Mesalamine Intolerance in Three Children with Crohn’s Disease

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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-
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 pretilial 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 (183,000–369,000/mm³), high CRP 2.69 mg/dl (<0.1 mg/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 the steroid treatment 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 2**

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 176,000/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.

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