THE AMERICAN JOURNAL OF GASTROENTEROLOGY
© 2003 by Am. Coll. of Gastroenterology
Published by Elsevier Inc.

Vol. 98, No. 5, 2003
ISSN 0002-9270/03/$30.00
doi:10.1016/S0002-9270(03)00135-7

Treatment of Chronic Constipation With Colchicine: Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

G. Nicholas Verne, M.D., Richard H. Davis, P.A.-C., Michael E. Robinson, Ph.D., James M. Gordon, M.D., Ervin Y. Eaker, M.D., and Charles A. Sninksy, M.D.

Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, Florida; Medical University of South Carolina, Charleston, South Carolina; Clinical and Health Psychology (UF), Gainesville, Florida; Gastroenterology Consultants of Tidewater, PLLC, Virginia Beach, Virginia; West Glenn Endoscopy Center, Shawnee, Kansas; and Digestive Disease Associates, Gainesville, Florida

OBJECTIVE: Refractory constipation is a common GI complaint seen by physicians in all practice settings. We have previously shown that *p.d.* colchicine (0.6 mg *t.i.d.*) increases the number of spontaneous bowel movements, hastens GI transit, and improves GI symptoms in patients with chronic constipation during an 8-wk, open-label therapeutic trial. The aim of this study was to determine if *p.d.* colchicine will increase spontaneous bowel movements and accelerate colonic transit in patients with idiopathic chronic constipation in a randomized, placebo-controlled, crossover trial.

METHODS: A total of 16 patients (15 women, one man) with a mean age of 47 yr (age range 25–89) with chronic idiopathic constipation who were refractory to standard medical therapy participated in the study. Patients randomly received either colchicine 0.6 mg *p.o. t.i.d.* or an identical placebo *p.o. t.i.d.* for a total of 4 wk in a double-blind, crossover fashion. Patients recorded their daily number of bowel movements and daily symptoms of daily nausea, abdominal pain, and bloating. Mean colonic transit was calculated at baseline, weeks 6 and 12.

RESULTS: Colchicine increased the number of bowel movements and accelerated colonic transit compared with baseline and placebo conditions. There were no significant differences between conditions on ratings of nausea and bloating. During colchicine administration, mean abdominal pain was greater than the baseline or placebo conditions, however, the pain decreased significantly by the last week the patient was on colchicine.

CONCLUSION: Colchicine increases the frequency of bowel movements and hastens colonic transit in patients with chronic constipation. Colchicine may be an effective agent available to practitioners to treat a subset of patients with chronic constipation who are refractory to standard medical therapy. (Am J Gastroenterol 2003;98:1112–1116. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Refractory constipation is a common GI complaint seen by physicians in all practice settings (1). The duration and severity of symptoms experienced by patients with constipation may provide insight into the underlying etiology of the constipation. Endocrine and metabolic abnormalities, medications, GI motility disturbances, pelvic outlet obstruction, and malignancies of the colon and other organs should be considered in the diagnostic workup (2–4). However, in most patients, no etiology is found.

Treatment of patients with refractory constipation includes a combination of fiber supplementation, stool softeners, osmotic agents, and/or regular administration of polyethylene glycol lavage solutions. There are few Food and Drug Administration-approved agents that stimulate GI motility and are useful in the treatment of constipation. Bisacodyl and anthraquinone drugs are frequently used for constipation. Misoprostol, a well-known prostaglandin E_1 analog, has also been shown to be effective in some patients with refractory constipation (5). Unfortunately, high doses (1200 μg/day) of misoprostol may be needed, which may have abortifacient properties and can cause menstrual-like cramping in premenopausal women, thereby limiting its general use. A subset of patients may not respond to medical therapy and ultimately require subtotal colectomy (6).

Colchicine is used on a regular basis for familial Mediterranean fever and acute gouty arthritis. However, one of the common side effects is diarrhea. A recent study has shown that *p.o.* colchicine is effective in treating refractory constipation in developmentally disabled patients who require large doses of laxatives (7). We have previously shown that *p.o.* colchicine (0.6 mg *t.i.d.*), in a similar dose used in familial Mediterranean fever, increases the number of spontaneous bowel movements, hastens GI transit, and improves GI symptoms in patients with chronic constipation during an 8-wk, open-label therapeutic trial (8, 9). Thus, the

Table 1. Results

			Base	Colchicine	Base	Colchicine
Subject	Age (yr)	Sex	Colonic Transit (h)		Bowel Movements (wk)	
1	50	F	72	40	1.5	10.5
2	33	F	63	17	3	10.5
3	43	F	72	11	1.5	10
4	41	F	66	6	1	9.5
5	25	F	71	17	8	16.5
6	42	F	24	16	4.5	11
7	53	F	67	3	2.5	11
8	39	F	62	25	1	5
9	38	F	43	16	2	7
10	49	F	66	21	1	11
11	69	M	62	52	2.5	9
12	42	F	72	43	3	5
13	30	F	72	63	3	4.5
14	89	F	68	33	1	6
15	55	F	72	62	4.5	6.5
16	56	F	57	41	3	26
Means			63.1 ± 12.9	29.1 ± 19.1	2.7 ± 1.8	9.9 ± 5.3

Values represent mean ± SD.

aims of our current study were to: 1) confirm the findings of our previous pilot trial and, 2) to determine if *p.o.* colchicine will increase the number of spontaneous bowel movements and accelerate colonic transit in patients with refractory constipation in a randomized, placebo-controlled, crossover trial.

MATERIALS AND METHODS

Subjects

We prospectively studied 16 patients with chronic constipation who were referred to the Medical University of South Carolina, Charleston, South Carolina, and the University of Florida, Gainesville, Florida, Gastroenterology Clinics from July, 1995 to June, 1997. The study was approved by the Institutional Review Boards at both universities, and each subject gave written informed consent before inclusion into the study. A total of 16 patients (15 women, one man) with a mean age of 47 yr (age range 25–89) participated in the study (Table 1). All of the patients had idiopathic constipation without evidence of diabetes mellitus, thyroid disease, collagen vascular disease, neurological disease, or evidence of prior GI surgery. All patients reported a long history of constipation for >10 yr and had two or more of the Rome II criteria for constipation (1). The patients enrolled did not respond to routine medical therapies for constipation including fiber supplementation, bisacodyl, and anthraquinone drugs.

Women of childbearing age were not allowed to participate unless they practiced approved contraceptive methods and had a negative serum pregnancy test. Patients were screened and eliminated if they had any evidence of thyroid, renal, liver, or hemopoietic abnormalities, diabetes mellitus, mechanical bowel obstruction, or previous GI surgery. Each subject had a negative colonic evaluation with an air-contrast barium enema/flexible sigmoidoscopy or a colonoscopy. Colonic transit was delayed in all subjects as documented by radiopaque markers (10). Before entry into the study, all patients had an anorectal manometry to exclude pelvic floor dysfunction and had normal perineal descent as assessed clinically on examination. All patients were on 3.4 g of psyllium *t.i.d.* during the baseline colonic transit study and throughout the entire study.

Study Design

The study design was a prospective, randomized, double-blind, placebo-controlled, crossover trial. All patients were asked to stop laxative use at the start of the study and to refrain from laxative use during the entire 12 wk of the study. However, if patients did not defecate after 14 days while in the study, they were allowed to use a single Fleets enema (CB Fleet Company Inc, Lynchberg, FL) to relieve symptoms of constipation. Each patient kept a daily diary during the entire 12 wk of the study. Patients recorded the total number of spontaneous bowel movements they had each week. They also recorded daily nausea, abdominal pain, and bloating using a 0–5 visual analogue scale. A separate visual analogue scale was used for each symptom of nausea, abdominal pain, and bloating, which ranged from 0, "no nausea, abdominal pain, or bloating," to 5, "severe nausea, abdominal pain, or bloating." The scale consisted of a 5-cm line on which patients were instructed to place a vertical line to indicate their daily rating. The distance from the extreme left (0) was measured in mm and expressed as a continuous variable. Laboratory studies (*i.e.*, liver, renal, complete blood count) were obtained at baseline, and at weeks 6 and 12. Mean colonic transit was calculated at baseline, weeks 6 and 12, using radiopaque markers (Sitzmarks, Fort Worth, TX). Each patient swallowed a capsule with 24 markers on day 1, 2, and 3, and an abdominal x-ray

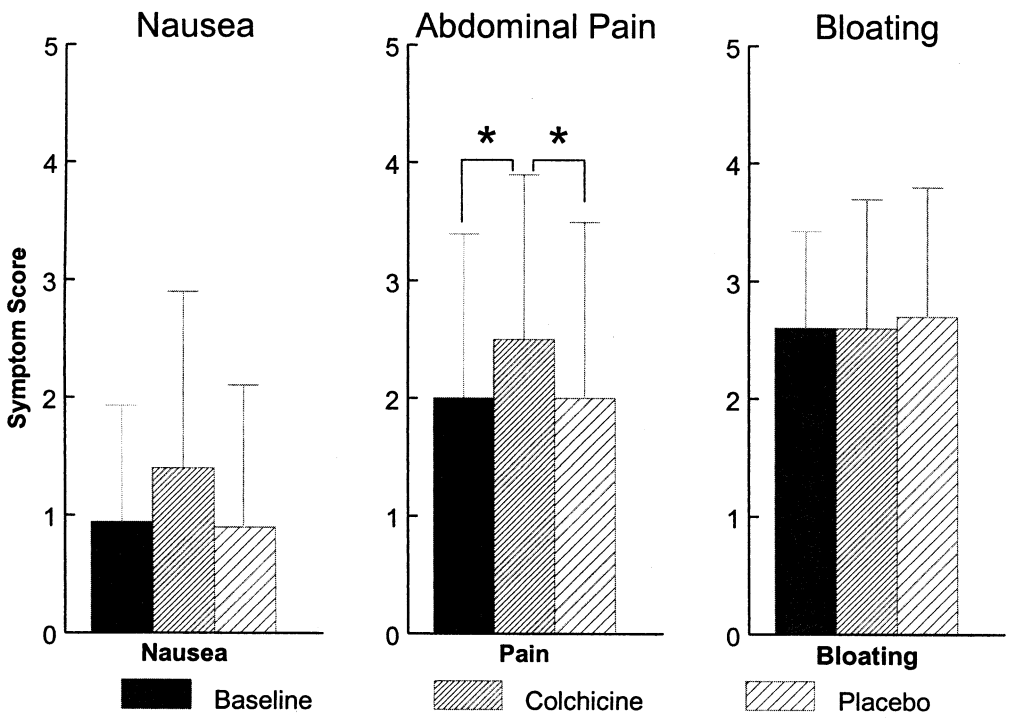

Figure 1. Bar graphs representing mean nausea, abdominal pain, and bloating scores during baseline, colchicine, and placebo. Values represent mean ± SD. *$p < 0.05$.

was performed on day 4. Mean colonic transit time was calculated as the number of markers remaining in the colon on day 4 as previously described (10).

The first 2 wk of the study served as baseline, and neither drug nor placebo was administered (Fig. 1). After the second week, each patient randomly received either colchicine 0.6 mg *p.o. t.i.d.* or an identical placebo *p.o. t.i.d.* for 4 wk. Neither the patient nor the examiner knew the order of the treatment condition. At the conclusion of the 4 wk, a 2-wk washout period was performed during which time colonic transit was not measured. After this, each patient then received another 4 wk of either colchicine 0.6 mg *p.o. t.i.d.* or an identical placebo *p.o. t.i.d.* in a crossover fashion. At the conclusion of the study, each patient had received both drug and placebo. The order that the drug and placebo were administered was counterbalanced across all patients. The patients were carefully monitored for evidence of adverse events secondary to colchicine administration.

Data Analysis

Separate one-way repeated measures analyses of variance were conducted for each dependent variable. Condition, baseline, drug, or placebo served as the within-subjects factor in all analyses. Table 1 and Figure 1 illustrate these analyses.

RESULTS

None of the patients used laxatives or required a Fleets enema to relieve constipation during the study. None of the patients experienced adverse events from colchicine that required them to drop out of the study. None of the patients developed any laboratory abnormalities (*i.e.*, liver, renal, complete blood count) requiring them to withdraw from the study.

Bowel Movements

Colchicine produced a significantly greater number of bowel movements compared with baseline and placebo conditions ($p < 0.001$) (Table 1). All patients noted an increase in their bowel movements within 3 days of taking colchicine. Within 2 wk after administration of colchicine, all patients noted that their bowel movements and symptoms had reverted back to baseline. At the conclusion of the study, patients requested to continue colchicine because of the marked improvement in their constipation.

Colonic Transit Time

Analysis of variance results indicated that colchicine significantly accelerated transit times compared with baseline and placebo conditions ($p < 0.001$) (Table 1).

GI Symptoms

There were no statistically significant differences between conditions on ratings of nausea ($p = 0.03$) (Fig. 1). Results of the analysis of variance on abdominal pain scores indicated a significant effect for condition. During colchicine administration, the mean abdominal pain reported was slightly greater than the baseline or placebo conditions, but patients were able to remain on the treatment ($p < 0.03$)

(Fig. 2). The patients described the pain as a mild, generalized, crampy abdominal pain that was associated with defecation. The abdominal pain significantly decreased by the 4th wk of colchicine therapy. There were no statistically significant differences between conditions on bloating scores ($p = 0.7$) (Fig. 1).

DISCUSSION

The results of our randomized, double-blind, placebo-controlled, crossover study demonstrates that colchicine increases the frequency of spontaneous bowel movements and hastens colonic transit in patients with chronic constipation. These findings confirm our earlier open-label, pilot study in which colchicine 0.6 mg *p.o. t.i.d.* was administered for 8 wk and was effective in treating medically refractory constipation (8). In both of our studies, there was a significant increase in the number of spontaneous bowel movements and an acceleration of colonic transit. However, unlike our previous study, patients in the current study did not have a significant improvement in their symptoms of nausea, abdominal pain, and bloating while on colchicine compared with placebo (Fig. 1). Several explanations may account for these disparate findings. First, the high placebo response rate characteristically present in functional bowel disorders could have accounted for some of the symptom improvement in our initial pilot study, which was a therapeutic trial without administration of a placebo (8, 11, 12). Another possible explanation is that the dose of colchicine was high enough in some patients to produce symptoms of nausea and abdominal pain that are characteristically seen in patients who receive hourly colchicine when hospitalized for a gouty arthritis attack. A smaller dose of colchicine (*i.e.*, 0.6 mg *p.o. q.d.-b.i.d.*) may have been effective in increasing spontaneous bowel movements without causing other GI side effects. Some of these patients may also have underlying visceral hypersensitivity in addition to colonic inertia. In addition, colchicine may have induced GI complaints by increasing motility and/or secretion in the small bowel leading to distension of the gut. However, all of the patients reported that the slight increase in abdominal pain they experienced with colchicine did resolve by the last week of colchicine therapy. Finally, in our current study, there may have been carryover effects of colchicine (because of the crossover design if colchicine arm administered first) that were not eliminated by the 2-wk washout period. If colchicine's actions continued beyond the 2-wk washout period, the placebo arm may have had greater efficacy in accelerating colonic transit than would normally be seen. Despite this possible carryover effect, colchicine was still more effective than placebo in increasing the number of bowel movements and accelerating colonic transit.

All of the patients that were enrolled in the study complained of long-standing constipation. It should be noted that patients 5 and 15 had more than three bowel movements/wk and had significantly delayed colonic transit times of 71 and 72 h, respectively. However, these patients had a normal anal manometry and no evidence of pelvic outlet obstruction. They did complain of passing very small stool volumes during each bowel movement. If our study design had included the measurement of total stool weight, it could be anticipated that patients 5 and 15 would exhibit decreased total stool weights. Thus, this may explain the disparity between colonic transit and the actual number of bowel movements noted by these two patients. Alternatively, patient 6 had 4.5 bowel movements/wk and exhibited a colonic transit time of only 24 h.

The exact mechanism of action by which colchicine causes diarrhea and increases GI transit remains unclear. Increases in prostaglandin synthesis, intestinal secretion, and GI motility may play a role (13). Previous studies have shown that colchicine increases net intestinal secretion by decreasing water and electrolyte absorption and may increase secretion through a cyclic adenosine monophosphate (AMP)-mediated activity (14–17). Increased GI motility may also play a role in colchicine's actions. Colchicine has been shown to stimulate myoelectric activity in the rat small intestine (18–20). Other studies have shown that long-term therapy with colchicine for familial Mediterranean fever may cause a mild, reversible malabsorption (21–23).

Long-term therapy with *p.o.* colchicine is safe, and has very few side effects that have been reported in the literature in patients who have been treated for several yr. The most common and well-known side effect of *p.o.* colchicine therapy is diarrhea, although some patients may also develop nausea, vomiting, and abdominal pain with its acute use (13). Diarrhea usually occurs in most patients after a mean *p.o.* dose of 3.6 mg over a 24-h period (24). Other rare side effects have been reported with colchicine including myopathy and neuropathy (25). These patients typically present with proximal muscle weakness and elevation of serum creatine phosphokinase (CPK) levels. However, these symptoms usually remit 3–4 wks after colchicine is discontinued.

In summary, our current study provides further evidence that colchicine increases the frequency of spontaneous bowel movements and hastens colonic transit in patients with constipation. The results of our study may have been influenced by the fact that 15 of 16 of the subjects were women. Thus, the results of this study may not necessarily be applicable to men treated with colchicine. Future studies in both male and female patients with constipation are needed with varying doses of colchicine administered over longer periods of time. Colchicine may prove to be beneficial in patients with chronic constipation who are refractory to standard medical therapy.

ACKNOWLEDGMENTS

The authors would like to thank Janice Freeman for her work on the project. This work was supported by research

funds from Charles A. Sninsky, M.D., and the Digestive Disease Center, Charleston, South Carolina.

Reprint requests and correspondence: G. Nicholas Verne, M.D., Malcom Randall VAMC, Research Service (151), 1601 Southwest Archer Road, Gainesville, FL 32608.

Received June 25, 2002; accepted Oct. 10, 2002.

REFERENCES

1. Thompson WG. Functional bowel disorders and functional abdominal pain. Gut 1999;45(suppl II):1143–7.
2. Camilleri M, Thompson WG, Fleshman JW, et al. Clinical management of intractable constipation. Ann Intern Med 1994;121:520–8.
3. Wofford SA, Verne GN. Approach to patients with constipation. Curr Gastroenterol Rep 2000;2:389–94.
4. Locke GR, Pemberton JH, Phillips SF. American Gastroenterological Association medical position statement: Guidelines on constipation. Gastroenterology 2000;119:1761–6.
5. Soffer EE, Metcalf A, Launspach J. Misoprostol is effective treatment for patients with severe chronic constipation. Dig Dis Sci 1994;39:929–33.
6. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. Ann Surg 1999;230:627–38.
7. Frame PS, Dolan P, Kohli R, et al. Use of colchicine to treat severe constipation in developmentally disabled patients. J Am Board Fam Pract 1998;11:341–6.
8. Verne GN, Eaker EY, Davis RH, et al. Colchicine is an effective treatment for patients with severe idiopathic constipation. Dig Dis Sci 1997;42:1959–63.
9. Zemer D, Pras M, Sohar E, et al. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med 1986;314:1001–5.
10. Metcalf A, Phillips SF, Zinsmeister AR, et al. Simplified assessment of segmental colonic transit. Gastroenterology 1987;92:40–7.
11. Klein KB. Controlled treatment trials in the irritable bowel syndrome: A critique. Gastroenterology 1988;95:232–41.
12. Dunphy R, Verne GN. Drug treatment options for irritable bowel syndrome: Managing for success. Drugs & Aging 2001; 18:201–11.
13. Levy M, Spino M, Read SE. Colchicine: A state-of-the art review. Pharmacotherapy 1991;11:196–211.
14. Notis WM, Orellana SA, Field M. Inhibition of intestinal secretion in rats by colchicine and vinblastine. Gastroenterology 1981;81:766–72.
15. Venho VM, Koivuniemi A. Effect of colchicine on drug absorption from the rat small intestine in situ and in vitro. Acta Pharmacol Toxicol 1978;43:251–9.
16. Rachmilewitz D, Fogel R, Karmeli F. Effect of colchicine and vinblastine on rat intestinal water transport and Na-K-ATPase activity. Gut 1978;19:759–64.
17. Rachmilewitz D, Karmeli F. Effect of colchicine on jejunal adenylate cyclase activity, PGE_2, and cAMP contents. Eur J Pharmacol 1980;67:235–9.
18. Sninsky CA, Lynch DF. Why should microtubular inhibitors induce frequent activity fronts (AF) of the migrating myoelectric complex (MMC)? Gastroenterology 1986;90:1641.
19. Eaker EY, Sninsky CA. Taxol, a microtubular stabilizer, blocks the effects of colchicine on intestinal motility. Gastroenterology 1987;92:A1379 (abstract).
20. Sninsky CA. Vincristine alters myoelectric activity and transit in the small intestine in rats. Gastroenterology 1987;92:472–8.
21. Hart J, Lewin KJ, Peters RS, et al. Effect of long-term colchicine therapy on jejunal mucosa. Dig Dis Sci 1993;38:2017–21.
22. Ehrenfeld M, Levy M, Sharon P, et al. Gastrointestinal side effects of long-term colchicine therapy in patients with recurrent polyserositis (familial Mediterranean fever). Dig Dis Sci 1982;27:723–7.
23. Race TF, Paes IC, Faloon WW. Intestinal malabsorption induced by oral colchicine. Comparison with neomycin and cathartic agents. Am J Med Sci 1970;259:32–41.
24. Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med 1987;17:301–4.
25. Kuncl RW, Duncan G, Watson D, et al. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562–8.