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Long-term efficacy of bismuth carbomer enemas in patients with treatment-resistant chronic pouchitis

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SUMMARY

Background: Mucosal inflammation of the ileal pouch (pouchitis) is the major long-term complication after ileal pouch-anal anastomosis for ulcerative colitis. Broad-spectrum antibiotics are the mainstay of treatment, however, 15% of patients with pouchitis have a chronic, treatment-resistant disease.

Aim: To determine the safety and efficacy of bismuth carbomer enemas in achieving and maintaining remission in treatment-resistant chronic pouchitis.

Methods: Twelve patients with treatment-resistant chronic pouchitis were treated nightly for 45 days with enemas containing elemental bismuth complexed with carbomer. Diagnosis of pouchitis and response to treatment were evaluated with the Pouchitis Disease Activity Index (PDAI), which includes clinical, sigmoidoscopic and histological criteria. Serum bismuth concentrations were determined by atomic absorption.

Results: Ten of 12 patients (83%) went into remission, with a significant decrease of mean total PDAI score from 12 (range 9–15) to 6 (4–15) ($P < 0.002$), and were continued on bismuth carbomer enemas administered every third night for 12 months. Patients were monitored clinically, sigmoidoscopically and histologically every 2 months for evidence of recurrence (increase ≥ 2 in the clinical symptom portion of the PDAI). Six of 10 patients (60%) were able to maintain remission throughout the 12-month trial; 4/10 had an exacerbation, two of which occurred soon after discontinuing daily treatment. Serum bismuth levels were negligible in all patients and no side-effects were registered.

Conclusions: Our findings suggest that bismuth carbomer enemas are safe and effective in achieving and maintaining remission in patients with treatment-resistant chronic pouchitis.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is a well-established surgical procedure for the management of ulcerative colitis and familial adenomatous polyposis (FAP).[1, 2]

Pouchitis, a non-specific inflammation of the ileal reservoir, is the most frequent long-term complication following pouch surgery for ulcerative colitis.[3] This syndrome is characterized clinically by the presence of diarrhoea, rectal bleeding, faecal urgency, abdominal cramping, malaise and fever.[4, 5] Its exact cause(s) are poorly understood and pathogenetic theories abound, including faecal stasis with bacterial overgrowth, mucosal ischemia, Crohn's disease and recurrent ulcerative colitis.[6]

The medical treatment of pouchitis has been largely empirical, and antibacterial drugs are the mainstay of treatment, especially metronidazole, which is the only drug with efficacy shown in a controlled study.[7] Although most patients experience one or more short-term episodes of acute inflammation, which usually respond well to metronidazole, ≈15% of patients have a chronic pouchitis (duration of symptoms for more than

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4 weeks) requiring continued medical treatment (with high incidence of side-effects), with recurrence within a few weeks of discontinuation of therapy and with high probability of having to undergo a pouch excision. Recently bismuth citrate enemas were shown to be as effective as 5-aminosalicylic acid enemas in patients with distal ulcerative colitis.[8]

The aim of our study was to evaluate the efficacy and safety of bismuth-citrate carbomer enemas in achieving and maintaining remission in a group of patients with chronic, treatment-resistant pouchitis.

MATERIALS AND METHODS

Selection of patients

The study was performed in accordance with the Declaration of Helsinki and all amendments, and was approved by the Local Ethics Committee; all patients gave written informed consent.

Eligible patients were older than 18 years of age, with a confirmed diagnosis of chronic treatment-resistant pouchitis.

Pouchitis was defined as a score of ≥ 7 using an 18-point Pouchitis Disease Activity Index (PDAI), which includes clinical, endoscopic and acute histological criteria (Table 1).[9]

Chronic pouchitis was defined as continuous symptoms for more than 4 weeks and the need for drugs (antibacterial/anti-inflammatory drugs) on more than 15 days per month to control symptoms.

Treatment resistance was defined as no response after combined treatment with antibiotics (such as metronidazole, or ciprofloxacin or amoxycillin/clavulanic acid), plus mesalazine or steroid enemas for at least 4 weeks.

Patients with clinically important hepatic, renal, cardiovascular or psychiatric conditions, patients with perianal disease and pregnant or lactating women were excluded. Patients who had taken any bismuth preparations within one week of study entry were also excluded.

Study drugs

The study drug consisted of 100 mL enemas containing 230 mg of elemental bismuth complexed with carbomer, a synthetic polyacrylate (Tillotts Pharma AG,

Table 1. Pouchitis Disease Activity Index (PDAI)

Criteria		Score
Clinical		
Post-operative stool frequency:	Usual	0
	1–2 stools/day more than usual	1
	3 or more stools/day more than usual	2
Rectal bleeding:	None or rare	0
	Present daily	1
Faecal urgency/abdominal cramps	None	0
	Occasional	1
	Usual	2
Fever (temperature >100°F):	Absent	0
	Present	1
Endoscopic		
Oedema		1
Granularity		1
Friability		1
Loss of vascular pattern		1
Mucus exudate		1
Ulcerations		1
Acute histological		
Polymorph infiltration	Mild	1
	Moderate + crypt abscess	2
	Severe + crypt abscess	3
Ulceration per low-power field (average)	< 25%	1
	≥ 25%, ≤ 50%	2
	> 50%	3

Ziefen, Switzerland). Patients were instructed to administer the enema at bedtime and to return packages containing the enemas at each clinic visit. Compliance was checked by the study personnel; patients were considered non-compliant if they consumed less than 75% of the study drug during their treatment period.

Study design

The study included two treatment phases: (i) an acute phase treatment, in which enemas were administered nightly for 45 days; and (ii) maintenance phase treatment, in which only patients who went into clinical remission after the acute phase entered, with enemas administered every third night for 12 months.

Follow-up visits were planned after 45 days and after 2, 4, 6, 8, 10 and 12 months during the maintenance treatment period. Treatment was to continue throughout the study, unless the patient had to withdraw due to substantial side-effects, was lost to follow-up, suffered intercurrent illness, relapse or poor compliance. Patients were free to withdraw from the study, if they wished, at any time.

Response to treatment after the acute phase, i.e. clinical remission, was defined as a decrease in the clinical symptom portion of the PDAI ≥ 2 points.

Relapse during maintenance treatment was defined as an increase in the clinical symptom portion of the PDAI ≥ 2 points.

Twelve patients (4 females, 8 males; median age 36 years, range 21–47) with chronic treatment-resistant pouchitis were studied.

The median follow-up time after pouch surgery was 48 months (range 6–104).

Evaluation and scheduling

Symptom assessment, endoscopic and histological evaluations were performed at screening and at all post-baseline study visits using the PDAI score. Patients demography, medical history and physical examination were recorded.

Endoscopic mucosal biopsies were taken in the pouch from areas that appeared to have the most active inflammation.

Stool culture and microscopic examination for parasites were performed to exclude enteropathogens.

All 12 patients discontinued chronic antibacterial or anti-inflammatory therapy on entry to the study.

Failed therapy during the current pouchitis flare included metronidazole + mesalazine enemas (6 patients); metronidazole + steroid enemas (3 patients), amoxycillin/clavulanic acid + steroid enemas (1 patient) and ciprofloxacin + mesalazine enemas (2 patients).

Laboratory screening was performed at baseline, at the end of acute phase treatment (after 45 days) and after 6 and 12 months during maintenance treatment.

Serum bismuth concentrations were measured at baseline and every 4 months during maintenance treatment by atomic absorption spectrophotometry.[10]

Statistical analysis was performed using the Wilcoxon rank sum test.

RESULTS

Baseline characteristics of patients are shown in Table 2.

Clinical outcome of patients by treatment is shown in Figure 1. No patients withdrew from the study. Ten of 12 treated patients (83%) went into remission after 45 days and entered the maintenance treatment phase. The mean PDAI scores before and after therapy were 12 (range 9–15) and 6 (range 4–15), respectively ($P < 0.002$). Figure 2 shows the changes in total PDAI score for all 12 patients after the acute treatment phase. As can be seen, there was a significant decrease in the overall PDAI score which was due to a significant decrease of the score of either the clinical symptoms or the sigmoidoscopic or histological portion of the PDAI, and all 10 patients who went into clinical remission had a total score of < 7 at the end of the acute phase.

During maintenance treatment four patients relapsed two within 2 months and the remaining two after 4 and 5 months, respectively) while six remained in remission, with total PDAI always < 7, at the end of the 12 months of follow-up.

Table 2. Baseline characteristics of patients

• Male/Female	8/4
• Median age (years)	36
• Median follow-up (months)	48
• Failed therapy (number of patients)	
Metronidazole + mesalazine enemas	6
Metronidazole + steroid enemas	3
Ciprofloxacin + mesalazine enemas	2
Amoxycillin/clavulanic acid + steroid enemas	1

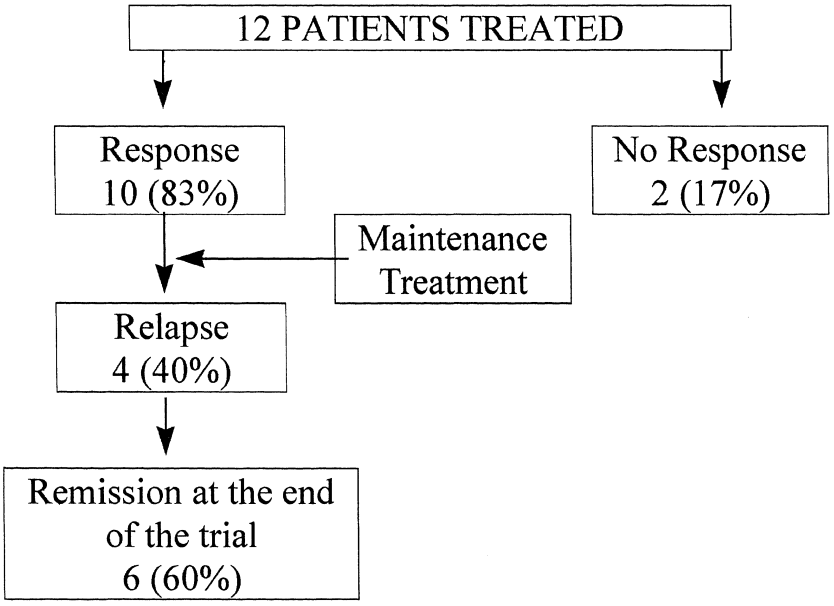

Figure 1. Clinical outcome of 12 patients with treatment-resistant chronic pouchitis, who received bismuth carbomer enemas.

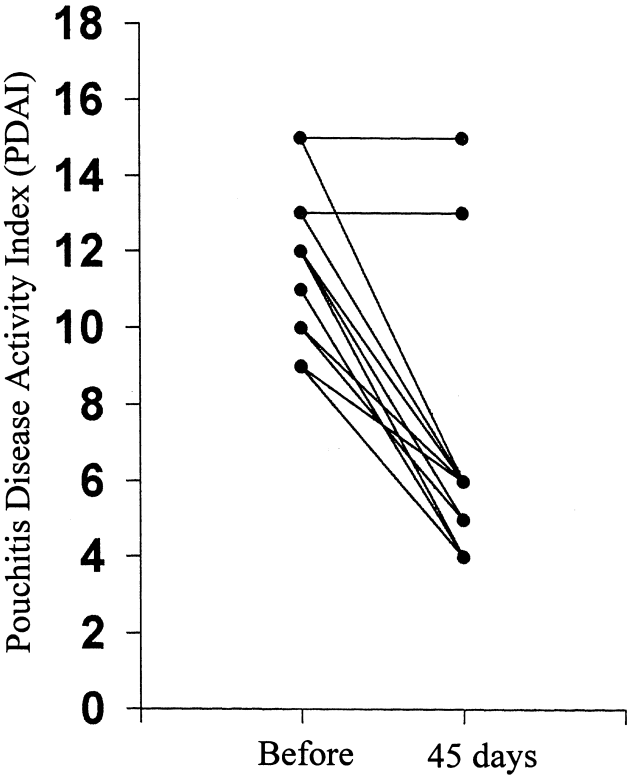

Figure 2. Total PDAI values for each patient before and after acute treatment with bismuth carbomer enemas (before vs. 45 days, $P < 0.002$).

Safety

No side-effects and no significant changes from baseline values in any of the laboratory parameters examined were registered.

Bismuth serum concentration

Bismuth levels were negligible and always in a safe range (< 5 μg/g), and there was no bismuth accumulation during the study. Median concentrations (range) at 4, 8 and 12 months were, respectively, 4.6 μg/g (3.7–4.8), 4.2 (3.5–4.6) and 3.9 (3.3–4.4).

DISCUSSION

The results of this open study suggest that bismuth carbomer enemas are safe and effective in achieving and maintaining remission in patients with treatment-resistant chronic pouchitis.

Pouchitis remains the most common long-term complication after pouch surgery for ulcerative colitis. Its cumulative frequency largely depends on the duration of follow-up[1, 2, 11–13] and definition of pouchitis used. Treatment of pouchitis is empirical, and broad-spectrum antibiotics are the mainstay of treatment. Most patients have a good response to metronidazole, which reduces the bacterial counts of bacteroides[14] and the leukocyte infiltration in the pouch.[15] One double-blind placebo-controlled trial showed a significant reduction of bowel

movements, without improvement in endoscopic appearance or histological grade of activity.[7] No attempt has been made to compare metronidazole with other modes of therapy. About 15% of patients with pouchitis have a chronic disease, either a treatment-responsive form, which requires maintenance metronidazole therapy, with a high incidence of side-effects, such as disgeusia, nausea and peripheral neuropathy (occurring in up to 80% of patients over 6–12 months), or a treatment-resistant form that does not respond to the antibiotic treatment.[6] Alternative approaches have been tried in patients resistant to antibiotic treatment, such as corticosteroid[3] or 5-aminosalicylic enemas[16] and short-chain fatty acid enemas,[17] with only some clinical benefit.

Treatment with bismuth carbomer enemas in this study resulted in a significant improvement in clinical symptoms, and endoscopic and histological activity. Moreover, long-term results together with the low serum bismuth levels obtained throughout the study, indicate the usefulness of this approach as a maintenance of remission in a group of otherwise intractable patients.

Mechanisms of action of this preparation are not yet established.

The aetiology and pathogenesis of pouchitis are not well understood; however, the bacterial flora appears to be one important factor. Recently it has been suggested that pouchitis may be the result of instability of the flora in the pouch of susceptible patients, which determines a dysbiosis with an impairment of protection of pouch mucosa by the mucus gel layer due to increased activity of bacterial and host-derived proteolytic enzymes.[18]

Bismuth, which forms a viscous, mucous-like, soluble complex with carbomer, is known to have a toxic effect on enzyme systems of bacteria, and may interfere with bacterial adherence through this mechanism.[19] Carbomer, a synthetic polyacrylate, can promote gel formation with mucin monomers from colonic mucosa and has faecal protease inhibiting activity.[20] Recently, a carbomer enema determined a marked improvement in clinical, sigmoidoscopic and histological activity in patients with active distal ulcerative colitis.[21]

Our preliminary findings suggest that bismuth carbomer enemas are safe and efficacious in achieving and maintaining remission in treatment-resistant pouchitis. This preparation may act by increasing the integrity of the mucus gel layer, reducing bacterial adherence and possibly killing some types of micro-organisms.

A randomized double-blind trial of bismuth carbomer enemas is warranted in patients with pouchitis.

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