

Mesalamine Intolerance in Three Children with Crohn's Disease

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Key Words

Children · Crohn's disease · Mesalamine · Side effect

Abstract

Objective: To present the mesalamine-induced acute exacerbation of symptoms and inflammatory markers in children with Crohn's disease (CD). **Clinical Presentation and Intervention:** Three children who presented with CD had acute exacerbation of colitis symptoms or elevated inflammatory markers when mesalamine was added to treatment while tapering/ceasing steroid treatment. While on steroid treatment, the patients maintained clinical and laboratory remission, but with the initiation of mesalamine treatment, they had abdominal pain and bloody mucoid diarrhoea and/or elevation of white blood cell count, C-reactive protein level and erythrocyte sedimentation rate. Bacterial pathogens were excluded from the urine, throat and blood cultures, parasites with stool examination, viral pathogens with serology. Within 3–7 days after the mesalamine treatment had been stopped, the patients showed improvement of colitis symptoms and normalisation of white blood cell count, C-reactive protein level and erythrocyte sedimentation rate. **Conclusion:** In this study mesalamine mimicked CD relapse in children with CD while tapering or after stopping steroid treatment. Awareness of this side effect of mesalamine could prevent a misdiagnosis of steroid dependency.

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Introduction

Mesalamine is frequently used to induce or maintain remission in mild to moderately active inflammatory bowel disease. Nausea, abdominal pain and skin rashes are the most common side effects [1, 2]. We describe 3 patients with Crohn's disease (CD) who had acute exacerbation of colitis symptoms or elevated inflammatory markers while tapering/stopping steroid treatment during mesalamine treatment.

Case Reports

Case 1

A 9-year-old girl was admitted to our hospital with a 2-month history of 10–15 bouts of mucoid bloody diarrhoea per day and crampy lower abdominal pain that was relieved after defaecation. She lost weight, was fatigued and had oral aphthous lesions. Except for consanguinity, her family history was unremarkable. She was pale and growth retarded [height 120 cm (<3%), body weight 16.2 kg (<3%) and height standard deviation score 1.92]. Physical examination revealed aphthous lesions on the gingiva, an anal fissure, hyperaemic perianal skin tags, and increased bowel sounds. Laboratory data (with their normal range in parentheses) were: haemoglobin level (Hb) 8.2 g/dl (10.9–13.3 g/dl), mean corpuscular volume 62.9 fl (77–95 fl), platelet count 646,000/mm³ (183,000–369,000/mm³), white blood cell count 25,400/mm³ (4,700–10,300/mm³), C-reactive protein level (CRP) 9.2 mg/dl (<0.1 mg/dl), erythrocyte sedimentation rate (ESR) 48 mm/h (0–20 mm/h), se-

rum albumin level 2.8 g/dl (3.7–5.6 g/dl) and protein level 4.8 g/dl (5.9–8 g/dl). Leucocytes and erythrocytes were found in the stool, but no enteric pathogens were seen. The endoscopic and histopathological findings of the colon and terminal ileum were compatible with CD. She was put on prednisolone (2 mg/kg/day). Her complaints resolved, and laboratory tests improved during the second week. After 4 weeks of steroid treatment, mesalamine was added for the first time, and the steroid was tapered by 5 mg/week. The day after stopping prednisolone, while taking only mesalamine, she had a fever (38.5°C), abdominal pain, nausea and bloody mucoid diarrhoea (8–9 times per day). Her physical examination was normal except for the anal fissure. Laboratory tests showed a platelet count of 546,000/mm³, white blood cell count of 12,500/mm³, ESR of 45 mm/h and a CRP level of 8.6 mg/dl; gross blood and mucus were seen in the stool, but bacterial pathogens and parasites were negative. Urine, throat and blood cultures, viral markers, and *Toxoplasma*, *Brucella* and *Salmonella* were negative, ruling out acute infection. This clinical picture was compatible with an acute exacerbation of the disease. She was given her first dosage of infliximab (5 mg/kg) because of the serious side effects caused by the steroid treatment. Broad-spectrum antibiotic treatment was begun. However, her fever persisted and increased to 39.9°C with shivering and did not differ between day and night; there were frequent bowel movements (20–22/day) with blood and mucus and increased inflammatory serological markers. At that point, mesalamine was thought to be the cause of the fever, mimicking CD, and the drug was discontinued. Her temperature normalised, and the frequency of bowel movement decreased to 3–4/day within 36 h. Three days after stopping the mesalamine treatment, she had no more complaints. The inflammatory markers decreased significantly within 1 week. She was put on azathioprine, and no exacerbation was observed during the 2-year follow-up period.

Case 2

A 14-year-old girl was admitted to our hospital with a 1-month history of crampy abdominal pain, abdominal distension, swelling of the legs and eyelids, and weight loss (8 kg/month). Her medical and family histories were unremarkable. She was well developed [height 160 cm (50–75%), body weight 41 kg (3–10%)] but pale. She had ascites and pretibial oedema. Laboratory tests (with their normal range in parentheses) were: Hb 10.5 g/dl (12–16 g/dl), mean corpuscular volume 75.4 fl (77–95 fl), thrombocytosis 608,000/mm³ (185,000–335,000/mm³), hypo-albuminaemia 1.7 g/dl (3.7–5.6 g/dl), hypoproteinaemia 3.4 g/dl (5.9–8 g/dl) and a high CRP level of 3.39 mg/dl (<0.1 mg/dl). The ESR and stool examination were normal; occult blood in the stool was negative. Urinalysis was normal, and gastrointestinal protein loss was thought to be the cause of the hypoproteinaemia. Ileocolonoscopy revealed normal mucosa, except for an area of focal swelling in the caecum of approximately 1 × 1 cm. Histopathologically, mild active ileitis, focal active colitis, focal cryptitis in the caecum and mild active colitis with focal erosions in the other parts of the colon were documented. Based on the clinical, laboratory and histopathological findings, CD was diagnosed, and prednisolone treatment (60 mg/day) was administered. On corticosteroid treatment, she had no complaints; the ascites and pretibial oedema resolved; the albumin levels increased (3.1 g/dl), and the CRP normalised. Mesalamine was added to the steroid treatment for the first time after 1 month of therapy, and the steroid was tapered by 5 mg/week. While she was taking 20 mg/day prednisolone and 50 mg/kg/day mesala-

mine, laboratory tests revealed recurrence of anaemia (Hb: 9.4 g/dl), hypo-albuminemia (2.8 g/dl) and elevated ESR (68 mm/h) and CRP level (2.6 mg/dl), although she had no complaints. It was thought to be mesalamine intolerance, and thus the mesalamine was stopped, while the steroid was continued at 20 mg/day. After 7 days, the ESR (21 mm/h) and CRP level (0.42 mg/dl) had decreased markedly, while the albumin level (3.1 mg/dl) had increased slightly. Azathioprine treatment was begun (100 mg/day), and the steroid was tapered again. During the subsequent 20 months, on azathioprine only, she remained asymptomatic with Hb, albumin, ESR and CRP levels in the normal ranges.

Case 3

A 7-year-old girl was admitted to our hospital with a 15-day history of anorexia, weight loss (3.5–4 kg/month), abdominal pain, 10–15 bloody, mucoid bowel movements per day, recurrent high fever (39–40°C) and joint pain. Except consanguinity, her family history was unremarkable. She was growth retarded: height 100 cm (<3%), body weight 13.2 kg (<3%), height standard deviation score –3.6 and pale. Physical examination revealed clubbed fingers, perianal skin tags, and increased bowel sounds. Laboratory tests (with their normal range in parentheses) were: Hb 8.8 g/dl (10.9–13.3 g/dl), mean corpuscular volume 69.5 fl (77–95 fl), thrombocytosis 716,000/mm³ (183,000–369,000/mm³), high CRP 2.69 mg/dl (<0.1 mg/dl) and ESR 58 mm/h (0–20 mm/h). Stool examination revealed leucocytes and erythrocytes but was negative for enteric pathogens. The endoscopic and histopathological findings of the ileum and colon were compatible with CD. Prednisolone (2 mg/kg/day) was begun, and under corticosteroid treatment, she had no complaints, and inflammatory markers decreased. Mesalamine was added for the first time in the third week of corticosteroid treatment. After 4 weeks, the corticosteroid was tapered by 2.5 mg/week. The patient complained of bloody mucoid diarrhoea and abdominal pain while on mesalamine and steroid (20 mg/day) treatments. Laboratory tests revealed thrombocytosis of 464,000/mm³ and a high CRP of 2.24 mg/dl. This was thought to be mesalamine intolerance, and the mesalamine was stopped. After 3 days, all symptoms and signs had resolved. Azathioprine treatment was begun and the steroid treatment tapered off. She has remained asymptomatic on azathioprine for 9 months of follow-up.

Discussion

These cases indicated that mesalamine treatment induced exacerbations of either colitis-like symptoms or elevation of inflammatory markers in patients with CD. The 3 patients who were newly diagnosed with CD had achieved remission with steroid treatment, but colitis-like symptoms, elevation of inflammatory markers and decrease in albumin levels were observed after mesalamine had been added while tapering/ceasing steroid. The improvement of their symptoms and laboratory findings within 3–7 days after mesalamine had been stopped thereby indicated that mesalamine was the causative factor.

However, in previous reports [1, 2] 80–90% of patients who had adverse reactions to sulphasalazine tolerated mesalamine, a non-sulpha-based 5-aminosalicylic acid agent; hence, it was assumed that thereby the sulphapyridine moiety of sulphasalazine was responsible for the adverse reactions. The mechanism of the adverse reactions of mesalamine is not clear [3–7]. Colitis-like symptoms had been described in the treatment of ulcerative colitis using sulphasalazine, but also similar presentations had been reported with mesalamine in adults with ulcerative colitis [2–4]. There are a few reports on mesalamine-related colitis in children with ulcerative colitis [8, 9], while it is scarce in children and adults with CD [5]. In both children and adult cases, abdominal pain, diarrhoea (may be bloody), fever and arthralgias were reported within 24–48 h of starting mesalamine treatment, and these symptoms resolve within 24–48 h of stopping the drug which were similar to our 3 cases. Fine et al. [10] reported that mesalamine can stimulate leucotriene synthesis, causing intestinal inflammation in inflammatory bowel

disease. Corticosteroids decrease the production of leucotrienes and inflammation by interfering with phospholipase activity. When combined with corticosteroids, the side effects of mesalamine may be masked by the effects of the corticosteroids [10]. But while tapering or ceasing steroid treatment, its inflammatory side effects could emerge, as was seen in our patients. This side effect is not dose associated [2, 4, 6]. There are conflicting reports on the relation between mesalamine toxicity and inflammatory marker levels (no change versus increased white blood cell count or ESR) and whether or not these markers accompany the colitis-like symptoms [5, 7].

Conclusion

In this study mesalamine mimicked CD relapse in children with CD while tapering or after stopping steroid treatment. Awareness of this side effect of mesalamine could prevent a misdiagnosis of steroid dependency.

References

- 1 Loftus E-V, Kane S-V, Bjorkman D: Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2004;19:179–189.
- 2 Schroeder K-W: Role of mesalazine in acute and long-term treatment of ulcerative colitis and its complications. *Scand J Gastroenterol* 2002;S236:42–47.
- 3 Goldstein F, DiMarino A-J: Diarrhea as a side effect of mesalamine treatment for inflammatory bowel disease. *J Clin Gastroenterol* 2000;31:60–62.
- 4 Gupta M-K, Pollack S, Hutchings J-J: Mesalamine induced symptom exacerbation of ulcerative colitis: case report and brief discussion. *World J Gastrointest Pharmacol Ther* 2010;1:132–134.
- 5 Iofel E, Chawla A, Daum F, et al: Mesalamine intolerance mimics symptoms of active inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;34:73–76.
- 6 Austin C-A, Cann P-A, Jones T-H, et al: Exacerbation of diarrhoea and pain in patients treated with 5-aminosalicylic acid for ulcerative colitis. *Lancet* 1984;i:917–918.
- 7 Chakraborty T-K, Bhatia D, Heading RC, et al: Salicylate induced exacerbation of ulcerative colitis. *Gut* 1987;28:613–615.
- 8 Shimodate Y, Takanashi K, Waga E, et al: Exacerbation of bloody diarrhea as a side effect of mesalamine treatment of active ulcerative colitis. *Case Rep Gastroenterol* 2011;5:159–165.
- 9 Hojsak I, Pavic A-M, Kolacek S: Mesalamine treatment mimicking relapse in a child with ulcerative colitis. *World J Pediatr* 2014;10:371–373.
- 10 Fine K-D, Sarles H-E Jr, Cryer B: Diarrhea associated with mesalamine in a patient with chronic nongranulomatous enterocolitis. *N Engl J Med* 1998;338:923–925.