’Etoile, France), and susceptible to amoxicillin-clavulanate and gentamicin. She was started on intravenous amoxicillin-clavulanate at a dose of 1,000/200 mg every 8 h and received intensive supportive care, which resulted in prompt improvement of the symptoms, hemodynamic stabilization, and resolution of diarrhea. After 5 days of intravenous amoxicillin-clavulanate, stool cultures tested negative. Amoxicillin-clavulanate was administered intravenously for 14 days and switched to oral administration at a dose of 1,000/125 mg for 7 more days. Two days after completing this regimen, watery diarrhea reappeared and stool cultures were again positive for C. coli with the same susceptibility pattern. Susceptibility to fosfomycin was then tested (MIC of 1 mg/liter by Etest), and the patient was started on oral FT at 3 g every 48 h for 6 weeks, with prompt resolution of diarrhea and no side effects. She has remained asymptomatic since the completion of treatment, and stool cultures at 5 weeks and 12 months tested negative.

Case 2. An 83-year-old woman was referred for persistent diarrhea. She had undergone thymectomy to treat thymoma at the age of 57 years. As a consequence, she developed Good’s syndrome with hypogammaglobulinemia and had bilateral bronchiectasis colonized with Pseudomonas aeruginosa. She was receiving intravenous gamma globulin every 2 weeks. Her usual medications included bronchodilators and azithromycin at 250 mg every 48 h for the last 4 years. She also had frequent respiratory exacerbations.
that were treated with levofloxacin. She had experienced one episode of *Campylobacter enteritis* 10 years previously.

The patient consulted for intermittent watery diarrhea of 6 months’ duration. Stool cultures 3 months before had grown *C. coli* that was resistant to erythromycin (MIC of >256 mg/liter) and ciprofloxacin (MIC of >32 mg/liter), as tested by Etest, and susceptible to amoxicillin-clavulanate. She was prescribed oral amoxicillin-clavulanate at 875/125 mg every 8 h for 10 days with no significant improvement. At 1 week after completing this regimen, stool cultures were again positive for *C. coli* with the same susceptibility pattern. Susceptibility to fosfomycin was tested (MIC of 0.75 mg/liter by Etest). The patient was started on FT at 3 g every 48 h and completed 4 weeks of treatment with good tolerance and resolution of diarrhea. After 6 months of follow-up, she has remained asymptomatic, and stool cultures at 2 weeks and 6 months after completing treatment were negative.

The value of this report resides in the possibility raised by the outcome of the 2 patients presented: a lengthy course of oral FT may be effective to treat recurrent *Campylobacter* species enteritis caused by strains resistant to first-line drugs. *C. jejuni* and *C. coli* are among the most prevalent enteric pathogens worldwide, but only a minority of patients experience recurrent *Campylobacter* species enteritis. The disease can have a protracted course but can also present as an acute and potentially life-threatening infection (5), as occurred in one of our patients. Certain conditions, such as chronic intestinal diseases, diabetes, liver disease, metastatic cancers, and AIDS, as well as hypogammaglobulinemia and the use of proton-pump inhibitors, may be associated with a higher risk of acquiring the infection (9). Humoral immunity plays a crucial role against *Campylobacter* spp., and recurrent infection has been reported in patients with conditions associated with impaired humoral immunity (5), as was the case of both our patients. Of note, recurrence has also been described in an immunocompetent patient who had received antibiotic treatment. In this case, the absence of protective *Campylobacter*-specific systemic, mucosal, and cellular immune responses was well characterized (10).

Some data suggest that *Campylobacter* spp. have the ability to persist in the intestinal tract (11) and that recurrent infection is likely caused by the same microorganism rather than by reinfection. In these cases, treatment with antibiotics at the usual dosage and duration may fail to eradicate the pathogen. Exceptionally, in *vivo* development of macrolide resistance following appropriate antibiotic use has been described (12).

Antibiotic resistance in *Campylobacter* species infection has increased substantially over the last years (1, 2, 4). Resistance rates of 93.8% for ciprofloxacin and 16.9% for erythromycin were found in 65 *Campylobacter* species strains (52 *C. jejuni*, 9 *C. coli*, and 4 *Campylobacter* spp.) isolated from stool cultures in our center (M. N. Larrosa, unpublished data). Antibiotic resistance may be of even greater concern in patients with hypogammaglobulinemia and bronchiectasis, who have frequent infections and are often exposed to antibiotics such as fluoroquinolones and macrolides for treatment or long-term prophylaxis of respiratory infections.

Our 2 patients with recurrent *C. coli* enteritis had hypogammaglobulinemia, and the causative strains were resistant to both macrolides and fluoroquinolones. The prevalence of macrolide resistance is higher in *C. coli* human isolates than in *C. jejuni* isolates, reaching 18% to 23% in recent surveys (4). It has also been noted that macrolide-resistant strains are often resistant to fluoroquinolones and other antimicrobial groups (13). These infections are a therapeutic challenge, and there is some evidence that drug-resistant strains may be associated with more severe and prolonged illness (14). When these 2 drugs with intracellular activity cannot be used, amoxicillin-clavulanate, tetracyclines, carbapenems, and aminoglycosides are possible therapeutic alternatives (13). In both our patients, amoxicillin-clavulanate therapy failed, leaving few alternatives for oral therapy. Beta lactams have poor intracellular penetration and achieve low serum levels with oral administration. This may partially explain the failure to eradicate the microorganism. Recurrence was prompt, and strains with identical susceptibility patterns were isolated, suggesting persistence of the microorganism rather than reinfection. Once susceptibility to fosfomycin had been confirmed, both patients were successfully treated with prolonged oral FT, which allowed early hospital discharge.

Fosfomycin-tromethamine is an old drug that has been recently rediscovered for the treatment of multidrug-resistant infections and other difficult-to-treat infections (15, 16). It diffuses and distributes well into tissues and is excreted unchanged in urine (38%) and feces (18%) (15), characteristics that are potentially useful for eradicating intracellular and luminal reservoirs of *Campylobacter*. Fluoroquinolone-resistant *Campylobacter* species organisms are usually susceptible to fosfomycin (6). However, reports on its use for the treatment of *Campylobacter* species enteritis are limited to 2 articles from Japan published in the 1980s: a case series of pediatric patients who showed good clinical response after fosfomycin treatment (7) and a clinical trial including 47 fosfomycin-treated patients (43 of them pediatric patients) that reported a reduction in the symptoms and shortening of *Campylobacter* excretion in stool samples compared with the symptoms and duration of *Campylobacter* excretion for an untreated group (8). To our knowledge, this is the first report of recurrent *Campylobacter* species enteritis treated successfully with a prolonged course of oral FT. The treatment was well tolerated. Although prolonged oral FT therapy has not been used extensively, we have some experience with the drug in patients with chronic bacterial prostatitis. Oral FT at 3 g every 48 to 72 h for 6 weeks proved to be safe and well tolerated (16).

Our study has some limitations. First, it is uncertain whether similar success might have been achieved with a more prolonged, high-dose, intravenous course of amoxicillin-clavulanate. Second, given that both our cases had infection due to *Campylobacter* species strains with relatively low MICs (0.75 to 1 mg/liter), we cannot assert that FT therapy will be equally effective with less susceptible isolates. Further studies are needed to establish MIC breakpoints and define resistance rates in different geographical areas. Third, it is uncertain whether a shorter course of FT could have cured the infection. In our patients, we decided to administer a long course of therapy in order to ensure the eradication of persistent reservoirs and to avoid further recurrences. Despite these limitations, considering that the drug is generally well tolerated, safe, easy to administer, and cost-effective, we believe it constitutes a good alternative, particularly when no other oral drugs are available.

In conclusion, our experience suggests that a prolonged course of oral fosfomycin-tromethamine, one of the “forgotten antibiotics,” may be considered a safe and effective alternative therapy for patients with recurrent enteritis caused by *Campylobacter* spp. resistant to first-line drugs.
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