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Double-Blind Crossover Trial of Metronidazole versus Placebo in Chronic Unremitting Pouchitis

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Metronidazole has been used to treat pouchitis, but there are no controlled data that show it is effective. Chronic unremitting pouchitis is a form of the disorder particularly difficult to manage. Diarrhea is the main symptom of pouchitis, which results from acute inflammation of the mucosa of an ileal reservoir. To test the hypothesis that metronidazole (400 mg thrice daily for seven days) is no better than placebo at reducing stool frequency in chronic unremitting pouchitis, a double-blind placebo-controlled crossover study has been performed. Thirteen patients who had undergone restorative proctocolectomy for ulcerative colitis were studied. The diagnosis of pouchitis was based on clinical, endoscopic, and histological criteria. At entry all patients had symptomatic pouchitis and were passing more than six stools/24 hr or had consistently bloody stools with at least four of six endoscopic criteria of mucosal inflammation. The median frequency of defecation decreased by 3 bowel actions/24 hr (conservative 95% confidence intervals 0–4/24 hr) on metronidazole but increased by a median of 1/24 hr on placebo. The difference between the median number of bowel motions, when treatment with metronidazole was compared to placebo, was 4 motions/24 hr ($P < 0.05$) in favor of metronidazole. There was no significant change in the endoscopic or histological grade of inflammation, in the serum C-reactive protein level, or symptomatic scores. In a parallel study, metronidazole did not alter stool frequency in asymptomatic patients without pouchitis who had endoscopically normal reservoirs (six polyposis, six colitis). Metronidazole significantly reduces the frequency of defecation when compared with placebo in chronic pouchitis. The reduction in stool frequency is, however, of limited symptomatic benefit to the patient.

KEY WORDS: ulcerative colitis; pouchitis.

Pouchitis is associated with acute inflammation of the mucosa of an ileal reservoir (1). It is the most common late complication of restorative proctocolectomy (2) with a cumulative incidence of 30% reported after two years of prospective follow-up (3). It is almost always confined to patients with ulcerative colitis, being extremely rare in adenomatous polyposis (4–8). It causes frequent loose stools, often containing blood. Malaise and fever are common. Stool frequency correlates well with both endoscopic and histological features of acute inflammation (9, 10). Metronidazole is the most widely used treatment, but there are no controlled data to show whether it is effective (1). Pouchitis may occur as an acute disease, resolving rapidly, or it may take the form of a chronic unremitting disorder. This latter condition poses a difficult clinical problem that may threaten the survival of the res-

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TABLE 1. SCORING SYSTEM FOR ENDOSCOPIC INFLAMMATION AND HISTOLOGICAL ACUTE INFLAMMATION IN RESERVOIR MUCOSA

	Score
Endoscopic feature*	
Absent vascular pattern	1
Granularity	1
Oedema	1
Ulceration	1
Mucosal bleeding on contact	1
Spontaneous mucosal bleeding	1
Histological feature†	
Polymorph infiltration	
None	0
Mild and patchy infiltrate in surface epithelium	1
Moderate with crypt abscesses	2
Severe with crypt abscesses	3
Ulceration	
None	0
Mild superficial	1
Moderate	2
Extensive	3

*From Moskowitz et al (9).
†From Shepherd et al (10).

ervoir itself. In this study we set out to determine whether metronidazole is of benefit in these particular patients.

MATERIALS AND METHODS

The study tested the hypothesis that metronidazole was no better than placebo at reducing diarrhea in patients with chronic unremitting pouchitis. It consisted of a double-blind placebo-controlled crossover trial with stool frequency as the primary end point. Thirteen patients entered the study. All had undergone restorative proctocolectomy for ulcerative colitis, and 12 had chronic recurrent or unremitting pouchitis based on symptoms, endoscopic findings, and histological appearances. The patients were entered into the study when they had active pouchitis as judged by symptoms (stool frequency of more than 6/24 hr or consistently bloody stools), and mucosal inflammation visible endoscopically (score of >4, Table 1).

Patients were randomized to receive either metronidazole 400 mg by mouth three times a day or placebo for two weeks. They then stopped the drug for a one-week washout period, which was considered sufficient to avoid any carry-over effect since the known actions of metronidazole are short-lived. If pouchitis was still present after one week or if it subsequently recurred, a further two weeks of treatment was given with the alternative drug. Assessments were made at the beginning and end of each two-week course of treatment. Each assessment included recording the frequency of defecation, the quantity of blood in the stool (none, little, a lot), general well-being (score 0–3), C-reactive protein, examining the stool for pathogens, endoscopic assessment of the reservoir, and histological examination of a biopsy from the reservoir (9, 10) (Table 1).

To assess whether metronidazole might reduce stool frequency independently of any effect on pouchitis, 12 further patients without clinical, endoscopic, or histological features of pouchitis were studied before and after a two-week course of metronidazole. Six had undergone restorative protocolectomy for ulcerative colitis and six for familial adenomatous polyposis.

The data were analyzed using nonparametric statistics to determine the efficacy of metronidazole using two-tail tests. Conservative 95% confidence intervals are given. Where relevant, results are expressed so that a positive difference indicates an improvement with metronidazole.

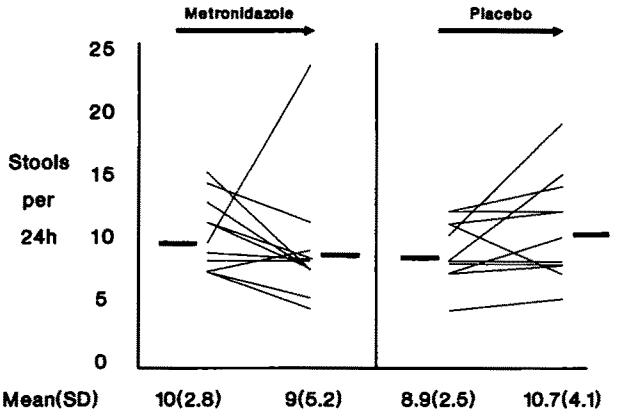

Fig 1. Stool frequency before and after metronidazole and placebo. Bars represent mean values.

RESULTS

Eleven of the 13 patients completed the crossover trial. One was withdrawn because of an episode of intestinal obstruction. One patient completed the first course of treatment (metronidazole) and subsequently had no relapse of pouchitis.

Placebo had no effect on stool frequency in the 11 patients who received the treatment, with a median increase in bowel actions of 1/day (95% confidence interval: reduction 0.5 to increase of 4.5 per day). Metronidazole reduced stool frequency in the 12 patients who received it by a median of 3 bowel actions/day ($P < 0.05$) (95% confidence interval: 0–4/day) (Figure 1).

Stool frequency improved in eight of 11 receiving metronidazole, worsened in two, and was unchanged in one. The subject who received metronidazole but did not cross over also showed an improvement, but its magnitude in relation to placebo is unknown. Using unpaired nonparametric analysis reveals a median improvement induced by metronidazole of 4 bowel actions/day ($P < 0.05$, 95% confidence interval: 1–6). However, metronidazole treatment resulted in no significant change in endoscopic score for mucosal inflammation when compared with placebo (difference

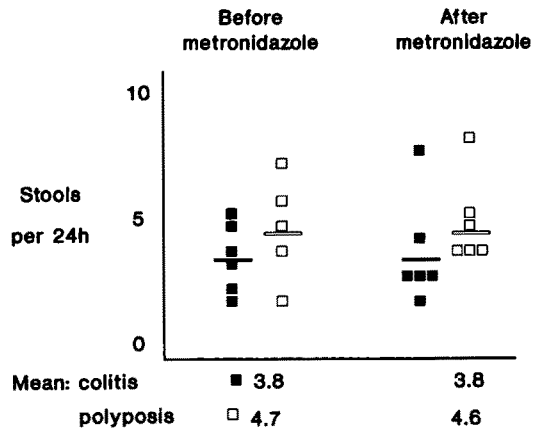

Fig 2. Stool frequency before and after metronidazole in six colitis and six adenomatous polyposis patients with a normal reservoir. Bars represent mean values.

between medians = 1.0; 95% confidence interval: −1 to 2). No significant effect was seen on the score of general well-being (difference between medians = 0; 95% confidence interval: −1 to 2), C-reactive protein (difference between medians = 8.5; 95% confidence interval: −9 to 30), the appearance of blood in the stool (difference between medians = 0; 95% confidence interval: 0–1), or the histological grade of inflammation (difference between medians = 1; 95% confidence interval: 0–1). No pathogenic bacteria were grown from any of the stool specimens.

One patient had a mouth ulcer on starting metronidazole, which had healed on completing the course. The following side effects were reported by six patients (55%) while taking metronidazole: unpleasant taste, 2; nausea, 2; vomiting, 1; abdominal discomfort, 1; headache, 1; skin rash, 1.

Metronidazole had no significant effect on stool frequency in the 12 patients without pouchitis (Figure 2).

DISCUSSION

This study has shown that metronidazole significantly reduced diarrhea in chronic pouchitis when compared with placebo. The patients selected for this study had chronic unremitting pouchitis following restorative proctocolectomy. This disease entity may differ from acute episodes of pouchitis, which are often seen, and it is not possible to extrapolate our results to the treatment of acute pouchitis.

The effect of metronidazole in pouchitis is unlikely to be due to a nonspecific effect on pouch function since no effect was observed in patients without active pouchitis. Pouchitis is extremely rare in patients who have had a proctocolectomy for polyposis and is more usual in patients who had ulcerative colitis. Inclusion of both groups in the control experiment without pouchitis makes a selective effect on patients with previous colitis (as opposed to polyposis) highly unlikely.

The mechanism for any effect of metronidazole on pouchitis remains unknown. Metronidazole might act by killing pathogenic bacteria, by altering bacterial metabolism, by an immunosuppressive effect (11), or by acting as an electron sink, reducing damage caused by oxygen free radicals. A direct bacteriocidal action is unlikely because no conventional pathogen has been identified in pouchitis despite detailed bacteriological investigation in patients who, like those in the present study, mostly had long-standing chronic pouchitis (12–16). Bacteriological studies have not been performed in patients with an acute attack of pouchitis, and it may be inappropriate to apply this study's findings to patients with acute pouchitis. Lower concentrations of total conjugated bile acids and tauroconjugated bile acids have been reported from the reservoirs of patients with pouchitis compared with those without pouchitis whether the underlying pathology had been colitis or polyposis (17). This suggests that pouchitis may be accompanied by increased bacterial bile salt deconjugation, which could be diminished by metronidazole's effect on bacterial metabolism.

The decrease in stool frequency that we observed was generally small and of little symptomatic value to the patient. One element in the beneficial effect of metronidazole was the lack of deterioration in stool frequency, which was seen in patients on placebo and presumably reflects a natural tendency of untreated pouchitis to worsen without therapy. In contrast, stool frequency improved while on metronidazole, and the combination of these effects resulted in a statistically significant difference. It remains unclear why one subject improved slightly while on placebo while two deteriorated on metronidazole. The anecdotal data of other authors suggest that metronidazole may have a larger effect than we have observed and, as our results have wide confidence, intervals they do not rule out such a possibility.

In conclusion the study has shown that metronidazole reduces bowel frequency significantly in patients with unremitting pouchitis. This effect is small and of limited clinical value in patients with chronic unremitting pouchitis.

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