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Desensitization after fever induced by mesalazine

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Key words: 5-aminosalicylic acid; desensitization; drug fever; mesalazine.

• Mesalazine is the 5-amino derivative of salicylic acid (5-ASA), an anti-inflammatory agent structurally related to the salicylates which is effective in inflammatory bowel diseases. It is considered to be the active component of sulfasalazine (sulfapyridine and 5-ASA).

We report a case of successful desensitization to mesalazine in a patient who had had fever on two previous occasions when mesalazine had been administered.

Desensitization to mesalazine in patient with fever caused by this drug.

The patient was a 29-year-old man with a history of Crohn's disease from 1987. He remained asymptomatic without treatment from 1991, but he suffered a slight recurrence in September 1997, confirmed by colonoscopy and biopsy, and started mesalazine (Claversal®, SB SmithKline Beecham) as maintenance treatment (1 g/8 h). Five days after beginning the treatment, he developed fever (up to 40°C), tiredness, headache, thoracic pain, myalgias, and arthralgias. The patient improved without treatment by 3–4 days after mesalazine was stopped. Two weeks later, mesalazine was readministered, and similar symptoms occurred, but earlier (within 3 days). He was admitted to the hospital. Physical examination did not reveal abnormalities. His axillar temperature was 38.5°C. Analyses (complete blood count, eosinophil count, blood chemistries, liver enzymes, coagulation studies, complement levels, serum protein electrophoresis, immunoglobulin levels, and urinalysis), chest radiography, and electrocardiogram were normal, excepting erythrocyte sedimentation rate (45 mm in the first hour). Blood, urine, and feces cultures were negative. Abdominal echography showed a thickened bowel wall in the right lower quadrant. Mesalazine was discontinued, and treatment with prednisone (30 mg/day orally) was initiated. The patient recovered and was discharged 6 days later. Prednisone was subsequently tapered. He had not been treated with mesalazine or sulfasalazine previously. There was no past history of drug allergy, atopy, or ASA intolerance.

The patient was referred to us 6 weeks after the last episode. He had finished the prednisone treatment 2 weeks before, and he was asymptomatic. After obtaining written, informed consent, we performed single-blind, placebo-controlled oral challenge tests in the hospital. Pure mesalazine powder was provided by the manufacturer. Placebo and mesalazine were administered to the patient in white opaque capsules on different days, with an interval of 2 weeks between each challenge test. The same protocol of administration was used for placebo and mesalazine: the first day, progressive doses of 50, 100, 150, and 200 mg with an interval of 1 h in the hospital; then, 500 mg/8 h at home for 7 days. Placebo challenge was negative, but 24 h after starting mesalazine, the patient developed symptoms as described previously; 12 h later, he presented with 38.5°C fever. He was treated with paracetamol and methylprednisolone, improving 12–24 h later.

Because of the several fever episodes caused by mesalazine and the lack of better

Table 1. Mesalazine desensitization protocol

Solution 10 mg/ml		Solution 100 mg/ml	
Day	**Dose**	**Day**	**Dose**
1	0.1 ml=1 mg	17	3 ml=300 mg
2	0.2 ml=2 mg	18	4 ml=400 mg
3	0.4 ml=4 mg	19	5 ml=500 mg
4	0.8 ml=8 mg	20	6 ml=600 mg
5	1.5 ml=15 mg	21	7 ml=700 mg
6	2 ml=20 mg	22	8 ml=800 mg
7	3 ml=30 mg	23	9 ml=900 mg
8	4 ml=40 mg	24	10 ml=1000 mg
9	5 ml=50 mg	25	12 ml=1200 mg[1]
10	6 ml=60 mg	26	14 ml=1400 mg[1]
11	7 ml=70 mg	27	16 ml=1600 mg[1]
12	8 ml=80 mg	28	18 ml=1800 mg[1]
13	9 ml=90 mg	29	20 ml=2000 mg[1]
14	10 ml=100 mg	30	22 ml=2200 mg[2]
15	15 ml=150 mg	31	26 ml=2600 mg[2]
16	20 ml=200 mg	32	30 ml=3000 mg[2]

[1]Divided into two doses.
[2]Divided into three doses.

therapeutic alternatives, we decided to carry out a desensitization protocol (Table 1). Mesalazine solutions were prepared by the pharmacy at two concentrations (10 and 100 mg/ml) for easy dispensing. As the usual initial adult dose of mesalazine is 3 g daily in divided doses, it was the highest dose tested. The patient had no recurrence of the fever either during or after the mesalazine desensitization schedule (his current mesalazine daily regimen is 500 mg/8 h).

Drug fever is pyrexia that develops coincidentally with the administration of a drug and disappears with discontinuation, for which no other cause can be established by a careful examination and laboratory investigation. The pathogenesis of fever by drugs remains unknown in most cases. To our knowledge, this is the first case described in the literature of a patient with fever induced by mesalazine who was successfully desensitized. Although there are some cases reported of mesalazine causing fever associated with other symptoms – hypotension (1); vasculitic rash, arthritis, pericarditis, and pericardial effusion (2); and watery stools and vomiting (3) – in our case, all symptoms could be explained by fever alone.

Tolerance induction through exposure to graded doses has been proposed as a safe means to suppress the allergic response, although the mechanism by which tolerance is induced is unclear. Regarding our results, we think that desensitization is an important therapeutic strategy in cases similar to ours.

Although Nakajima et al. suggest that mesalazine is effective for the treatment of patients who are intolerant of sulfasalazine (4), other authors report allergic reactions to 5-ASA in patients who had previously experienced similar reactions to sulfasalazine, a fact which suggests that 5-ASA is responsible for these reactions rather than sulfapyridine (3, 5, 6).

In conclusion, mesalazine treatment can induce fever in some patients, but desensitization is possible.

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IgE response to *Anisakis* compared to seafood

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Key words: allergen; *Anisakis*; fish allergy; IgE; RAST; seafood.

• Anisakiasis is a human gastrointestinal disease caused by ingestion of larvae of the nematode family Anisakidae (especially *Anisakis simplex*) in raw or undercooked fish or squid. Typical symptoms are sharp epigastric pain or diffuse abdominal pain; anisakiasis is often misdiagnosed as appendicitis. On the other hand, acute allergic symptoms such as urticaria or angioedema, associated with the ingestion of mackerel or other fish, may be caused by type I allergic reaction. Kasuya et al. (1) observed that *Anisakis* larvae were the real causative agent in some cases of urticaria following seafood ingestion. Montoro et al. (2) reported that recidivous acute urticaria in 16 patients was caused by allergic reaction to *A. simplex*, not to fish. Eosinophilic gastroenteritis was correlated with presence of *Anisakis* in a study by Gomez et al. (3). Serologic diagnosis of *Anisakis* and seafood allergy is often based on quantification of specific IgE antibodies. In a study of normal (nonallergic) subjects, the incidence of IgE antibodies to *Anisakis* was 47/1008 cases (4.7%) (Garcia-Palacios et al. [4]).

Among 34 400 cases, IgE positivity was 29.8% for *Anisakis*, significantly higher than for mackerel (4.0%) or other seafood species.

However, there have been no studies on the comparative incidence of IgE responses to seafood and *Anisakis* in a large sample of allergic patients. Here we describe the incidence of serum IgE specific to *A. simplex*, various fish species, and squid in a Japanese population.

Sera from patients throughout Japan were collected from Mitsubishi Kagaku Bio-Clinical Laboratories during 1994–7. Initial diagnoses were urticaria or food allergy. Serum levels for antigen-specific IgE against *A. simplex*, mackerel, sardine, saurel (horse mackerel), salmon, cod, tuna, and squid were assayed with the Pharmacia CAP System FEIA (Pharmacia & Upjohn, Uppsala, Sweden). Results greater than 0.70 UA/ml (score 2) were considered positive, to avoid false positives, according to the manufacturer's instructions. The total number of single assays was 34 400, including 2022 combined assays on *Anisakis* and seafood allergens. The chi-square test was used for statistical analyses.

In single assays, specific IgE against *Anisakis* was detected in 629 out of 2108 patients (29.8%), an incidence significantly higher than that for any other allergen tested ($P<0.001$ in all comparisons). For mackerel, CAP-positive specific IgE was observed in only 343 out of 8539 patients (4.0%). For sardine,