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Bismuth carbomer foam enemas for active chronic pouchitis: a randomized, double-blind, placebo-controlled trial

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SUMMARY

Background: Bismuth carbomer liquid enemas are equivalent to mesalamine enemas for active distal ulcerative colitis.

Aims: In this study, the efficacy and safety of bismuth carbomer foam enemas for active chronic pouchitis was determined in a placebo-controlled trial.

Patients: Forty adult patients with active chronic pouchitis were randomly assigned into either concurrent therapy for pouchitis or no concurrent therapy. Topical corticosteroids and mesalamine were withdrawn prior to the study.

Methods: Patients received either bismuth carbomer (270 mg elemental bismuth) ($n = 20$) or placebo ($n = 20$) foam enemas for 3 weeks. Clinical assessment was performed at baseline and at 3 weeks using the pouchitis disease activity index score which incorporates symptoms, endoscopy and histology. Serum bismuth concentrations were determined by atomic absorption spectrophotometry.

Results: At 3 weeks nine of 20 patients (45%) in both the bismuth and placebo groups had improved. Ten patients discontinued prematurely because of worse diarrhoea (three in each group) or abdominal cramping after enema use (one from the bismuth group and three from the placebo group). No other side-effects were noted. Serum bismuth concentrations were negligible in all patients.

Conclusions: Bismuth carbomer foam enemas (270 mg bismuth) nightly for 3 weeks are safe but not efficacious for active chronic pouchitis.

INTRODUCTION

Abdominal colectomy with mucosal proctectomy and ileal pouch–anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery.[1] Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years.[2] The syndrome of pouchitis includes: (a) symptoms (increased stool frequency, rectal urgency and incontinence, abdominal cramping, and fever); (b) endoscopic inflammation (oedema, granularity, contact bleeding, loss of the vascular pattern, increased mucus exudate and ulcers); and (c) histological inflammation (neutrophil infiltration and ulcers, in addition to chronic inflammatory changes of villous atrophy, crypt hyperplasia and chronic inflammatory cells).[3–5] Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.[5] The importance of bacteria is underscored by the apparent efficacy of antibiotics for pouchitis.

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The medical treatment of pouchitis has been largely empiric.[5] There are only two placebo-controlled trials, both using metronidazole.[6,7] In one study a single patient with chronic pouchitis was treated in a blinded crossover '*n* of 1' trial with significantly worse symptoms with placebo compared to metronidazole 250 mg daily.[6] In the second study, 13 patients with chronic pouchitis were treated in a double-blind crossover trial with metronidazole 400 mg three times daily or placebo for 14 days, and there was a significant reduction in stool frequency with metronidazole.[7] In the latter study, 55% of the metronidazole-treated patients developed side-effects, including nausea, vomiting, abdominal discomfort and skin rash. Chronic administration of metronidazole at a high dose of 20 mg/kg per day for the treatment of Crohn's disease caused symptomatic peripheral neuropathy in up to 85% of patients, and is a limiting factor in using maintenance metronidazole to suppress chronic pouchitis.[8] A number of other empiric therapies have been reported.[5]

Bismuth citrate, bismuth subsalicylate and oral bismuth carbomer liquid have been used with some success for the treatment of active distal ulcerative colitis.[9–11] More recently, bismuth complexed with carbomer (an acrylic acid polymer) and administered as a liquid enema was reported to result in clinical improvement in 10 of 12 patients in an open trial.[12] The rationale for the use of bismuth and bismuth carbomer in ulcerative colitis and pouchitis includes both non-specific anti-diarrhoeal effects and anti-bacterial effects. Some preparations of bismuth no longer in use caused neurotoxicity when taken in high doses, such as bismuth subnitrate in France and bismuth subgallate in Australia.[13,14] In contrast, currently used bismuth formulations (bismuth citrate, bismuth subsalicylate, bismuth carbomer) result in low serum bismuth concentrations and have been safe.[9–14]

In this paper the results of a 3-week randomized, double-blind, placebo-controlled trial with bismuth carbomer foam enemas (270 mg elemental bismuth) daily for active chronic pouchitis are presented.

MATERIALS AND METHODS

Study design

This was a randomized, double-blind, placebo-controlled study. Patients were stratified into two groups: (a) those with symptoms despite metronidazole or other therapies for pouchitis; and (b) those who had failed or were unable to tolerate metronidazole or other therapy for pouchitis and were not on specific medication for pouchitis at study entry. Stratification was performed to ensure a balance between treatment groups, but no statistical analysis between strata was undertaken. Randomization was then performed separately within each strata. Assignment to therapy or placebo was determined according to a computer-generated randomization scheme.

Patients

Forty adults who had previously undergone total colectomy with mucosal proctectomy and ileal J–pouch anal anastomosis for ulcerative colitis,[15] and who had active chronic pouchitis refractory to standard therapy, were recruited from the Inflammatory Bowel Disease Clinic at our institution between February 1994 and April 1996. Patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a pouchitis disease activity index (PDAI) score of at least 7 points on an 18-point scale.[3] All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis (Table 3). Patients who had taken any bismuth preparation within 1 week of study entry and those who had taken any per-rectal medication within 5 days of study entry were excluded. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch. Patients with perianal disease including abscess, fistula, fissure, anal sphincter weakness or stricture were excluded. This study was approved by the Mayo Foundation Institutional Review Board, and all patients gave written consent.

Procedures

At baseline, patients were evaluated by: (a) symptom assessment; (b) physical examination; (c) laboratory studies including a complete blood count, blood chemistries and a serum bismuth concentration measured by graphite furnace atomic absorption spectrophotometry;[16] (d) an endoscopic examination of the ileal pouch and the ileum for a few centimetres proximal to the pouch; and (e) endoscopic mucosal biopsies in the pouch from areas that appeared to have the most active inflammation. The PDAI was determined from the baseline data, and patients with a score of a least 7 were randomized for therapy. During the treatment

period, patients recorded the following each day: number of stools, rectal bleeding, faecal urgency or abdominal cramps, fever, the number of hours the enema was retained in the pouch and any new symptoms. After 3 weeks of therapy patients returned and underwent symptom assessment, physical examination, laboratory studies and endoscopic examination of the pouch with mucosal biopsies.

Study medication

Bismuth citrate carbomer foam enemas were provided by Tillotts Pharma AG (Ziefen, Switzerland), and contained 513 mg of bismuth citrate (containing 270 mg of metallic bismuth) complex with carbomer (a synthetic high molecular weight polymer of acrylic acid crosslinked with polyalkenyl polyether), xanthan gum and other excipients. The resulting 23.4 g of foam was packaged in individual dose canisters that contained *n*-butane as a propellant to empty the study preparation from a multi-layer bag, but no *n*-butane was mixed with the foam or expelled from the canister. The freshly delivered foam expanded at 37 °C to ≈10 times its initial volume to a final volume of ≈230 mL. A placebo preparation of identical appearance, viscosity and volume was made using xanthan gum, and it was packaged in identical containers. Patients took one study enema at bedtime nightly for 3 weeks.

Statistics

All analyses were performed using the intention-to-treat principle. Comparisons within groups between data at baseline and study completion were based on the signed rank test. For the primary analysis, the proportion of patients who improved or achieved remission were compared in each group using a Chi-squared test for proportions. The Wilcoxon rank sum test was used to compare PDAI scores between groups and the Wilcoxon signed rank test within groups.

The primary measure of efficacy was comparison of the pre-treatment PDAI and the post-treatment PDAI, with remission defined as a reduction in the PDAI to 0 and improvement defined as a reduction in the PDAI by at least 3 points. Pre-treatment and post-treatment histology scores and laboratory parameters were also compared. The serum bismuth levels were compared to the usual range for patients not taking bismuth preparations (<20 ng/mL), and to serum levels in patients treated with oral bismuth preparations (<60 ng/mL).

The sample size was based on estimates of a 25% response in the placebo group and a 70% response in the therapy group. Eighteen patients were needed in each group to assure 80% power with a two-sided *P*-value of 0.05. A 10% dropout rate was assumed, so an additional two patients were recruited in each group giving a total of 40 patients in the study.

RESULTS

Demographic characteristics

Forty of 42 patients who were evaluated and met the entry criteria elected to enter the study from February 1994 through to April 1996. The demographics of the

Table 1. Patient characteristics*

Characteristic	Treatment group	
	Bismuth	Placebo
Number of patients	20	20
Age: mean (range)	37 (22–60)	40 (18–62)
Number of men/women	10/10	12/8
Number of cigarette smokers: current/former/never	1/6/13	1/2/17
Years since diagnosis of ulcerative colitis: median (range)	8 (2–35)	9 (3–32)
Months of pouch function: median (range)	35 (5–108)	45 (4–161)
Months since the first episode of pouchitis: median (range)	31 (2–129)	42 (3–151)
Months of current pouchitis episode: median (range)	6 (0.5–79)	4 (0.8–151)

* There were no significant differences in the results.

Table 2. Therapy for pouchitis

Therapy	Bismuth* 20 patients		Placebo* 20 patients	
	No. of patients: current	previous	No. of patients: current	previous
Antibiotics				
Metronidazole	1	17	3	16
Ciprofloxacin	5	17	6	15
Amoxycillin/clavulanic acid	0	2	1	6
Tetracycline	0	2	0	3
Trimethoprine/sulphamethoxazole	0	0	1	0
5-Aminosalicylic acid				
Sulphasalazine	0	3	1	5
Oral mesalamine	0	1	0	5
Mesalamine enemas	0	3	0	3
Mesalamine suppositories	1	6	0	3
Corticoseroids				
Prednisone	6	12	1	7
Hydrocortisone enemas	1	5	0	5
Immune modifiers				
Azathioprine	2	1	0	0
Cylcosporin	2	0	0	0
FK506	1	0	0	0
Antidiarrhoeals				
Loperamide	5	3	5	3
Codeine sulphate	1	0	0	1

* There were no statistical differences detected between groups with respect to medication used at baseline (current) or for previous medication for pouchitis (prior to baseline).

patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis or in the medication previously used for treatment of pouchitis. All patients had been on medication for pouchitis previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2). More patients in the bismuth group had been on corticosteroids or immune modifier therapy, but the differences were not significant.

Disease activity

There was no significant difference in the response to therapy in the treatment or the placebo groups with regard to remission or improvement. Nine of 20 patients (45%) in both the treatment and placebo groups improved, defined as a reduction in the PDAI score of 3 points or more. (The two subjects in the bismuth group with incomplete scores at the end of the treatment were considered as 'not improved'.) The median PDAI scores for the bismuth group before and after therapy were 12 (range 8–17) and 9 (range 2–16), compared to median PDAIs in the placebo group of 11 (range 7–16) and 9 (range 2–16), respectively. No patient achieved remission with a PDAI score of 0. Baseline clinical scores were different and there were no significant differences in the initial or final endoscopic or histological scores between the two groups (Table 3).

Adverse events

One patient who received bismuth carbomer had worsening of diarrhoea after 3 days, requiring their admission to hospital for intravenous fluids. Two additional patients in the bismuth carbomer group and three patients in the placebo group had to discontinue treatment because of worsening of symptoms, but none developed dehydration or had to be admitted to hospital. Four patients had cramping discomfort in the pouch after taking the enema; three of the patients were receiving placebo and one receiving study medication. Two of the patients who developed

Table 3. Disease activity at baseline and completion of treatment

	Bismuth		Placebo	
	Baseline median (range)	Completion* median (range)	Baseline median (range)	Completion median (range)
Clinical score	4 (2–6)†	2 (0–6)*	4 (1–5)	3 (0–4)‡
Endoscopy score	5 (1–6)	4 (0–6)*	5 (1–6)	4 (1–6)
Histology score	3 (2–5)	2 (2–5)	2 (2–6)	2 (2–6)
Total score (PDAI)	12 (8–17)	9 (2–16)‡	11 (7–16)	9 (2–16)‡

* Two subjects missing data at completion in bismuth group.
† $P < 0.5$ for within-group change: baseline vs. completion (signed rank test with two missing values at completion filled in by overall (groups) baseline values).
‡ $P < 0.05$ for baseline comparison of groups using rank sum test.

cramps with the study enemas discontinued them because of the discomfort; one each in the treatment group and the placebo group. One patient in the treatment group developed maxillary sinusitis during the study, diagnosed at the time of the follow-up visit. One patient in the placebo group developed right lower abdominal pain and the study medication was discontinued.

No significant changes occurred in the laboratory studies at week 3 compared with baseline values. Serum bismuth concentrations were negligible at baseline and all concentrations were below 20 μg/L at week 3 (the therapeutic range for bismuth is <50 μg/L).[17]

DISCUSSION

Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by concerns for neurotoxicity with peripheral neuropathy. No other agents have been studied in placebo-controlled trials. In this study, a bismuth carbomer foam enema formulation was no more effective than placebo for active chronic pouchitis refractory to other therapies. There are several possible explanations for this lack of efficacy. First, the dose of bismuth may have been too low. The study enemas contained 513 mg of bismuth citrate, or 270 mg of elemental bismuth. This compares to the nearly 10-fold higher bismuth content (2.4 g) in the 4.2 g dose of bismuth subsalicylate (Pepto-Bismol) recommended for the treatment of diarrhoea. In our study, bismuth serum concentrations were negligible, with most of the values less than 5 ng/mL and all the values below 10 ng/mL, which is in the normal range for serum bismuth (<20 μg/L) in individuals who are not taking bismuth-containing medication. Serum bismuth concentrations from recommended doses of bismuth subsalicylate and ranitidine bismuth citrate have also been in the safe range of <50 μg/L.[17] Clearly, the dose of bismuth citrate could be increased in the enema preparation without an increase in toxicity, and additional dose-ranging studies are needed to determine whether the higher concentration of bismuth would be more efficacious. At present, the pharmacokinetic characterization of the bismuth carbomer is not adequate to determine how much free bismuth is released. Perhaps free bismuth is required for efficacy and the bismuth carbomer complex does not release free bismuth.

Another possible explanation for the lack of efficacy of the bismuth enemas is that the placebo was also effective therapy. Of interest, gum resin appeared effective for ulcerative colitis in a recent trial.[16] As noted, 45% of patients in each group improved, a higher proportion than might be expected in patients with chronic symptoms refractory to other therapies. The placebo was designed to have the same viscosity, volume and appearance as the bismuth preparation. It may be that the coating action of the foam functioned as a protective barrier in the pouch, shielding the mucosa from the effects of faecal stasis, or that the placebo could have acted simply as a washing agent to clear stool and bacteria from the pouch.[18]

The treatment period in this study was 3 weeks, which may have been too short a time to demonstrate efficacy of the study medication. In an open label trial lasting 45 days, bismuth carbomer enemas appeared effective for chronic treatment-resistant pouchitis.[12] Perhaps a longer treatment period in this current study would have shown a therapeutic benefit.

The bismuth preparation may not have been effective in this trial because only patients who were refractory to therapy were selected. All of the patients had failed or were intolerant to metronidazole. Five of the patients had previously undergone orthotopic liver transplantation for primary sclerosing cholangitis and had pouchitis despite combination immune modifier therapy with FK 506 and prednisone in two patients, and cyclosporin A, azathioprine and prednisone in three patients. Four of the five liver transplant patients received the bismuth enemas, with improvement in two patients. Perhaps the bismuth preparation at the dose used would be effective in patients with mild disease who had not failed other therapy.

The PDAI, the scoring system used to determine the primary end-points in this study, consists of clinical, endoscopic and histological data. This index has not been used previously in a clinical trial. In this trial, there were no significant differences in the treatment and placebo scores for the overall PDAI and for each individual component scores (clinical, endoscopic and histological). This consistency supports the use of the PDAI in clinical trials as a valid instrument.

The bismuth carbomer foam enema was safe and well tolerated. Although one patient who received the bismuth enemas required admission to hospital for severe diarrhoea, the worsening diarrhoea appeared to be due to activity of the underlying disease and not an adverse effect of the study preparation. Four patients had cramping in the pouch after using the enema; three in the placebo group and one in the bismuth group. This was probably due to the expanded final volume of the foam, about 230 mL, and not due to the constituents of the enema preparations themselves. It is possible that the four patients who developed cramping discomfort had smaller volume pouches which were more distended by the enemas than in the other patients, but pouch volumes were not measured in this study.

In conclusion, the bismuth carbomer foam enema at the dose used was not effective for the treatment of chronic ileal pouchitis. The preparation was safe, with negligible blood levels. Additional studies using a higher bismuth dose and in patients with less severe disease should be considered.

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