

tion tests, and histamine-release tests were negative for all of these drugs. Specific IgE antibodies against H could not be determined for technical reasons. Prick tests with the same drugs in different vehicles (ether and methanol) and in different concentrations (0.1, 1, and 10 mg/ml) were negative. We did not perform intradermal tests because both ether and methanol were irritants. The oral provocation tests began with a dose of 40 mg of pure H (provided by Boehringer Mannheim SA, Barcelona, Spain). Within 30 min. the patient developed a severe reaction with hypotension (60/30 mmHg); heart rate of 140 beats/min; edema of the face, hands, and uvula; dyspnea; dysphagia; and dysphonia. She required admission to an intensive care unit and administration of subcutaneous epinephrine, as well as intravenous fluids, dexchlorpheniramine, and methylprednisolone. Recovery from this reaction was obtained over the next 2 h. Intravenous dexchlorpheniramine and methylprednisolone were continued for 48 h, enabling the patient to be discharged. Laboratory investigation, including urinalysis; tests for blood cell and differential counts, electrolyte levels, coagulation, arterial blood gases, creatine phosphokinase, lactic dehydrogenase, immunoglobulins, C3 and C4 components of complement, total hemolytic complement (CH50), and circulating immune complexes; and biochemistry profile gave normal results. We did not perform oral provocation tests with other coumarins or cromoglycate because of the serious reaction to H.

H was introduced for human use over 20 years ago. However, we have not found any references in the literature about adverse reactions with this drug, excepting diarrhea (2). We describe an anaphylactic-type reaction by H, a previously unreported complication of this drug. Clinically, it is clear that H caused the syndrome suffered by our patient. A definitive diagnosis can be established from the algorithm of Karch & Lassagna (4) and the "imputability concept" (5). However, it is more difficult to establish the mechanisms implicated in the reaction. In our case, the clinical history made it possible to exclude drug overdose, drug side-effect, and drug interaction. But other conditions, such as drug intolerance, drug idiosyncrasy, drug allergy, or pseudoallergic reaction, which can occur in certain susceptible patients, should be taken into account (6). To confirm drug allergy, one must demonstrate a relevant immunologic reaction to the drug or its metabolites. H has a low molecular mass (176.16 Da) so it is not immunogenic and requires complexing with a carrier protein to elicit an immunologic response. Often, the organic radicals formed by these complexes do not cross-react antigenically with the parent compound, and testing with the drug itself does not utilize the antigen responsible

for the symptoms (7, 8). For those reasons, we cannot come to definitive conclusions regarding our *in vivo* and *in vitro* negative results with H. It is clear that our patient suffered a severe immediate reaction to this drug, but we cannot establish the exact mechanism. Neither an IgE-mediated reaction nor other possible mechanisms of an immediate reaction (such as direct mediator release, anaphylotoxins of the complement cascade, immunocomplex aggregation, etc.) could be demonstrated.

We advised the patient to avoid drugs with similar chemical structure, such as other coumarins and chromones, because of the severity of the reaction.

Key words: anaphylaxis; drug allergy; hymecromone; hypersensitivity; umbelliferones.

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Tryptase – at last a useful diagnostic marker for anaphylactic death

THE postmortem diagnosis of anaphylactic shock has previously been based on the circumstances of death and absence at autopsy of specific pathologic and toxicologic findings which could explain death. Analysis of histamine and degradation products in blood is not feasible after death (1). Measurement of total IgE and IgE antibody with

Table 1 Summary of two case histories

	Suspected allergen	Tryptase	S-IgE	RAST positivity
Case 1 (44-year-old man)	Penicillin	28 µg/l	300 kU/l	Penicillin V and G
Case 2 (17-year-old boy)	Food	5.5 µg/l	3100 kU/l	Paprika, lentils, etc.

RAST is possible but will not prove that death was preceded by acute anaphylactic reaction. However, measurement of mast-cell-specific tryptase, which is relatively stable in postmortem blood (2), has made it possible to confirm or exclude anaphylaxis as a cause of sudden, unexpected death. We report two cases in which tryptase was analyzed postmortem, and the circumstances indicated death by anaphylaxis (Table 1).

■ The first case was that of a 44-year-old, obese man with known allergy to penicillin. One hour

IgE antibodies and a high tryptase level in postmortem blood strongly indicate fatal anaphylaxis.

before death, he had received oral penicillin V from his doctor for acute sinusitis. Autopsy 4 days after death resulted in no specific pathologic findings. The toxicologic screening was negative. The tryptase concentration in serum was 28 µg/l (normal range <5 µg/l). RAST was positive for penicillin G (1.6 kU/l) and penicillin V (2.0 kU/l). The total IgE in serum was 300 kU/l.

■ The other patient was a 17-year-old boy with a known asthmatic condition who showed acute symptoms of dyspnea after eating at an Oriental kebab restaurant. On his way home, he collapsed in the street approximately 1 h after the presumed challenge, and could not be resuscitated. At autopsy 3 days later, no obvious cause of death was found. The toxicologic tests were negative. Tryptase in serum was 5.7 µg/l. The RAST test showed IgE antibodies against paprika (2.8 kU/l), lentils (3.9 kU/l), almonds (808 kU/l [sic]), peanuts (759 kU/l [sic]), hazelnuts (21 kU/l), and paranuts (5.6 kU/l), whereas beef (the main ingredient of kebab) was negative. Total IgE in serum was substantially elevated at 3100 kU/l (normal <263 kU/l).

In the first case, the patient was allergic to penicillin, he was exposed to oral penicillin V, and he died suddenly and unexpectedly. The laboratory findings, including markedly elevated tryptase concentration, slightly elevated total IgE, and positive RAST for penicillin V, support the hypothesis that death was caused by anaphylaxis.

In the other case, tryptase was slightly, and total IgE was substantially, elevated. The IgE antibodies found, especially those against lentils and paprika, might have been of importance, as these vegetables are common ingredients in many dishes at Oriental kebab restaurants, and might have been involved in the allergic reaction. His extreme sensitization to almonds and peanuts might also have been of significance. The temporal relationship between ingestion of food and the symptoms, and his atopic disposition were corroborated by the laboratory findings, and strongly indicated that death was actually caused by anaphylactic reaction.

■ Elevation of tryptase is sometimes seen in "control" cases postmortem, i.e., 5–10 µg/l and, in a few cases, >10 µg/l (5), a fact which has not yet been explained. Therefore, additional studies of control cases and anaphylactic deaths are necessary to define further the sensitivity and specificity of the test.

■ Thus, the diagnosis of anaphylaxis cannot be based solely on a slightly elevated tryptase value, as in our second case. In these circumstances, the diagnosis of anaphylaxis would require additional criteria such as:

- 1) the known atopic disposition of the deceased
- 2) a temporal relationship between exposure to the suspected allergen and death
- 3) the finding of specific IgE antibodies against the suspected allergen although they might have been consumed in the anaphylaxis.

■ In conclusion, tryptase analysis seems to be useful in the investigation of suspected anaphylactic and sudden unexpected deaths.

Key words: autopsy; fatal anaphylaxis; tryptase.

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