Clinical Journal of Gastroenterology (2019) 12:578–582
https://doi.org/10.1007/s12328-019-00985-9

CASE REPORT

Hyposensitization trial using salazosulfapyridine in a case of mesalamine intolerance

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Received: 21 June 2018 / Accepted: 18 April 2019 / Published online: 29 April 2019

Abstract
A 47-year-old Japanese man was diagnosed with pancolitis-type ulcerative colitis. He was treated with mesalamine in a pH-dependent release form. On day 16 of administration, he was admitted because of fever and abdominal pain. We diagnosed his symptoms to be the side effects of mesalamine. Hyposensitization using unmodified and a time-dependent release form mesalamine was performed. On day 7 of mesalamine hyposensitization, a colonoscopy was performed. The patient presented with the same allergic symptoms 9 h after the administration of an oral sodium phosphate solution. Eventually, he was orally administered a course of salazosulfapyridine (SASP) at an initial dose of 2.5 mg/day, which was increased to 2000 mg/day. It is generally recognized that SASP intolerance is an indication to switch from SASP to mesalamine. The need to switch treatment from mesalamine to SASP is, therefore, rare because allergic reactions to mesalamine do not occur frequently. We report a very rare case which was presented with abdominal pain and myalgia because of intolerance to mesalamine in whom hyposensitization with and introduction of SASP were successful.

Keywords Mesalamine · Oral sodium phosphate solution · Salazosulfapyridine · Ulcerative colitis

Abbreviations

OSPS	Oral sodium phosphate solution
SASP	Salazosulfapyridine
SP	Sulfapyridine
UC	Ulcerative colitis

Introduction

The compounds salazosulfapyridine (SASP) and mesalamine (5-aminosalicylic acid [5-ASA], also called mesalazine) are the mainstay drugs for treatment of ulcerative colitis (UC). SASP is composed of mesalamine linked to sulfapyridine (SP) via a diazo bond, which is cleaved by bacterial azoreductases in the colon, thereby releasing its two components [1]. SASP is a relatively safe and effective drug for maintaining remission in UC patients. However, up to 30% of patients cannot be treated with SASP owing to intolerance or hypersensitivity reactions often caused by the SP moiety [2]. Mesalamine lacks the SP moiety and has replaced SASP as the first-choice treatment for UC because it is less likely to cause sulfa-related adverse events, including severe allergic reactions [3]. Skin rash, megaloblastic anemia, and fever, which are usually SASP-related hypersensitivity reactions, rarely occur as reactions to the mesalamine component [4]. Thus, SASP intolerance is an indication to switch from SASP to mesalamine. The need to switch treatment from mesalamine to SASP is, therefore, rare because allergic reactions to mesalamine do not occur frequently. We report a rare case of a 47-year-old man who presented with abdominal pain and myalgia because of intolerance to mesalamine in whom hyposensitization with and introduction of SASP were successful.

Case presentation

A 47-year-old Japanese man with a 5-month history of continuous watery diarrhea but no history of other illnesses presented to our hospital. Total colonoscopy revealed slight swelling and thickening, erythema, mucopus, intramucosal hemorrhage after contact with the fiberscope, and patchy

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loss or blurring of vascular patterns (Fig. 1a–c). The signs were judged to be of moderate severity (Mayo endoscopic score of 2) [5]. Histological features on biopsy examination included the presence of an acute/chronic inflammatory cell infiltrate, crypt abscesses, goblet cell and mucin depletion, surface epithelial integrity, and crypt architectural irregularities. These histological features were assigned a Geboes score of 4 [6] and are consistent with UC.

The patient was administered mesalamine in a pH-dependent release form (pH-mesalamine; Asacol®), at 2400 mg/day. On day 15 of administration, his diarrhea partially improved (from 7 to 4 times per day) and white blood cell (WBC) count was elevated at 10,400/μL. As his symptoms were not completely controlled, we increased the pH-mesalamine dose to 3600 mg/day on day 15. On day 16 of administration, the patient was admitted to the emergency department of the hospital because of a high fever, abdominal pain, and myalgia. Blood examination revealed a significantly elevated WBC count (13,100/μL) and C-reactive protein level (27.08 mg/dL). Results of the blood, urine, stool culture, and QuantiFERON® tuberculosis tests were all negative. Results of autoimmune, viral, or cytomegalovirus markers were also all negative. Chest and abdominal computed tomography scans confirmed the absence of any lesion indicating infection and revealed enlarged testicles, which we diagnosed as seminoma. Total colonoscopy after emergency admission confirmed no exacerbation of UC (Fig. 1d–f). We assumed that the symptoms were the side effects of the pH-mesalamine treatment rather than being related to the UC exacerbation. We immediately discontinued the pH-mesalamine therapy, replacing it with methylprednisolone therapy for the drug allergy, and the symptoms rapidly improved. The patient had used a steroid-based treatment while receiving treatment for a testicular tumor. He went into clinical remission of his testicular tumor after undergoing surgery and chemotherapy.

We conducted a hyposensitization trial with unmodified (Pentasa® enema) and time-dependent release mesalamine (T-mesalamine Pentasa® tablet) instead of pH-mesalamine. We initially planned to administer unmodified mesalamine

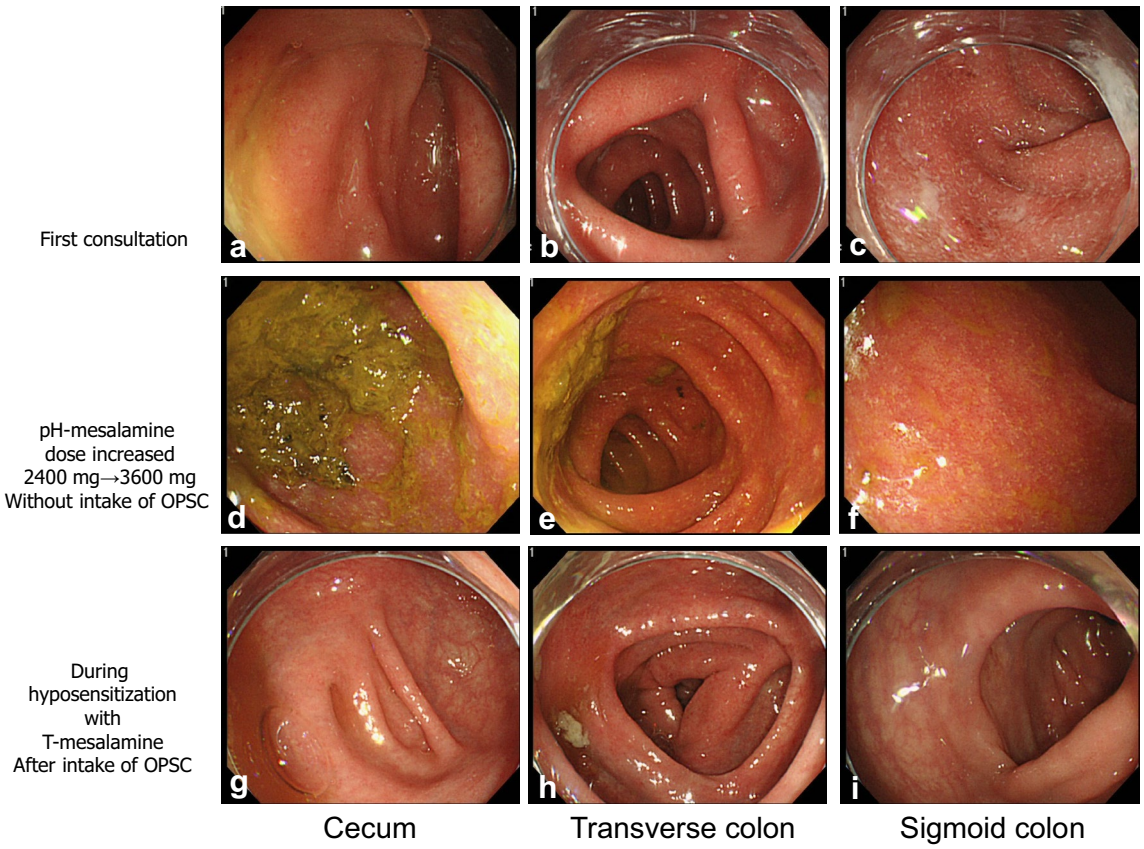

Fig. 1 Colonoscopic images of the present case. **a–c** Day after the first admission. The colonoscopy image shows slight swelling and thickening, erythema, mucopus, and intramucosal hemorrhage after contact with the fiberscope, and patchy loss or blurring of vascular patterns. **d–f** Day 16 after the first drug allergy event and with dose escalation with Asacol (pH-mesalamine) up to 3600 mg/day. The colonoscopy image shows no exacerbation of the UC. **g–i** Immediately before the second drug allergy event and after administration of oral sodium phosphate solution (OSPS). Total colonoscopy confirmed no exacerbation of the UC. **a**, **d**, **g** Cecum; **b**, **e**, **h** Transverse colon; and **c**, **f**, **i** Sigmoid colon

Table 1 Hyposensitization regimen for oral mesalamine enema and time-dependent release mesalamine (Pentasa® enema and Pentasa® tablet)

Day	Dose (mL)	Frequency (per day)	Daily total (mg)
Mesalamine enema (orally): mesalamine 1-g/100-mL container			
1	1.0	5	50
2, 3	5.0	3	150
4, 5	10	3	300
5–7	20	3	600
Mesalamine 500 mg/tablet			
8–10	125	3	375
11–13	250	3	750
14→	500	3	1500

Table 2 Hyposensitization regimen for salazosulfapyridine (SASP)

Day	Dose (mL)	Frequency (per day)	Daily total (mg)
SASP 500 mg/tablet per 5% dextrose in water/100-mL container			
1, 2	0.1	5	2.5
3, 4	0.2	5	5
5, 6	1.0	5	25
7, 8	5.0	5	125
9, 10	10	5	250
SASP 500 mg/tablet			
11, 12	250	2	500
13–83	500	1	500
84–167	500	2	1000
168–251	500	3	1500
252→	500	4	2000

orally at a dose of 50 mg/day, eventually increasing it up to 600 mg/day, and then administer T-mesalamine at a dose of 375 mg/day, eventually increasing it up to 1500 mg/day (Table 1). The hyposensitization was progressing well through until day 6. Colonoscopy was scheduled on day 7 of hyposensitization. Although colonoscopy confirmed that exacerbation of UC was not admitted (Fig. 1g–i), the high temperature and muscular pain reappeared 9 h after taking the oral sodium phosphate solution (OSPS) and 2 h after the colonoscopy. We immediately discontinued the T-mesalamine therapy and replaced it with methylprednisolone therapy for the drug allergy, and the symptoms rapidly improved.

The therapeutic strategy for the patient was to avoid immunosuppressive agents and long-term abuse of steroids because of the patient's history of seminoma. As the seminoma was in its early stage (UICC-TNM 2009: stage IIa) and a good long-term prognosis could be expected for the patient, we pursued aggressive hyposensitization with SASP. We started SASP at a low dose, and gradually increased it up to the original dose. The results of the patch and drug lymphocyte stimulation tests during pH-mesalamine, T-mesalamine, and SASP administration were all negative. After his second allergic episode, the patient was orally administered SASP at 2.5 mg/day, and the dose was eventually increased up to 1500 mg/day [Table 2]. The patient remains in remission with SASP after 7 years of drug allergy at a dose of 2000 mg/day.

Discussion

We report the case of a patient who experienced intolerance of both time- and pH-dependent forms of mesalamine, in whom hyposensitization with and introduction of the SASP regimen were successful. The first point of discussion is the problem of mesalamine intolerance on the day of colonoscopy and how it was influenced by the OSPS. As presented in Fig. 2, when SASP is administered orally, the diazo bond is hydrolyzed by colonic bacterial enzymes, causing the release of mesalamine and SP throughout the colon [1] (Fig. 2a). The kinetics of unmodified mesalamine (oral mesalamine enema) differ; it is preferentially absorbed in the upper small intestine and is rapidly N-acetylated in the intestinal epithelium (Fig. 2b) [7]. The Pentasa® tablet consists of microspheres of mesalazine encapsulated within an ethylcellulose semipermeable membrane. This structure allows time- and moisture-dependent release of the active drug, independent of luminal pH. Mesalazine is gradually distributed throughout the gastrointestinal tract from the duodenum to the rectum (Fig. 2c) [8]. The enteric-coated formulations include pH-mesalamine (Asacol®), which is coated with Eudragit S® and dissolves at pH greater than 7.0 [9]. The mean pH of the digestive system in active UC patients is 5.82 in the proximal small bowel, 7.08 in the distal small bowel and 6.01 in the right colon [10]. Asacol® is decomposed and absorbed in the area from the distal small bowel to the colon (Fig. 2d). Although we cannot decide conclusions for the intolerance from this single case whether mesalamine itself or a metabolite is to blame, we speculate that this intolerance may have occurred because unmodified mesalamine carried by the OSPS rapidly reached the deeper proximal ileum, in which intestinal immune system is developed (Fig. 2e).

We consider the possibility that stimulation with bowel preparation and colonoscopy itself exacerbated this phenomenon. Although bowel preparation is considered safe in UC patients except in case of acute severe or fulminant colitis, it has been identified as a trigger for toxic megacolon, and some evidence suggests that colonoscopy may exacerbate symptoms of UC, even in cases of endoscopic disease remission [11]. The etiology of flares is unknown. Prospective

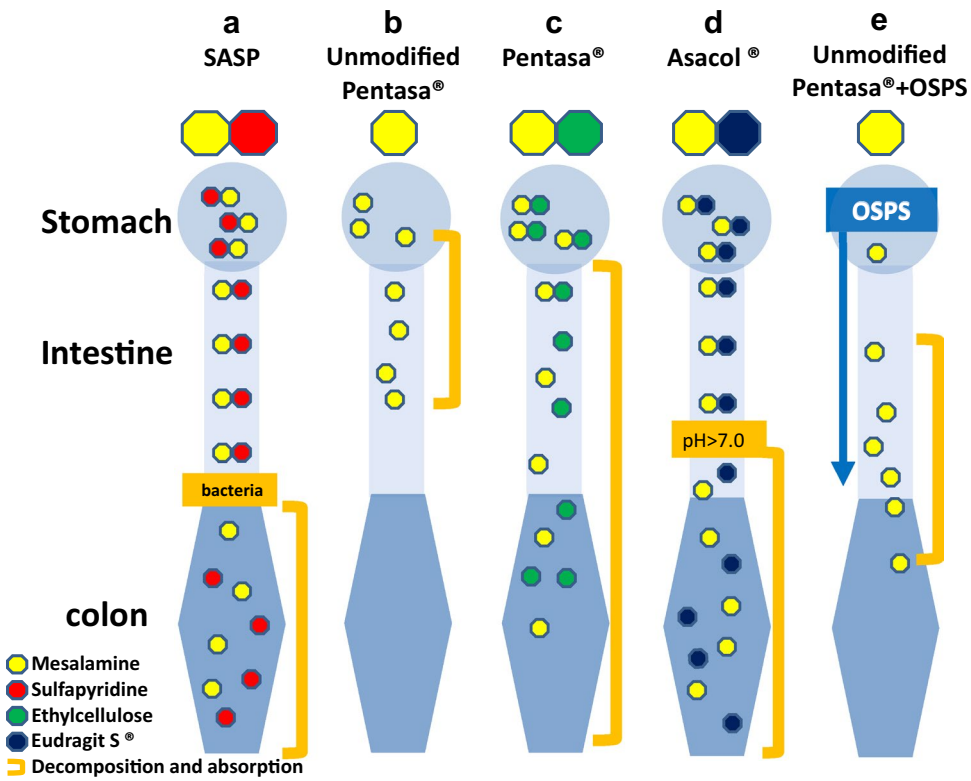

Fig. 2 Suspicions from the schematic of the pharmacokinetics. The right curly brackets indicate the sites where mesalamine begins to be metabolized and absorbed. **a** Salazosulfapyridine is decomposed into mesalamine and SP by colonic bacterial enzymes around the entire colon. **b** Unmodified mesalamine (oral mesalamine enema) is decomposed and absorbed in the proximal small bowel. **c** Pentasa® is a timed-release formulation containing a semipermeable membrane that releases the drug gradually in the area from proximal small bowel to the colon. **d** The enteric-coated formulations include Asacol®, which is coated with Eudragit S® and dissolves at a pH of 7.0 in the distal small intestine. **e** The OSPS-derived unmodified mesalamine (oral mesalamine enema) at a high concentration rapidly reached the distal small bowel due to OSPS

studies are needed to better define this possible association and the relative underlying pathophysiological mechanisms.

The second point of discussion is how to overcome drug intolerance to SASP and mesalazine. The typical mesalazine-related side effects include fatigue, non-productive cough, fever, dyspnea, and chest pain [12]. Bousseaden et al. [3] reported the case of a patient intolerant to SASP who developed a severe hypersensitivity reaction to oral mesalamine and had to undergo coloproctectomy eventually. Some reports have described allergic reactions to mesalamine in patients who had previously experienced similar reactions to SASP. This phenomenon revealed that mesalamine, rather than SASP and/or SP, might be responsible for these reactions [13, 14].

Switching from mesalamine to SASP therapy because of allergy to mesalamine has not been reported in the literature. Although several trials of hyposensitization have been reported, no accepted protocol has been established. As the Pentasa® tablet is a timed-release formulation containing a semipermeable membrane, the dose of mesalamine is difficult to adjust after grinding the Pentasa® tablet lock completely. In Japan, as we could not avail mesalamine granules until recently, we did not create a delicate and complex protocol for the desensitization. To overcome this problem, a pure mesalamine powder was prepared for hyposensitization [15, 16]. Oustamanolakis and Koutroubakis [17] used mesalamine granules for hyposensitization. Those authors reported that a granule formulation offers accurate doses of mesalamine. In Japan, recently, with the availability of Pentasa® granules, delicate hyposensitization can be achieved. In the case of SASP, a complex program of desensitization was empirically developed with gradually increased doses of SASP administered over many weeks [18].

The efficacies of mesalamine and SASP are well studied. The latest Cochrane Database indicates that 54% of patients treated with mesalamine failed to enter remission compared with 58% of those who were treated with SASP. Furthermore, mesalamine was superior to placebo and not more effective than SASP [19]. SASP was significantly superior to mesalamine for maintaining remission. Forty-eight percent of patients who received mesalamine experienced a relapse compared with 43% of patients who received SASP [20]. Finally, SASP is not as well tolerated as mesalamine. Twenty-nine percent of patients who received SASP experienced an adverse event compared with 15% of the patients who received mesalamine [19]. Patient outcomes after switching from mesalamine to SASP therapy because of allergy to mesalamine have not been reported. In conclusion, hyposensitization with SASP is a possible alternative treatment for UC even if intolerance to mesalamine is observed.

Compliance with ethical standards

Conflicts of interest The authors state that they have no conflict of interest.

Human/animal rights All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all the patients for being included in the study.

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