

# Mesalamine treatment mimicking relapse in a child with ulcerative colitis

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**Background:** There are reports on mesalamine-induced bloody diarrhea mimicking ulcerative colitis (UC) relapse, mostly in adults.

**Methods:** Herein we present a case of a child with UC who developed relapse of hemorrhagic colitis related to mesalamine.

**Results:** A 10-year-old girl developed severe symptoms mimicking UC relapse 3 weeks after introduction of mesalamine therapy. After mesalamine was withdrawn, her symptoms improved, but deteriorated again during the challenge of mesalamine despite concomitant use of corticosteroids.

**Conclusion:** This is the first case report on such a young child during the concomitant use of corticosteroids.

*World J Pediatr* 2014;10(4):371-373

**Key words:** 5-aminosalicylic acid;  
mesalamine;  
ulcerative colitis

## Introduction

Mesalamine is a first-line therapy in the treatment of ulcerative colitis (UC) in children.<sup>[1]</sup> As a side-effect, mesalamine can cause bloody diarrhea, but much less often than previous formulations.<sup>[2,3]</sup> There are also few reports describing a development of severe UC-like clinical picture caused by mesalamine.<sup>[4-9]</sup>

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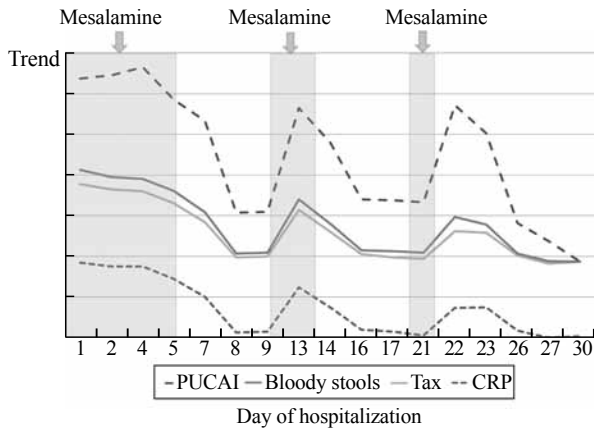
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doi: 10.1007/s12519-014-0485-x

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## Case report

A 10-year-old girl was diagnosed with a mild left sided UC. With a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of 15, she was treated with mesalamine (salofalk, perorally 80 mg/kg per day). Her symptoms disappeared seven days after the treatment. Three weeks after the initial diagnosis, she developed bloody diarrhea accompanied with fever and abdominal pain. At that point she was admitted to our hospital with a PUCAI score of 45, C-reactive protein (CRP) 37 mg/L (normal range, 0.1-2.8 mg/L), erythrocyte sedimentation rate (ESR) 25 mm/3.6 ks (normal range, 2-20 mm/3.6 ks), leukocyte count  $11.6 \times 10^9/L$  (normal range,  $4.4-11.6 \times 10^9/L$ ), fecal calprotectin 7660 mg/kg (normal values, <50 mg/kg) and normocytic normochromic anemia. Abdominal ultrasound revealed distended bowel loops but no dilatation of the transverse colon on abdominal X-ray. Stool cultures were negative for bacteria, parasites and *Clostridium difficile* toxins A and B. She was diagnosed with an acute relapse of UC and intravenous corticosteroid therapy (1 mg/kg/day) was given. On the fourth day of hospitalization, mesalamine therapy was discontinued. After two days, she became afebrile and inflammatory markers decreased (Fig.). Stools normalized within the next 2 days and steroids were changed to peroral. A small amount of blood in normally formed stools was observed on the 12<sup>th</sup> day of hospitalization, prompting us to introduce mesalamine suppositories (salofalk, 16.6 mg/kg per day per rectal). Next day she presented with bloody diarrhea, became subfebrile with a PUCAI score of 45 and increased inflammatory markers (CRP, 24.7 mg/L) (Fig.). We did not assume that the relapse was related to mesalamine. Rectoscopy was performed to reveal inflamed mucosa (Mayo score 2). Biopsies were cytomegalovirus (CMV) negative and the degree of inflammation was in concordance with a UC relapse. On the 3<sup>rd</sup> day, mesalamine was removed from therapy and after two days her clinical condition and laboratory results improved. We assumed that the relapse could be drug-related. After her condition was stabilized but still received a full dose of oral corticosteroids, an open challenge test was performed. She received 400 mg of mesalamine (asacol, 11 mg/kg per day). On the



**Fig.** Course of clinical and laboratory markers in relation to mesalamine use. PUCAI: Pediatric Ulcerative Colitis Activity Index; Tax: axillary temperature; CRP: C-reactive protein.

next day, she developed bloody diarrhea, again she was becoming subfebrile with a PUCAI score of 55 and an increase of CRP (15 mg/L). Three days after the discontinuation of mesalamine, her symptoms improved.

Based on the clear connection between symptoms and mesalamine therapy, she was diagnosed to be intolerant to mesalamine. Corticosteroids were slowly discontinued during the next 3 months, and an azathioprine maintenance therapy was introduced.

## Discussion

This case report emphasizes that mesalamine therapy can induce the development of a UC-like clinical picture. In this report, the patient is the youngest child presenting with this unusual correlation. There are several studies which evaluated the side-effects of mesalamine, and diarrhea was reported as an adverse event in 0.36 per million days of therapy.<sup>[10]</sup> It occurs less frequently after the treatment with mesalamine than with other formulations (2% vs. 10%).<sup>[3]</sup> Scheurlen et al<sup>[11]</sup> proposed that the mechanism of diarrhea caused by olsalazine could be a concentration-dependent inhibition of ileal and colonic  $\text{Na}^+\text{K}^+\text{ATPase}$  which increases fluid load to the colon. Interestingly, Goldstein et al<sup>[12]</sup> reported five cases of inflammatory bowel disease with diarrhea as a side-effect of mesalamine treatment assuming that diarrhea was not allergic but dose-dependent. The similar dose-dependent effect was also found in a single pediatric patient.<sup>[8]</sup> In the reports addressed above, diarrhea was mainly watery without or just tingled with blood. However, infrequently mesalamine can cause severe diarrhea mimicking a relapse of UC, mainly seen in adult patients.<sup>[4,7]</sup> But such reports on children are scarce.<sup>[8,9]</sup> Kapur et al<sup>[5]</sup> found

that this side-effect is not only clinical but also may cause endoscopic and histological changes consistent with a relapse of UC but without specific drug-related reaction. The possible mechanism by which mesalamine can mimic or lead to a "true" relapse of UC remains unclear. Fine et al<sup>[4]</sup> proposed that mesalamine might exacerbate colitis similarly to non-steroidal anti-inflammatory drugs (NSAIDs) due to their similar biochemical structure. By inhibiting the enzyme cyclooxygenase and consequently decreasing prostaglandin synthesis, most NSAIDs are thought to shunt arachidonic acid into a lipoxygenase pathway for the production of leukotrienes, thus leading to intestinal inflammation and diarrhea.<sup>[13]</sup> Fine et al<sup>[4]</sup> suggested that mesalamine can stimulate leukotriene synthesis similar to NSAIDs, causing an intestinal inflammation in patients with inflammatory bowel disease. Furthermore, steroids which are often used concomitantly with mesalamine may inhibit phospholipase activity and leukotrienes synthesis masking a mesalamine intolerance until they are stopped or tapered down.<sup>[9]</sup> However, this was not the case in our patient; she presented with severe symptoms after a single low dose of mesalamine while still receiving a full dose of corticosteroids (1 mg/kg per day). This could indicate that the reported response was not immunologically mediated.

Additionally, we did not observe that the reaction was dose-dependent as reported in other reports,<sup>[8]</sup> our patient relapsed even with the minimal dose of mesalamine (topical or oral) and regardless of product formulation. Interestingly, when the treatment with mesalamine was initiated, our patient tolerated a full dose during the first 3 weeks and the clinical picture of UC significantly improved. Only the two subsequent applications caused severe symptoms within the next 24 hours. Similarly, few reports already described that patients were tolerant to mesalamine at the beginning of the disease and become intolerant later on,<sup>[4,7]</sup> indicating a sensitization that occurred during the first course followed by a rapid response in the reintroduction of mesalamine.

In conclusion, clinicians should be aware that bloody diarrhea mimicking a relapse of UC can develop as a side-effect of mesalamine treatment, several weeks after the treatment, and even during the concomitant corticosteroid therapy.

**Funding:** None.

**Ethical approval:** Not needed.

**Competing interest:** None declared.

**Contributors:** Hojsak I, Pavić AM, and Kolaček S contributed to the patient treatment. Hojsak I and Pavić AM prepared the manuscript. Kolaček S critically reviewed manuscript.

## References

- 1 Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:340-361.
- 2 Pamukcu R, Hanauer SB, Chang EB. Effect of disodium azodisalicylate on electrolyte transport in rabbit ileum and colon in vitro. Comparison with sulfasalazine and 5-aminosalicylic acid. *Gastroenterology* 1988;95:975-981.
- 3 Loftus EV Jr, Kane SV, 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.
- 4 Fine KD, Sarles HE Jr, Cryer B. Diarrhea associated with mesalamine in a patient with chronic nongranulomatous enterocolitis. *N Engl J Med* 1998;338:923-925.
- 5 Kapur KC, Williams GT, Allison MC. Mesalazine induced exacerbation of ulcerative colitis. *Gut* 1995;37:838-839.
- 6 Bousseaden A, Ajana FZ, Essamri W, Benelbarhdadi I, Afifi R, Benazzouz M, et al. Mesalamine enema-induced exacerbation of ulcerative colitis. *Int J Colorectal Dis* 2009;24:1359-1360.
- 7 Gupta MK, Pollack S, Hutchings JJ. Mesalamine induced symptom exacerbation of ulcerative colitis: Case report and brief discussion. *World J Gastrointest Pharmacol Ther* 2010;1:132-134.
- 8 Shimodate Y, Takanashi K, Waga E, Fujita T, Katsuki S, Nomura M. Exacerbation of bloody diarrhea as a side effect of mesalamine treatment of active ulcerative colitis. *Case Rep Gastroenterol* 2011;5:159-165.
- 9 Iofel E, Chawla A, Daum F, Markowitz J. Mesalamine intolerance mimics symptoms of active inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2002;34:73-76.
- 10 Marteau P, Nelet F, Le Lu M, Devaux C. Adverse events in patients treated with 5-aminosalicylic acid: 1993-1994 pharmacovigilance report for Pentasa in France. *Aliment Pharmacol Ther* 1996;10:949-956.
- 11 Scheurlen C, Allgayer H, Kruis W, Erdmann E, Sauerbruch T. Effect of olsalazine and mesalazine on human ileal and colonic (Na<sup>+</sup> + K<sup>+</sup>)-ATPase. A possible diarrhogenic factor? *Clin Invest* 1993;71:286-289.
- 12 Goldstein F, DiMarino AJ Jr. Diarrhea as a side effect of mesalamine treatment for inflammatory bowel disease. *J Clin Gastroenterol* 2000;31:60-62.
- 13 Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987;107:513-516.

*Received October 9, 2013*

*Accepted after revision December 25, 2013*