

Sodium Cromoglycate in the Management of Chronic or Recurrent Enterocolitis in Patients With Hirschsprung's Disease

By R.J. Rintala and H. Lindahl
Helsinki, Finland

Background/Purpose: Chronic or recurring enterocolitis is a rare but perplexing complication of Hirschsprung's disease affecting especially patients with altered immune defense such as those with Down's syndrome. Sodium cromoglycate (SCG) is a nonabsorbable mast cell stabilizing agent that has been documented to be effective in the treatment of inflammatory bowel disease. The authors studied the effect of SCG in Hirschsprung patients with refractory chronic or recurrent enterocolitis.

Methods: Eight patients (4 with Down's syndrome, 2 with other chromosomal aberrations, 2 otherwise healthy; age range from 4 to 22 years) with chronic (5 patients) or recurrent (>6 episodes/year, 3 patients) enterocolitis received 100 to 200 mg of SCG 4 times a day depending on the age of the patient. The chronic diarrhea or recurrent bouts of enterocolitis in the patients were refractory to dietary management and enteral antibiotics. Before the treatment all patients had ileocolonoscopy, the results of which showed macroscopic and histological chronic inflammation in all cases. No neuronal abnormalities were detected in biopsy results. None of the patients had colonic dilatation or increased anorectal resting pressures suggesting outlet obstruction.

Results: The follow-up of the patients ranges from 8 months to 26 months. Three of the 5 patients with chronic enterocolitis responded favorably. In these 3 patients the median number of daily bowel movements decreased from 6 to 3, and none experienced bouts of abdominal distension. Diarrhea-related soiling decreased also significantly. Two of the 3 patients with recurrent enterocolitis have remained asymptomatic, and none has required antibiotics after the onset of SCG treatment; one patient had an episode of enterocolitis after 12 months treatment. Two patients with chronic enterocolitis did not respond to SCG. No side effects of SCG were encountered.

Conclusions: This preliminary and nonrandomized study suggests that SCG is an effective treatment modality for chronic or recurrent enterocolitis in patients with Hirschsprung's disease. Because SCG is not absorbed from the intestinal tract there are no systemic side effects.
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INDEX WORDS: Hirschsprung's disease, enterocolitis, sodium cromoglycate.

POSTOPERATIVE ENTEROCOLITIS is the main complication in patients who have undergone surgical repair for Hirschsprung's disease. The reported incidences range from 10% to 33%.¹⁻³ Many patients have more than one attack of enterocolitis.⁴ The frequency of bouts of enterocolitis tends to decrease with time.⁵ A small proportion of patients continue to have persisting symptoms, such as diarrhea and abdominal distension, or frequently recurring attacks of enterocolitis. The exact nature of chronic or recurring enterocolitis is poorly understood; outlet obstruction or abnormal mucosal defence mechanism have been suggested to play a role in the pathogenesis.^{6,7} Chronic symptoms are especially common in children with Down's syndrome, who, in addition to other malformations, have altered

immune defence associated with abnormal T-lymphocyte function.⁸

Sodium cromoglycate (SCG) is a nonabsorbable mast cell stabilizing agent that has been documented to be effective in the treatment of inflammatory bowel disease.⁹ It also has been used in food allergies.¹⁰ We aimed to perform an open, nonrandomized study to explore the possible benefit of SCG in Hirschsprung patients with refractory chronic or recurrent enterocolitis.

MATERIALS AND METHODS

During 1997 and 1998, 8 consecutive patients, with symptoms of chronic or frequently relapsing enterocolitis, were enrolled to the sodium cromoglycate trial. The age range of the patients was from 4 to 22 years. All patients had undergone repair of Hirschsprung's disease during the first year of life. The original reconstruction was Duhamel operation in 2 patients and transanal endorectal coloanal anastomosis¹¹ in 6 patients.

Five of the patients had symptoms of chronic enterocolitis. Three of them had Down's syndrome and 2 other chromosomal aberrations. All these patients had chronic diarrhea or loose stools (median 6 bowel movements per day; range from 4 to 12). Exacerbations of the condition were common (several times per year) and were characterized by abdominal distension, nausea and vomiting, and poor appetite. The continuous loose stools caused mild to moderate soiling in 3 of the 5 patients. The dietary management of the patients consisted of a low

From Children's Hospital, University of Helsinki, Finland.
Address reprint requests to R.J. Rintala, MD, PhD, Professor of Paediatric Surgery, Children's Hospital, University, P.O. Box 281, FIN-00029 HYKS, Finland.

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residue, lactose-free diet. Enteral antibiotics were used at the time of exacerbation of symptoms. During the preceding year, 2 of the patients had required hospitalization for exacerbation of symptoms. Three patients (1 with Down's syndrome and 2 with normal chromosomes) had frequent attacks of enterocolitis (>6 episodes per year). During these bouts the patients had diarrhea, abdominal distension, nausea or vomiting, and poor appetite. Between the episodes of enterocolitis the patients were continent and had 1 to 3 bowel movements a day. The enterocolitis episodes were managed with enteral antibiotics and bowel decompression by saline enemas if necessary. All patients required hospitalization with intravenous fluid therapy at least once a year before the onset of SCG treatment. The dietary management of these patients was similar to those with chronic enterocolitis.

All patients had repeated stool cultures, the results of which did not show specific infective agents in any case; particularly, *Clostridium difficile*—growth was not isolated in any case. The most commonly used antibiotics were metronidazole and norfloxacin. Long-term symptom control with this treatment modality was poor in 5 cases and partial in 3.

All patients underwent ileocolonoscopy before the onset of SCG therapy. Standard biopsies for H&E staining were taken from the terminal ileum, cecum or ascending colon, hepatic flexure, splenic flexure, descending colon, and neorectum. Before SCG treatment, 5 patients had anorectal manometry; the manometric techniques have been published elsewhere.¹²

The SCG treatment was initiated with 100 mg of the drug 4 times a day enterally. The regimen was continued for 6 weeks, when the patients were reassessed. In 2 older patients (ages 10 years and 22 years) who did not respond initially, the dose was increased to 200 mg 4 times a day. The following clinical reassessment was performed 4 months after the onset of the therapy. In patients who did not benefit from the therapy, the medication was discontinued. In the responders, a trial to taper the dose to the minimal effective level was made.

RESULTS

At endoscopy the macroscopic findings were consistent with mild to moderate colitis predominantly in the left colon. None of the patients had megacolon. The histology results findings showed chronic inflammation in all cases, especially in the distal biopsies. In histology there were no specific findings suggesting other forms of chronic colonic inflammatory disease such as ulcerative colitis or Crohn's disease. Biopsy results from distal ileum were normal in all patients. Biopsy specimens for acetylcholinesterase staining were taken from the distal colon in 5 patients. No neuronal abnormalities were detected either in standard histology or in the acetylcholinesterase-stained samples.

On rectal examination, all patients had normal sphincter tone. The anorectal resting pressures in the 5 patients

undergoing manometry were within the normal range of healthy children and did not differ from the resting pressures of patients with Hirschsprung's disease but without postoperative enterocolitis.

Three of the 5 patients with chronic enterocolitis responded favorably. The median follow-up period of these patients is 14 months (range from 8 to 26 months). In these 3 patients the median number of daily bowel movements decreased from 6 to 3 (range from 1 to 5). The consistency of the stools became more solid, and soiling related to loose or diarrheic stools diminished. The effect of SCG became apparent in a few weeks after the onset of the therapy. During the follow-up, none of these 3 patients have required antibiotics for exacerbation of symptoms. These 3 patients have continued the SCG therapy throughout the follow-up period. In one of them the daily dose of SCG was tapered to 200 mg from the original dose of 400 mg per day and in one to 400 mg from the original dose of 800 mg.

Two of the patients with chronic enterocolitis did not respond to the therapy after a trial of 4 months, and SCG treatment was discontinued. One of these 2 patients gained benefit from a predominantly intraluminally acting glucocorticoid, budesonide. All the 3 patients with recurrent enterocolitis responded favorably to SCG treatment. Two patients (follow-up period 8 months and 14 months) have remained completely asymptomatic and have had no attacks of abdominal distension or diarrhea after the onset of the therapy. One patient had an episode of enterocolitis requiring antibiotics after a rotavirus gastroenteritis 1 year after the onset of SCG therapy. All these patients have continued the SCG therapy throughout the follow-up period. The daily dose of SCG has remained in 400 mg in 1 and was tapered to 300 mg in 2. The clinical features of the patients are summarized in Tables 1 and 2.

DISCUSSION

The prevalence of chronic or frequently recurring enterocolitis among patients with surgically repaired Hirschsprung's disease is unknown. It is clear that this problem affects more commonly patients with defective immune systems such as those with Down's syndrome. In the current series 4 of the 8 patients had Down's syndrome and 2 more had other chromosomal aberra-

Table 1. Clinical Features of Patients With Chronic Enterocolitis

Patient No., Age, Associated Abnormalities	Pretreatment Stool Frequency	Posttreatment Stool Frequency	SCG Dose/24 hr	Outcome/Follow-Up
1, 22 yr, Down's syndrome	6	5	800 mg	Poor/4 months
2, 10 yr, Down's syndrome	12	5	800→400 mg	Good/26 months
3, 7 yr, Down's syndrome	5	3	400→200 mg	Good/14 months
4, 7 yr, syndromic chromosomal aberration	4	1	400 mg	Good/8 months
5, 6 yr, syndromic chromosomal aberration	8	6	400 mg	Poor/4 months

Table 2. Clinical Features of Patients With Recurrent Enterocolitis

Patient No., Age, Associated Abnormalities	Frequency of Pretreatment Enterocolitis Episodes	Frequency of Posttreatment Enterocolitis Episodes	SCG Dose/24 hr	Outcome/Follow-Up
6, 8 yr, Down's syndrome	1-2/ mo	1/yr	400 mg	Good/18 months
7, 6 yrs	6-8/yr	No episodes	400→300 mg	Good/14 months
8, 4 yrs	1/ mo	No episodes	400→300 mg	Good/8 months

tions. Postoperative enterocolitis also has been attributed to bowel outlet obstruction.⁶ In the current series none of the patients had a stricture or stenosis of the bowel outlet. Moreover, the anal resting pressures of the patients did not differ from those of Hirschsprung's patients with no enterocolitis or from those of healthy children.

The clinical diagnosis of chronic or recurring enterocolitis is not always straightforward. Many patients with Hirschsprung's disease have abnormal colonic motility,¹³ which may cause bacterial overgrowth and paradoxical diarrhea. In the current series the diagnosis of chronic enterocolitis was confirmed in all patients by ileocolonoscopy and segmental biopsies.

The treatment of acute enterocolitis traditionally has been comprised of decompression of the colon, bowel rest, and antibiotics. However, there are no generally accepted treatment guidelines for chronic or recurring enterocolitis. In our institution the standard treatment has been low residue, lactose-free diet to diminish substrates for bacterial overgrowth, and enteral antibiotics at times of symptom exacerbation. In the current series the symptoms of the patients were poorly controlled by this therapy regimen.

The likely mode of action of SCG is stabilization of mast cells by decreasing the release of histamine from these inflammatory cells.¹⁴ SCG has been used widely for allergic conditions of the respiratory tract. More recently, SCG has proven to be effective in the treatment of food allergies and inflammatory bowel disease.^{9,10} SCG is not absorbed significantly from the alimentary tract and, therefore, has no systemic side effects. Clinically, chronic and recurring enterocolitis resembles inflammatory bowel disease (IBD), especially ulcerative

colitis. As therapeutic modalities for ulcerative colitis are relatively nonspecific and mainly aim at suppression of the inflammatory activity in the large bowel mucosa, it may be speculated that similar therapy may be effective also for chronic enterocolitis after repair of Hirschsprung's disease. SCG was selected for the current open trial because it is well tolerated and lacks systemic side effects. To our knowledge, the use of SCG or any other anti-inflammatory therapy for IBD has not been reported before in conjunction of postoperative enterocolitis after repair of Hirschsprung's disease.

Significant clinical improvement was detected in 6 of our 8 patients. In the 3 responders with diarrhea or frequent loose stools related to chronic enterocolitis the quality of life improved significantly as the solidification of the stools and decreased stool frequency diminished soiling. All these patients were mentally retarded and did not cope well with the frequent soiling episodes before SCG therapy. One of the 2 nonresponders received more potent antiinflammatory agent, local glucocorticoid therapy with budesonide, which resulted in significant improvement. The patients with recurrent bouts of enterocolitis have remained free of symptoms except for one patient who had a single attack following viral gastroenteritis.

The current study suggests that chronic and recurring enterocolitis is associated with chronic inflammatory changes in the large bowel mucosa. The study also gives strong preliminary evidence that anti-inflammatory medication that has been shown to be effective in patients with IBD appears to alleviate the symptoms in the majority of patients suffering from chronic or recurrent enterocolitis.

REFERENCES

1. Carneiro PMR, Brereton RJ, Drake DP, et al: Enterocolitis in Hirschsprung's disease. *Pediatr Surg Int* 7:356-360, 1992
2. Ikeda K, Goto S: Diagnosis and treatment of Hirschsprung's disease in Japan. An analysis of 1628 patients. *Ann Surg* 199:400-405, 1984
3. Rescorla FJ, Morrison AM, Engles D, et al: Hirschsprung's disease. Evaluation of mortality and long-term function in 260 cases. *Arch Surg* 127:934-941, 1992
4. Elhalaby EA, Coran AG, Blane CE, et al: Enterocolitis associated with Hirschsprung's disease: A clinical-radiological characterization based on 168 patients. *J Pediatr Surg* 30:76-83, 1995
5. Fortuna RS, Weber TR, Tracy TF Jr, et al: Critical analysis of the operative treatment of Hirschsprung's disease. *Arch Surg* 131:520-524, 1996
6. Carcassonne M, Guys JM, Morrison-Lacombe G, et al: Management of Hirschsprung's disease: Curative surgery before 3 months of age. *J Pediatr Surg* 24:1032-1034, 1989
7. Teitelbaum DH, Caniano DA, Qualman SJ: The pathophysiology of Hirschsprung's-associated enterocolitis: Importance of histologic correlates. *J Pediatr Surg* 24:1271-1277, 1989
8. Nair MPN, Schwatz SA: Association of decreased T-cell-mediated natural cytotoxicity and interferon production in Down's syndrome. *Clin Immunol Immunopathol* 33:412-424, 1984
9. Grace RH, Gent AE, Hellier MD: Comparative trial of sodium cromoglycate enemas with prednisolone enemas in the treatment of ulcerative colitis. *Gut* 28:88-92, 1987
10. Lunardi C, Bambara LM, Biasi D, et al: Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel

syndrome due to food intolerance. *Clin Exp Allergy* 21:569-572, 1991

11. Rintala R, Lindahl H: Transanal endorectal coloanal anastomosis for Hirschsprung's disease. *Pediatr Surg Int* 8:128-131, 1993

12. Rintala R: Postoperative internal sphincter function anorectal malformations—A manometric study. *Pediatr Surg Int* 5:127-130, 1990

13. Baillie CT, Kenny SE, Rintala RJ, et al: Long-term outcome and colonic motility after the Duhamel procedure for Hirschsprung's disease. *J Pediatr Surg* 34:325-329, 1999

14. Selbekk BH: Neurotensin-induced mast cell degranulation in human jejunal mucosa. Additive effects of IgE or compound 48/80 and inhibition by sodium cromoglycate. *Scand J Gastroenterol* 19:595-602, 1984