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Case Report: Anaphylactic Reaction to Guaifenesin

Manujendra Ray, MD, PhD¹
Bela Faltay, MD^{2,3}
Nairmeen Awad Haller, PhD^{1,3}

¹Department of Internal Medicine, Akron General Medical Center, Akron, OH; ²Department of Allergy and Immunology, Akron General Medical Center, Akron, OH; ³Northeastern Ohio Universities Colleges of Medicine and Pharmacy, Rootstown, OH

Abstract: Adverse drug reactions lead to a significant number of hospital admissions each year and thus contribute to the overall financial burden of health care. Some of these drug reactions are allergic responses. As the overall predictability of allergic responses to drugs remains low, efforts to improve our understanding of the processes underlying these responses continue as we strive toward the ultimate goal of primary prevention. Allergic reactions range from mild pruritic to severe systemic anaphylactic responses. We report a case of a young healthy man who developed an anaphylactic reaction to an over-the-counter expectorant. A skin test showed that the patient had an immunoglobulin E-mediated allergic response to guaifenesin, one of the components of commonly available cough medications. Our review of published literature showed that this is the first report of a severe allergic response to guaifenesin.

Keywords: drug allergy; anaphylaxis; guaifenesin; immunoglobulin E

Introduction

Guaifenesin (3-[2-methoxyphenoxy]-1,2-propanediol; guaicol glyceryl) is a commonly used expectorant, and is available over the counter (OTC) usually in combination with phenylephrine or dextromethorphan. As an expectorant, its primary function is to increase the volume of airway secretions, thereby facilitating the expulsion of otherwise tenacious sputum. Although clinical trials have failed to conclusively prove its efficacy in this role, it has continued to be prescribed for several decades.^{1,2} Common to most medications, the known side effects of guaifenesin include headaches, nausea, and vomiting. Over the years, urolithiasis, secondary to the use of large amounts of guaifenesin, has been reported occasionally.^{3,4} Although allergic reactions to dextromethorphan, a drug commonly found in combination with guaifenesin, have been described,⁵ we were unable to find any reports of allergic reactions to guaifenesin alone. Here, we report the first case of a systemic allergic response to guaifenesin.

Case History

A 22-year-old white man was seen in the clinic after having an adverse reaction to his sinus medications. The patient had a longstanding history of rhinosinusitis and had used several OTC medications for symptom relief, including Sudafed® and loratidine. Although these medications provided little or no relief, the patient did gain some reprieve from his symptoms after he started using Mucinex® DM. On one occasion, however, after taking this medication he developed sudden onset swelling of his throat and tonsils accompanied by shortness of breath and a choking sensation. Although the patient sought medical care, he was not admitted to the hospital. The patient has since avoided further use of the medication. The patient also reported a second incident that was attributed to aspirin; however, he has continued to use aspirin and nonsteroidal

Correspondence: Nairmeen Awad Haller, PhD, Department of Internal Medicine, Akron General Medical Center, ACC Ste 507, 400 Wabash Ave, Akron, OH 44307. Tel: 330-344-6001 Fax: 330-535-9270 E-mail: nhaller@agmc.org

anti-inflammatory drugs without any additional adverse reactions. At the time of presentation, the patient also complained of intolerance to eggnog and mushrooms, which he claimed gave him diarrhea. Although the patient had both a cat and dog, he denied allergies to them. The physical examination was normal except for hoarseness of voice, allergic shiners, nasal mucosal edema, and clear excessive postnasal drip.

Overall, several concurrent, potentially immune-mediated processes required further evaluation in this patient, the most critical of which was his severe response to a typically innocuous drug. Because Mucinex[®] DM consists of both dextromethorphan and guaifenesin, it was critical for us to ascertain which of these drugs was responsible for his reaction and to determine if this was a true allergic response. To address this issue, the patient was subjected to a skin prick (epidermal) test with dye-free liquid forms of guaifenesin and a guaifenesin–dextromethorphan combination, along with the standard positive and negative controls. The patient developed a significant wheal and flare response to both guaifenesin and the guaifenesin–dextromethorphan combination, clearly demonstrating an allergy to guaifenesin (Figure 1). Aspirin challenge was not performed because of the patient's history of repeated tolerance to the drug after his initial adverse reaction. Additional allergy testing and laboratory studies undertaken are given in Tables 1 and 2.

The patient has since been seen in the clinic on several occasions for follow-up and treatment for his allergic

Table 1. Results of Allergy Tests

Test	Class ^a	Units
Egg yolk	0/I	0.05 kU/L
Egg white	0/I	0.06 kU/L
Nutmeg	I	0.09 kU/L
Mushroom	0	< 0.05 kU/L
Cow's milk	0	< 0.05 kU/L
Oyster mushroom	0	< 0.05 kU/L

^aClass: 0 is negative; 0/I is equivocal; I, II, III, IV, V, VI denote increasing levels of specific immunoglobulin E antibody.

rhinosinusitis, and is currently being treated with nasal corticosteroids. He has not reported any adverse reactions to any other medications or foods since his initial visit. A recent skin prick test for environmental allergens demonstrated an equivocal (4 mm wheal) reaction to dust mites, trees, and cat dander, as well as penicillium, while the remainder were negative. Histamine revealed a large reaction (13 mm wheal, 40 mm flare).

Discussion

Adverse reactions to medications are diverse in presentation and pathogenesis. Some reactions can occur in normal patients and include reactions to drug overdose, side effects to medications at therapeutic dosages, secondary effects of drugs, and drug interactions. However, some reactions occur only in a small percentage of individuals and are referred to as *hypersensitivity reactions*. These include intolerance to medications such as side effects at subtherapeutic doses, idiosyncratic drug reactions or drug effects due to pharmacogenetic variations, and immune-mediated reactions.⁶ Immune-mediated reactions to drugs can be subclassified further into types 1 to 4 based on the Gell-Coombs classification, ranging from immunoglobulin E (IgE)-mediated anaphylactic type reactions to T-cell-mediated delayed-type hypersensitivity reactions.^{7,8}

Based on this patient's history, it was apparent that he had experienced an anaphylactic type reaction. Although double-blind, placebo-controlled, graded ingestion challenge is the gold standard for diagnosing adverse drug reactions, an important caveat to this test is the risk of a severe and possibly uncontrollable reaction to the offending agent. However, open challenge was discussed with the patient, but in light of his previous reaction he declined. Guaifenesin is commercially available in many drug formulations, usually in combination with decongestants or cough suppressants such as dextromethorphan and hydrocodone (no longer available in the United States). Opioids are known to induce anaphylactoid reactions via the nonimmune-mediated release

Figure 1. Immunoglobulin E skin prick test for hypersensitivity to guaifenesin (G) [wheal/flare = 8/20]; a guaifenesin–dextromethorphan combination (DM) [9/20] (dye-free over-the-counter preparations for both guaifenesin and the guaifenesin–dextromethorphan combination were used which included the following inactive ingredients, all of which are not present in Mucinex[®] DM: acesulfame K, artificial flavors, aspartame, hydroxypropylmethylcellulose, menthol, methylparaben, potassium sorbate, and purified water [may contain citric acid to adjust pH]); normal saline negative control (C) [0/2]; and histamine-positive control (H) [10/45]. A significant wheal and flare is seen in response to guaifenesin and the guaifenesin–dextromethorphan combination, verifying the hypersensitivity to guaifenesin.

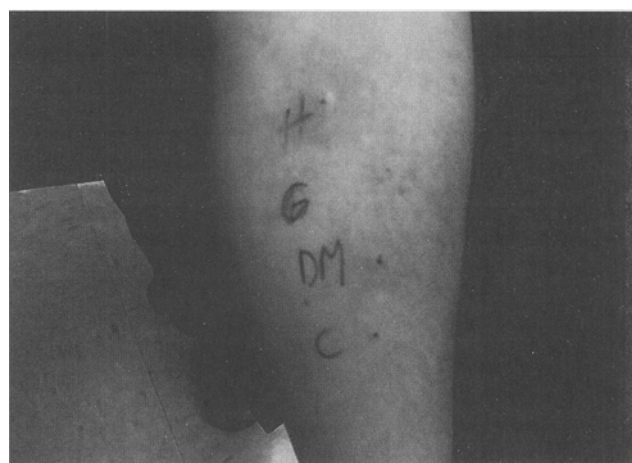


Table 2. Results of Laboratory Tests

Test	Result
Complement C1q, quantitative	15.0 mg/dL
Antinuclear antibody	Negative
White blood cell	5.8/mm ³
Hemoglobin	15.1 g/dL
Hematocrit	42.8%
Platelets	209/mm ³
Neutrophils	2.5/mm ³
Lymphocytes	2.6/mm ³
Monocyte	0.4/mm ³
Eosinophil	0.3/mm ³
Basophil	0.0/mm ³
Erythrocyte sedimentation rate	5 mm/h
C4 complement	17 mg/dL
C1 esterase inhibitor	25 mg/dL
Immunoglobulin E	6 IU/mL

of large amounts of histamine, leading to a systemic response that mimics anaphylactic reactions. There also have been reports of IgE-mediated reactions to opioids, including dextromethorphan.^{5,9} Our skin test results indicated that the patient had a true allergy to guaifenesin. Due to the limited availability of reagents at the time the test was conducted, we were unable to test for dextromethorphan sensitivity independently.

Although it is theoretically possible to develop an allergic reaction to any medication, some are inherently more notorious than others because of their immunobiological properties. The general consensus is that the larger and more complex the structure of the molecule, the more immunogenic it is. Some drugs such as insulin naturally fulfill these criteria, whereas others, such as hydralazine, do so by binding to carrier molecules, a process called haptentation. Along similar lines is the premise that biomolecules under the size of 1 kDa are not allergenic.¹⁰ Guaifenesin is a small and relatively simple molecule; however, whether it can serve as a hapten is yet to be confirmed.

Although intrinsic factors can make certain drugs more immunogenic than others, several host factors appear to increase the likelihood of developing drug allergies. For a drug to induce an immune response it must be presented to T helper cells in the context of major histocompatibility complex (MHC) class II molecules. The diversity in MHC class II molecules allows for the presentation and recognition of a wide range of foreign molecules, but it also engenders the possibility of reacting to medications introduced in the

body. Although genetic variability appears to be one factor responsible for these adverse reactions, studies have also shown that individuals afflicted with viral illnesses, especially HIV, have a greater predisposition to develop drug hypersensitivity responses than noninfected individuals. Although the hypersensitivity responses to various drugs in HIV-positive individuals, including sulfamethoxazole and abacavir are not restricted to type I responses, they bring to light the importance of host-driven factors that affect the body's immune threshold.^{11,12} Similar studies have shown that individuals with systemic lupus erythematosus have a higher incidence of hypersensitivity responses to antibiotics.¹³

Summary

To the best of our knowledge, this is the first report of an anaphylactic response to guaifenesin. Although we believe that the tests we performed clearly demonstrate that our patient had a specific IgE-mediated response to guaifenesin, as with many tests performed to confirm unusual drug reactions, our test did not employ standardized reagents. If additional cases of guaifenesin hypersensitivity are identified, further studies, including reagent validation and double-blinded, placebo-controlled oral challenge (whenever possible) should be conducted to establish a comprehensive diagnostic scheme for this drug allergy. Although the common side effects from drugs, including headache, diarrhea, and nausea are often seen in daily practice, it is important to be aware of some of the less common but more serious side effects of the medications prescribed.

Conflict of Interest Statement

Manujendra Ray, MD, PhD, Bela Faltay, MD, and Nairmeen Awad Haller, PhD disclose no conflicts of interest.

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