Association of Penicillin Allergy with Idiopathic Anaphylaxis

Suresh J. Antony, MD, and Robert H. Fisher, MD
Milwaukee, Wisconsin

Idiopathic urticaria is a common and usually self-limited illness that is occasionally associated with life-threatening idiopathic anaphylaxis. A case is presented in which urticaria existed for 30 years before tests that revealed penicillin allergy as the probable cause. Our findings suggest that evaluation for penicillin allergy may be useful in some cases of urticaria.

Key words. Anaphylaxis; urticaria; angioneurotic edema; food hypersensitivity; penicillins allergy and immunology. (*J Fam Pract 1993; 37:499-502*)

Anaphylaxis accounts for 500 deaths in the United States each year,[1] and drug allergy is the most common cause. Persons may unknowingly ingest precipitating drugs by eating contaminated foods,[2-6] resulting in unpredictable serious allergic reactions. Our case report illustrates this problem and describes the evaluation of such a patient.

Case Report

A 74-year-old man was referred for evaluation of recurrent urticaria and idiopathic anaphylaxis, which he reported he had had since 1963. During that year, he experienced urticaria once or twice a month, which was apparently precipitated by an acute episode of anaphylaxis. The initial anaphylactic episode occurred while he was assisting a local veterinarian in the delivery of a calf. As he recalled, he was leaning over the veterinarian's medicine bag and began to develop numbness and swelling of his mouth and hands, a choking sensation in his throat, and shortness of breath. He was treated for anaphylaxis that included hypotension and angioedema.

His recurrent urticaria or angioedema was evaluated at another medical center, and he was reportedly found to have multiple allergies, including allergies to pollen, dust, and several foods, such as corn, rice, and oats. He was placed on a regimen of selective food avoidance and immunotherapy for 2 years with only slight improvement of his recurrent urticaria and angioedema. Some of these episodes followed the ingestion of 1 or 2 cups of milk, although skin testing for cow's milk was negative. The patient's idiopathic anaphylactic episodes then recurred approximately every 2 to 3 years. On some occasions, the patient had ingested small amounts of milk in his cereal without any difficulty. Further laboratory evaluation for his recurrent urticaria or angioedema included normal complement levels with a normal C1 esterase and complete blood count.

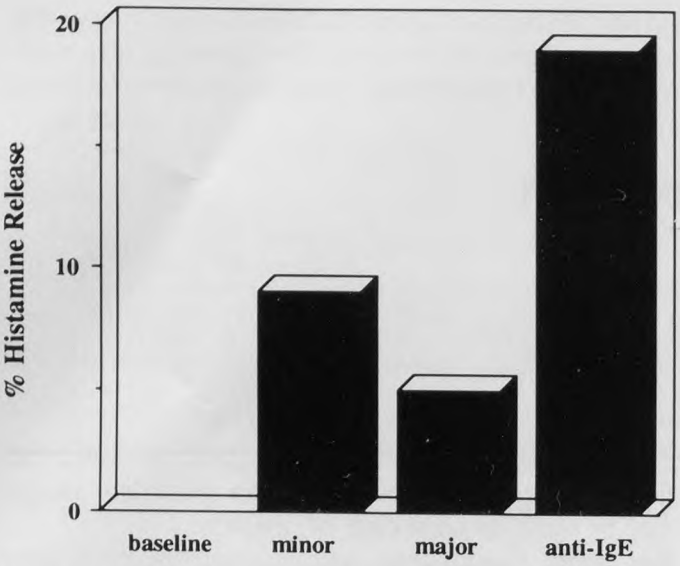
Approximately 20 years after his first anaphylactic episode, the patient was treated for bronchitis with oral amoxicillin. On the way home from his physician's office, the patient developed respiratory distress and the other symptoms of severe anaphylaxis resembling his previous idiopathic episodes. He was resuscitated but continued to have additional idiopathic episodes for the next several years. In retrospect, the patient stated that most of these episodes occurred following ingestion of hamburgers obtained from a restaurant chain and occasionally following ingestion of commercially purchased chicken and milk.

His past medical history was otherwise unremarkable, but the family history included urticaria in the father. Physical examination was normal; skin testing by the prick-test method for aeroallergens revealed large positive reactions to several trees as well as to ragweed. Results of skin testing for food allergies were negative for

Submitted, revised, July 28, 1993.

From the Department of Medicine, Division of Allergy and Immunology, Medical College of Wisconsin, Milwaukee. Requests for reprints should be addressed to Robert H. Fisher, MD, Allergy Division, Medical College of Wisconsin, 8700 W Wisconsin Ave, Milwaukee, WI 53226.

ISSN 0094-3509



Penicillin-induced basophil histamine release. Peripheral blood was drawn from the patient and studied for penicillin-induced histamine release. As a negative control, baseline spontaneous release was found to be 10% of the total basophil content, while anti-IgE as a positive control produced an additional 19% release. The minor determinant induced a release that was 9% over spontaneous release (43% of the positive control) and the major determinant induced 5% over spontaneous release (26% of positive). These findings further support immediate hypersensitivity to penicillin and are supported by the inability of penicillin determinants to cause histamine release greater than spontaneous in two normal subjects (not depicted).

chicken, beef, milk, eggs, soy, rye, wheat, peanut, corn, and many other foods.

Because of the patient's past history of penicillin hypersensitivity and negative skin testing for foods, skin testing for penicillin major and minor determinants was performed. Skin testing for the major determinant was carried out using the prick-test method with a commercially available benzylpenicilloyl polylysine (Pre-Pen, Schwarz Pharma, Milwaukee, Wis); minor determinant testing was performed with two separate preparations of a three-component mixture containing benzylpenicillin and benzylpenicilloate prepared in East Carolina University's allergy laboratories according to published protocols.[7] The estimated major and minor determinant drug delivered to the patient by the prick-test method was 30 to 60 U and 0.1 to 0.2 U, respectively.

Within 5 minutes of placement of the skin test, the patient began to experience generalized pruritus, soon followed by nausea, vomiting, diaphoresis, and hypotension. At this time he was found to have large positive skin reactions to both minor determinant preparations, but a negative response to the major determinant. He was treated for his anaphylaxis, and over the next 15 to 20 minutes his condition improved. At discharge, he was given a prescription for doxepin, 10 mg nightly, and was provided with a single dose of epinephrine in a self-injection system (EpiPen, Center Laboratories, Port Washington, NY). The patient was advised to avoid quantities of milk exceeding 1 to 2 oz and to avoid meat and poultry products purchased at the hamburger chain that had been associated with his earlier anaphylactic episodes.

Over the next 6 months, the patient was free of urticaria or angioedema, and indicated that he was tolerating meat and dairy products purchased from a local farm. Approximately 1 month after the patient's initial evaluation, peripheral blood was drawn for basophil histamine release studies. The basophils were incubated in the presence of a major determinant at a concentration of 3×10^{-5} mol/L and a minor determinant at 25 U/mL. A positive control using anti-IgE was performed. As shown in the accompanying figure, histamine release produced by the major determinant was approximately 50% greater than spontaneous release, while that produced by the minor determinant was 90% above spontaneous and approximately one half the positive control, further confirming the diagnosis of penicillin-induced urticaria and anaphylaxis. Basophils from two normal subjects failed to respond to either determinant.

Discussion

Anaphylaxis, which is often life-threatening, usually occurs through an antigen-antibody reaction that releases bioactive mediators from mast cells and basophils.[1,8] Other non–IgE-dependent inducers of anaphylaxis include exercise, nonsteroidal anti-inflammatory drugs, radiographic contrast media, and cold. There is also a group of patients, such as the patient in this report, who have idiopathic anaphylaxis in whom an antigen or precipitating factor is not identified.[8] A number of diseases may mimic idiopathic anaphylaxis, such as mastocytosis, hereditary angioedema, carcinoid syndrome, pheochromocytoma, and asthma.

Anaphylaxis has been reported to occur in 1 of every 2700 hospitalizations, (Table),[1] and to account for approximately 500 deaths in the United States each year. In addition, nearly all patients with fatal anaphylaxis are found to be asthmatic.[9] Food-hypersensitivity–related anaphylaxis is believed to result from IgE-dependent mediator release from mast cells and basophils. The prevalence of food hypersensitivity is estimated to be between 1% and 2%.[10] Some of the early symptoms of food hypersensitivity include oral pruritus, swelling of the lips, throat swelling, urticaria, and angioedema. Shortness of breath and wheezing can soon follow.[11] Foods that have

Causes and Incidence of Acute Anaphylactic Reactions

Cause	Incidence
Radio contrast media	1 in 1000–14,000
Hemodialysis	1 in 1000–5000
Penicillin	1 in 100
General anesthesia	1 in 300
Allergen immunotherapy	1 in 10,000,000
Insect stings	Uncertain (100 deaths per year)

Based on data from Metcalf DD. Acute anaphylaxis and urticaria in children and adults. In: Schocker I, ed. Clinical management of urticaria and anaphylaxis. New York: Marcel Dekker, 1993:2.

commonly been implicated as inducers of anaphylaxis include nuts, fish, eggs, and milk. Allergic reactions to milk have been reported to occur in as many as 7.5% of children, and 0.1% of these reactions progress to anaphylaxis.[12,13]

In the United Kingdom, levels of penicillin not exceeding 0.1 U/mL are permitted in milk.[14] One pint of milk containing far lower levels, such as 0.01 U/mL, would therefore contain 5 U of penicillin, and this amount has been found to cause anaphylactic reactions in highly penicillin-allergic patients.[2,3] There have been other reports of unusual cases of anaphylaxis resulting from penicillin in milk, soft drinks, and frozen foods.[4,5] Penicillin-induced anaphylactic reactions typically involve laryngospasm, hypotension, bronchospasm, and cardiac dysfunction in 2% to 13% of the penicillin-allergic population, and as many as 9% of these reactions are fatal.[15] Penicillin is the cause for approximately one fatal anaphylactic reaction per year in the United States.[16,17] Approximately 2% to 5% of the population have reported a history of a penicillin allergy; however, misdiagnosis often occurs because of faulty recall, naturally declining hypersensitivity, and misattribution of symptoms to an allergic cause. Skin-testing in these patients reveals positive skin tests in approximately 46% of patients with a history of anaphylaxis, 17% of patients with a history of urticaria and angioedema, and 7% with a history of maculopapular reactions.[18] Because misdiagnosis is common, and a negative skin test is highly predictive of a patient's ability to tolerate penicillin,[7] we chose to validate the patient's probable penicillin allergy by skin testing. Skin testing by the prick-test method is considered safe and has not caused any mortality in the United States.

Urticaria is one of the most common reactions to penicillin, and 24% of a Scandinavian group of patients suffering from chronic idiopathic urticaria were found to have penicillin allergies.[6] In addition, penicillin has been shown to exacerbate chronic urticaria.[19] Ormerod et al noted that the radioallergosorbent test (RAST) has been used for the diagnosis of penicillin allergy, and correlates relatively well with prick-testing.[14] However, although it is more specific than intradermal testing, it is generally less sensitive and may miss some cases of penicillin allergy. Basophil histamine release has also been used as an in vitro method for the detection of IgE-mediated allergy[20] and may be somewhat more sensitive and specific than the RAST. In our patient, the basophil histamine release as depicted in the figure was twice as high as the baseline and one half the positive control, suggesting it was a truly positive reaction.

Avoidance of the offending drug is the most effective method of avoiding anaphylaxis, but this may not always be possible. However, identifying and avoiding a local source of contamination, such as a local supplier of food products, should be helpful. To reduce unnecessary food restrictions, we prefer to confirm immediate hypersensitivity by testing before recommending strict avoidance. In most cases of suspected penicillin allergy, alternative antibiotics can be used. Skin testing for penicillin should be reserved for cases in which acceptable alternatives to penicillin are not available (such as for syphilis during pregnancy) or when the diagnosis of occult exposure causing urticaria or angioedema is suspected. Patients are advised to undergo repeat skin testing before use of β-lactam antibiotics to rule out the possibility of resensitization.

Desensitization of the patient's allergy to penicillin can be accomplished using orally administered β-lactam antibiotics,[15] but patients should still be advised to carry epinephrine with them in case of an emergency. Doxepin hydrochloride has proved to be useful in patients with urticaria, and reduces the degree of itching, swelling, and angioedema.[21] This drug is many times more potent than more traditional H1 blockers, and provides the added benefit of H2 blockade. We typically use this medication prophylactically for patients with histories of life-threatening reactions.

In summary, our case report suggests that the syndrome of idiopathic anaphylaxis and urticaria may at times be related to penicillin allergy, often resulting from the ingestion of small amounts of this drug contaminating food products. Physicians should be aware of this possibility when evaluating these patients. Prospective studies to further define the prevalence of penicillin as a cause for this syndrome are clearly necessary.

Acknowledgment

We wish to thank Debbie Nichols for her assistance in the preparation of this manuscript.

References

1. Metcalf DD. Acute anaphylaxis and urticaria in children and adults. In: Schocker I, ed. Clinical management of urticaria and anaphylaxis. New York: Marcel Dekker, 1993:2.
2. Jackson AC. Milk quality schemes. J Soc Dairy Technol 1982; 35:64–71.
3. Anonymous. Antibiotics tightening up. Milk Producer 1985; 4:22.
4. Wicher K, Reissman R. Anaphylactic reactions to penicillin (or penicillin-like substances) in a soft drink. J Allergy Clin Immunol 1980; 66:155–7.
5. Schwartz H, Sher T. Anaphylaxis to penicillin in a frozen dinner. Ann Allergy 1984; 52:342–3.
6. Boonk WJ, Ketel WG. The role of penicillin in the pathogenesis of chronic urticaria. Br J Dermatol 1982; 106:183–90.
7. Adkinson NF Jr. Tests for immunological drug reactions. In: Rose NR, Friedman H, Fahey JL, eds. Manual of clinical laboratory immunology. 3rd ed. Washington, DC: American Society for Microbiology, 1986:692–7.
8. Wiggins CA, Dykewicz SM, Patterson R. Idiopathic anaphylaxis: a review. Ann Allergy 1989; 62:1–4.
9. Sampson AH, Mendelson L, Rosen J. Fatal and near fatal anaphylaxis to food in children and adolescents. N Engl J Med 1992; 327:380–4.
10. Sloan AE, Powers ME. A perspective on popular perceptions of adverse reactions to food. J Allergy Clin Immunol 1986; 78:127–33.
11. Bochner BS, Lichtenstein LM. Anaphylaxis. N Engl J Med 1991; 324:1785–90.
12. Brock SA. Prospective appraisal of complaints of adverse reactions to food in children during the first three years of life. Pediatrics 1987; 79:683–8.
13. Host A, Husby S, Osterballe O. A prospective study of cows milk allergy in exclusively breast-fed infants. Acta Pediatr Scand 1988; 77:663–70.
14. Ormerod AD, Reid TM, Main RA. Penicillin in milk—its importance in urticaria. Clin Allergy 1987; 17:229–34.
15. Sullivan T, Yecies L, Shatz G, Parker C, Wedner J. Desensitization of patients allergic to penicillin using orally administered β lactam antibiotics. J Allergy Clin Immunol 1982; 69:275–82.
16. Idsoe O, Guthe T, Wilcox RR, et al. Nature and extent of penicillin side reactions, anaphylactic shock. Bull World Health Organization 1968; 38:159.
17. Erffmeyer JE. Adverse reactions to penicillin. Ann Allergy 1981; 47:288–300.
18. Green G, Rosenblum A, Sweet RG. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. J Allergy Clin Immunol 1977; 60:339–45.
19. Warin RP, Smith RJ. Challenge test battery in chronic urticaria. Br J Dermatol 1976; 94:401.
20. Nolte H, Sciotz P, Skov P. A new glass-microfiber based histamine analysis for allergy testing in children: results compared with conventional leukocyte histamine release assay, skin prick test, bronchial provocation test and RAST. Allergy 1987; 42:366–73.
21. Goldsobel A, Rohr A, Siegel S, et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol 1986; 78:867–73.