

fish. They include facial flush and then redness of the neck and upper part of the body, headache and dizziness, a burning sensation in the mouth or throat, palpable edema, and sometimes palpitations, nausea, and diarrhea. Vomiting is rare. In severe cases, bronchospasm, palpitations, fall in blood pressure, and sometimes supraventricular arrhythmia have developed. The symptoms generally resolve in 2–24 h, but durations of up to 3 days have been reported in the literature (5).

This disease generally occurs in small epidemics, since the contaminated fish may be eaten by several people. Sporadic cases are nonetheless reported. In our case, the symptoms that developed during the meal suggested food allergy, but contaminating substances (*Anisakis simplex* allergy [6], parasites, spices, preservatives, and toxins) can induce similar symptoms. In our case, certain factors cast doubt on the diagnosis of food allergy: the absence of a previous history of food allergy, the negative prick and RAST responses to fish, and the association of allergy-like symptoms with headache. But only rechallenge could decide, and it was negative for our patient.

The diagnosis of scombrototoxin poisoning is confirmed by assaying histamine in the flesh of the fish. In fresh, uncontaminated flesh, the histamine content is of the order of 1–5 mg per 100 g of fish (3). The US Food and Drug Administration has defined the toxicity level of histamine in tuna flesh as greater than or equal to 50 mg per 100 g fish.

The mechanism of the clinical reaction is conventionally considered one of histamine-induced shock (7). Generally, when caught, the fish is healthy but may become toxic in the course of the preservation and marketing process: proliferation of certain bacteria such as *E. coli*, *Klebsiella pneumoniae*, and *Morganella morganii*, which produce histidine decarboxylase, induces degradation of the histidine present in high quantities in scombroid flesh and the formation of histamine. This degradation of histidine to histamine mainly occurs when the temperature is 20–30°C. It cannot occur when refrigeration is implemented immediately after the fish is caught. Once the toxin has formed, neither freezing, canning, smoking, nor cooking will destroy it.

We did not assay the plasma or urinary histamine, since the patient consulted 3 weeks after the episode. In the literature, Sanchez-Guerrero et al. (8) demonstrated in two cases that serum histamine, urinary histamine, and methylhistamine levels were elevated at the time of poisoning. However, the tryptase level (indicator of mast-cell activation) was unchanged, suggesting that the causal mechanism is not IgE dependent.

Treatment of scombrototoxin poisoning is easy, but first, and above all, is prevention; i.e., maintaining

continuous refrigeration to preserve the fish, and discarding dubious fish. Scombrototoxin poisoning may occur with slices of tuna bought directly from the fishmonger or even, sometimes, with canned tuna. In the two cases reported by Stell (3), the histamine content of the tuna flesh was greater than 200 mg/100 g.

The outcome, as noted above, is generally spontaneously positive and may be accelerated by treating the symptoms present with antihistamines (H_1 -receptor antagonists) and, according to Blakesley, with the H_2 -receptor antagonist, cimetidine (9). In four cases in a noncontrolled study, corticosteroids were also used. In the event of shock, epinephrine is effective. Bronchodilators can be used in the event of bronchospasm.

Key words: fish poisoning; food allergy; scombrototoxin.

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Relative safety of meloxicam in NSAID-intolerant patients

INGESTION of aspirin or other agents that inhibit the cyclooxygenase (COX) system (i.e., non-

steroidal anti-inflammatory drugs [NSAID]) elicits respiratory, nasal, and gastrointestinal symptoms as well as dermal changes in a subset of patients. At the moment, it is widely accepted that inhibition of COX by NSAID is the mechanism responsible for the unwanted effects of those drugs (1). COX exists in two isoforms. COX-1 is constitutively expressed in most tissues and modulates normal cell activity. COX-2 activity is substantially increased in inflammatory conditions. Predominant COX-1 inhibition is thought to be responsible for the side-effects of NSAIDs (2).

The predominant COX-2 inhibitor meloxicam has been shown to produce less gastrointestinal damage than other NSAIDs (3). It has no effects on platelet aggregation and renal prostaglandin (PG) E_2 synthesis (4). There are no reports on tolerability of meloxicam in patients with pseudo-allergic reaction after ingestion of aspirin and NSAIDs.

Five consecutive patients with a history of NSAID intolerance and positive oral or inhalation challenge tests with NSAID were included. Oral and inhalation incremental challenge tests were performed according to the published protocols (5, 6).

The predominant COX-2 inhibitor meloxicam is better tolerated than other NSAID in patients with urticaria/angioedema after ingestion of NSAID.

Maximal cumulative doses used for oral provocations were 750 mg of aspirin, 75 mg of paracetamol (150% of an ordinary therapeutic dose), and 11 mg of meloxicam (therapeutic dose for meloxicam is 7.5–15 mg daily). Heart rate, blood pressure, and peak expiratory flow were measured before each dose and 1, 2, 6, and 24 h after the last dose. Patients were monitored for occurrence of skin changes, and symptoms were recorded. Intervals between challenges were at least 2 weeks.

- **Patient 1.** A 28-year-old man with hyperplastic rhinosinusitis and positive skin tests to house-dust mite and grass pollens was referred because of generalized urticaria and angioedema after ingestion of aspirin (500 mg of acetylsalicylic acid). In challenge tests, he tolerated 75 mg of paracetamol and 11 mg of meloxicam but reacted to 250 mg of acetylsalicylic acid.

- **Patient 2.** A 31-year-old man reported a few

episodes of facial angioedema with dyspnea after ingestion of acetylsalicylic acid. He tolerated 11 mg of meloxicam. After oral challenge with 250 mg of acetylsalicylic acid, facial angioedema appeared with dyspnea, but with no change in peak expiratory flow.

- **Patient 3.** A 42-year-old man with Bürger's disease, and positive skin tests to house-dust mite, grass pollens, and dog, was referred because of generalized angioedema and dyspnea after ingestion of Ketonal[®] (50 mg of ketoprofen). During inhalation challenge with lysine-aspirin in a cumulative dose of 43 mg, he developed erythema and pruritus of arms and angioedema of fingers with no change in expiratory flow. He later tolerated peroral challenge with 11 mg of meloxicam.
- **Patient 4.** A 40-year-old man with a history of lower back pain was referred because of repeated episodes of facial angioedema, generalized urticaria, and dyspnea after ingestion of acetylsalicylic acid. He tolerated 11 mg of meloxicam but reacted to 100 mg of acetylsalicylic acid with facial angioedema.
- **Patient 5.** A 26-year-old woman presented with newly developed intrinsic asthma (PD₂₀ was 0.07 mg). Shortly after the onset of asthma, she reacted to Ketonal[®] (50 mg of ketoprofen) with rhinorrhea, conjunctivitis, and dyspnea. She tolerated paracetamol. Bronchial challenge with lysine-aspirin was positive in a cumulative dose of 1.3 mg. Four hours after ingestion of a cumulative dose of 11 mg of meloxicam, she reported rhinorrhea and chest tightness. Her peak expiratory flow fell from 400 to 250 l/min. In a few hours, the reaction subsided spontaneously.

In patients with only cutaneous reaction after ingestion of aspirin, there were no signs and symptoms of intolerance after ingestion of meloxicam. In contrast, the patient with aspirin-induced asthma reacted with nasal symptoms and fall in peak flow. However, that patient showed the highest sensitivity to aspirin. It is possible that high sensitivity, and not presentation of NSAID intolerance as aspirin-sensitive asthma, was the cause of intolerance also of meloxicam.

We conclude that meloxicam is better tolerated than other NSAID in patients with urticaria/angioedema after ingestion of NSAID. Further studies with larger groups of patients and reproducibility studies are needed before a final decision about the safety of the predominant COX-2 inhibitor meloxicam in patients with intolerance of NSAIDs.

Key words: challenge tests; meloxicam; NSAID; intolerance.

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Anaphylaxis to walnuts and pine nuts induced by ACE

WE report a case of severe anaphylactic shock from walnuts and pine nuts which was unquestionably induced by the daily intake of an angiotensin-converting enzyme (ACE) inhibitor.

An 87-year-old woman had never been ill until April 1996, when hypertension was diagnosed. She was given Ramipril 2.5 mg/day. She displayed widespread pruritis with edema of the palms of the hands in June, and then three times in October, immediately after eating unspecified food items. These attacks were treated with antihistamines. On 6 January 1997, she suffered severe anaphylactic shock, beginning with edema of the lips and tongue, vomiting, collapse, and loss of consciousness. After a telephone call, the cake she had just eaten was stored in the freezer, and immunoallergic examination was performed on 29 January with four parts of the cake: cake mixture, dark cream, light cream, and dried fruit decoration. Parallel prick tests were performed for all the dried fruits and 32 standard food allergens, as well as latex and 12 standard aeroallergens. On a skin normally positive

to codeine (3 mm), the prick test was clearly positive to the light cream (3 mm), walnuts (4 mm), and pine nuts (10 mm). The CAST indicated a huge release of leukotriene C₄ from the leukocytes (2250 to 3100 pg/ml) ($N < 50$ pg/ml), and the basophil activation test (identification of CD63⁺ cells by flow cytometry) confirmed basophilic activation with respect to the walnuts. The RAST was negative to the walnuts and pine nuts. No oral provocation test was performed because of the severity of the shock.

This case clearly demonstrates the advantage of having the incriminated food available for skin and *in vitro* testing, in order to detect masked allergens. We later had confirmation of the presence of walnuts in the cream. On the other hand, the subject's total absence of allergic reaction until the age of 87 clearly indicates the role of the converting enzyme inhibitor in stimulating this reaction. The anaphylactic reaction is linked to the release of chemical mediators inducing the vasopermeability and vasodilation responsible for the collapse. It may be thought that angiotensin II, which is a powerful vasoconstrictor, opposes the risk of collapse, as seems to be indicated by the increased doses of angiotensin I and II at the time of anaphylaxis (1). Herrmann & Ring have also shown that patients displaying anaphylaxis to Hymenoptera venom have significantly reduced levels of angiotensin I and II compared with normal subjects (2).

Did an ACE inhibitor trigger anaphylaxis to pine nut masked allergens?

Converting enzyme inhibitors block the conversion of angiotensin I into angiotensin II. They may increase the severity of anaphylactic reaction during LDL apheresis or hemodia-

lysis (3). ACE inhibitors could also be responsible for the occurrence of allergic reactions or anaphylaxis to an allergen during specific immunotherapy (4). We suggest that food anaphylaxis should be systematically suspected in a patient displaying repeated allergic reactions with ACE inhibitors before concluding that these drugs are directly responsible (5).

Key words: angiotensin-converting enzyme inhibitor; pine nut anaphylaxis.

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