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Anaphylaxis to Pepto-Bismol

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Key words: anaphylaxis; bismuth subsalicylate; Pepto-Bismol.

● SALICYLATES ARE frequently used medications, and reactions to these medications and other nonsteroidal anti-inflammatory drugs (NSAIDs) are common, involving both allergic and nonallergic mechanisms (1,2). These reactions can be due to drug-specific IgE, or may be related to the nonspecific depletion of prostaglandin E_2 via inhibition of the cyclooxygenase enzyme (1).

First case of presumed allergy.

Bismuth subsalicylate, the active compound in Pepto-Bismol (Proctor and Gamble, Cincinnati, OH), is frequently used in the US for the prevention of traveller's diarrhoea and in the treatment of dyspepsia (3). Reactions known to be caused by bismuth-containing compounds include encephalopathy, erythroderma, and other skin reactions (3,4). To date, anaphylaxis to Pepto-Bismol has not been described. We present a case of anaphylaxis to Pepto-Bismol and demonstrate positive, reproducible skin prick testing (SPT) to this drug.

A 25-year-old man presented to our emergency department with acute urticaria. He had symptoms of acute gastroenteritis on the day before presentation, including nausea, vomiting and diarrhoea. He self-medicated with Pepto-Bismol, taking a total of eight caplets over the next 6 h. Approximately 30 min after the final dose, he experienced generalized urticaria for which he sought medical care. He denied symptoms of shortness of breath, wheezing, syncope, rhinorrhea, metallic taste or sensation of

impending doom. The patient had tolerated Pepto-Bismol in the past, as well as other NSAIDs, denied the use of other medications, and had not taken anything else by mouth (except water) for at least 12 h before the onset of urticaria.

Physical examination was notable only for generalized urticaria. The patient was admitted and treated with intravenous fluids and H_1 -blockers. Total serum tryptase at admission was elevated to 17 ng/ml (normal = 2–10 ng/ml).

The patient returned to our allergy clinic one month later for SPT to Pepto-Bismol. The skin test material was prepared in the following manner: two Pepto-Bismol caplets, each containing 262 mg of bismuth subsalicylate, were crushed and added to 10 ml of phosphate-buffered saline. After obtaining informed consent, SPT were performed using a prick and wipe method on the volar surface of the patient's forearm, using histamine sulfate 1 mg/ml and normal saline as positive and negative controls, respectively. SPT to the Pepto-Bismol solution caused a 9×12 mm wheal, surrounded by 20×25 mm erythema, along with appropriate responses to positive and negative controls. Five control subjects tolerant to Pepto-Bismol had negative SPT to the same solution. SPT were repeated two weeks later, showing a 6×8 mm wheal and a surrounding 14×18 mm erythema. A dot blot assay, as described previously (5), was unsuccessful in demonstrating *in vitro* IgE to Pepto-Bismol in the patient's serum.

It was concluded that our patient had allergic anaphylaxis to Pepto-Bismol based on the result of the serum tryptase as well as positive reproducible SPT (2). Our inability to demonstrate *in vitro* IgE is not surprising, given the inconsistent and difficult nature of measuring IgE antibodies against NSAIDs (6). Based on the proposed classification of reactions to cyclooxygenase inhibitors by Stevenson (6), our patient's reaction would be categorized as "single-drug anaphylaxis". In this type of reaction, previous sensitization has occurred, with the formation of drug-specific IgE, and cross-reactivity with other NSAIDs is unlikely (6).

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Post-streptococcal nonallergic urticaria?

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Key words: amoxicillin; antigen M; nonallergic urticaria; *Streptococcus pyogenes*.

● URTICARIA is apparently triggered by many causes, and the term chronic idiopathic urticaria has been used when no triggering factor can be identified (1). The term nonallergic urticaria is now preferred when evidence for an immunologic mechanism is lacking (2). Common antiallergic drugs are routinely used to treat the disease, but they have only a symptomatic effect. IgG autoantibodies directed against the IgE high-affinity receptor $Fc\epsilon RI$ (3) have been detected in 25–60% of subjects with urticaria, and several forms of autoimmunity have been associated with it. Infections from *Helicobacter pylori*

and *Giardia lamblia* have been investigated as possible causes of urticaria, with contrasting and disappointing results (4,5).

Group A streptococci (*Streptococcus pyogenes*) are known as triggers of post-infective syndromes. They produce exocellular toxins (streptolysine) and enzymes (jaluronidase, DNase), and possess a special cell wall component (antigen M)

that is able to elicit a specific antibody response in humans. We have therefore

assessed antipolysaccharide group-specific IgG antibodies to *S. pyogenes* (Microstrepto-Kit, Sieroterapico Srl, Milan, Italy) in sera of patients suffering from urticaria. Nine patients were enrolled, with clinical histories of recurrent urticaria episodes over a period of two months to seven years. We performed careful anamnesis and physical examination, as well as a urinalysis, urine culture, intradermal tests with autologous serum, and a set of laboratory investigations, to exclude common known causes of urticaria. Laboratory tests were for: parasites and *Helicobacter pylori* in stools; erythrocyte sedimentation rate; eosinophil count;

levels of antineutrophil cytoplasmic antibodies (ANCA), transaminases, gamma-glutamyl (GT), hepatitis C virus (HCV) and carcinoembryonic antigen (CEA) antibodies, α -fetoprotein, β 2-microglobulinemia, tissue polypeptide antigen (TPA), *H. pylori* and antithyroid antibodies, cryoglobulins, circulating immunocomplexes, mitogen and stress activated kinase (MSK), tissue polypeptide antigen (TAS), streptozyme, C-reactive protein, antinuclear antibodies (ANA), and extractable nuclear antigen (ENA). Allergy to common inhalant allergens and food allergens was also tested. Drugs were excluded as possible triggering factors. Eight patients had an abnormally high MSK titre (normal value $\leq 1:240$) but none of them had any sign of current infection. Four MSK-positive patients were also positive for *H. pylori* in stools and for antibodies to the same germ (Table 1). Antiallergic drugs were useful to decrease symptoms but were not curative in any patient. All MSK-positive patients were submitted to antibiotic therapy (oral amoxicillin, 2 g/day) for 15 days, plus colloidal bismuth (600 mg twice daily) if also *H. pylori*-positive. At the end of the treatment, six patients were completely asymptomatic and two showed a very important improvement. No worsening was detected in either group for at least two months

following treatment. In six patients the MSK titre was checked after treatment, which showed a decrease in all cases.

Our findings are supported and explained by the recent discovery of a collagen-like surface protein designated SclA (streptococcal collagen-like surface protein), whose gene seems to be co-regulated with the M protein (6). We suggest therefore the hypothesis that an asymptomatic chronic streptococcal infection is able to start, in some subjects, an autoimmune reaction leading to recurrent episodes of urticaria. The MSK titre decrease and the clinical improvement in all MSK-positive patients after the antibiotic treatment are consistent with the hypothesis.

Obviously, both our preliminary data and this hypothesis need to be confirmed using larger samples of patients who are accurately diagnosed and with a longer follow-up period.

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Table 1. Relevant data for mitogen and stress activated kinase(MSK)-positive patients

Case	Sex	Age	Time with disease (years/months)	MSK titre		Clinical situation	
				Before	After	After treatment	Before treatment (notes)
1	M	50	3 M	2720	1920	No symptoms	<i>H. pylori</i> positive: treated with colloidal bismuth. Transaminases slightly increased
2	F	42	5 Y	940	680	No symptoms	
3	F	36	7 Y	480	nd	No symptoms	<i>H. pylori</i> positive: treated with colloidal bismuth. Mild positivity to ID with autologous serum
4	F	29	3 Y	680	480	A few blisters	Mild positivity to ID with autologous serum
5	F	21	3 Y	2720	1920	A few blisters	<i>H. pylori</i> positive: treated with colloidal bismuth
6	F	32	2 M	1360	680	No symptoms	
7	M	24	3 M	1300	960	No symptoms	<i>H. pylori</i> positive: treated with colloidal bismuth. Patient referred 2 times to the E.R. for acute urticaria before therapy
8	F	20	2 M	680	nd	No symptoms	

nd: determination not performed.

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