Fucidic Acid Use in Metronidazole Nonresponders with *Clostridium difficile* Infection

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Dear Sir,

Clostridium difficile is the major identifiable etiologic agent of antibiotic-associated diarrhea and colitis [1]. Its clinical presentation ranges from asymptomatic carriage to toxic megacolon which requires surgical resection. The impact of *C. difficile* on patients with inflammatory bowel diseases (IBD) is still unknown at the present time. Recent reports have shown that the rate of *C. difficile* infection in IBD patients has increased [2]. It may be either an innocent bystander or a micro-organism that could play a role in IBD relapse.

We used fucidic acid orally for 10 days at a dose of 1,500 mg/day in 5 patients (3 with ulcerative colitis, 1 with Crohn's disease, 1 with chronic diarrhea who was diagnosed as Crohn's disease later) admitted

to our out-patient clinic with existing diarrhea in whom *C. difficile* toxin A was detected at stool examination. All patients except the one with metranidazole allergy had a history of prior metranidazole use for *C. difficile*-associated diarrhea (CDAD). On the 10th day of treatment stool examination for *C. difficile* toxin A was negative for all cases. Patient characteristics are presented in table 1. At the end of the treatment period, clinical symptoms of CDAD have been resolved and no recurrence of infection has been reported during the follow-up period.

Previous reports have suggested that diarrheal relapses of IBD may be associated or confused with enteric infection. Stool studies yielded a pathogen, mainly *C.*

difficile, in 5–20% of the relapsing IBD patients [3, 4]. Antibiotic use was significantly associated with *C. difficile* infection. Toxin-positive patients improved clinically with targeted antibiotics.

Mylonaki et al. [5] evaluated 237 relapses in 213 IBD patients for *C. difficile*. Enteric infection was found in 25 (10.5%) relapses in 24 patients. *C. difficile* toxin was detected in 13 (5.5%) cases. There was a significant association between infection and the need for hospital admission. In another study, Meyer et al. [6] evaluated 54 IBD patients during 62 relapses with 99 stool samples. Twelve stool tests were positive for enteric infections. *C. difficile* accounted for the majority of positive tests (10/12). Of these, 9 (90%) were associated with antibi-

Table 1. General characteristics of the patients

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	50	45	42	48	52
Sex	M	M	F	F	F
Primary disease	CD	UC	UC	UC	CD
Localization of disease	ileocolitis (fibrostenotic type)	pancolitis	pancolitis	pancolitis	ileocolitis (perianal fistula)
Prior metranidazole use	yes	yes	yes	yes	no*

* Metranidazole allergy.
CD = Crohn's disease.

otic use in the prior month versus 10 (22%) in the *C. difficile*-negative group ($p < 0.001$). All relapses resolved satisfactorily after treatment with adequate antibiotics, with or without corticosteroids.

CDAD was usually treated using metronidazole or vancomycin, with comparable response rates (80–90%) and relapse rates (5–25%) [7, 8]. Metronidazole is currently the first-choice agent due to its lower potential for selecting vancomycin-resistant enterococci and for economical concerns [9, 10]. Fucidic acid has been found to be effective against *C. difficile* in vitro [11, 12]. Moreover, an earlier open, non-blinded study demonstrated that fucidic acid is adequately effective in the treatment of CDAD [13]. Wullt and Odenholt [10] conducted a study to compare the efficacy of fucidic acid and metronidazole for the treatment of patients experiencing the first episode of CDAD. They found that 83% of the patients in the fucidic acid group clinically were cured in comparison to 93% in the metronidazole group at the first follow-up visit ($p = 0.116$). Recurrence of clinical symptoms and reappearance of *C. difficile* toxin was noted in 27% and 13% of the patients receiving fucidic acid, respectively, and in 29 and 10% given metronidazole at the second follow-up on days 35–40.

The results indicate that fucidic acid might be an effective treatment in cases

with prior metronidazole use (metronidazole nonresponders) in an initial episode of CDAD and can therefore be considered an adequate alternative for treatment of this disease. Further studies consisting of more patients are needed to support these findings.

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