

Using Test Dose Challenges to Restore Essential Therapy in Patients with Idiopathic Anaphylaxis and Pharmacophobia: Report of a Patient with Idiopathic Anaphylaxis and Statin Phobia

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ABSTRACT

Idiopathic anaphylaxis (IA) is a well-documented condition in which anaphylaxis occurs in the absence of an identifiable precipitant. However, many patients with IA find it difficult to accept this diagnosis and continue to search for an external cause. It is not uncommon for these highly anxious patients to discontinue essential medications that they feel are responsible for the reaction despite reassurance from their physicians to the contrary. In extreme cases, these patients may develop an actual phobia to preexisting medications and avoid them despite adverse conse-

quences to their health. To illustrate this concept, we report a case involving a female patient with familial hypercholesterolemia who experienced a single episode of IA and developed a "statin phobia," falsely implicating her medication (lovastatin) for the reaction. After 5 years of failed therapy with other antihyperlipidemic agents, the patient finally agreed to undergo test dosing to a similar statin agent atorvastatin. On successful completion of the test, she resumed therapy with atorvastatin and her low-density lipoprotein (LDL) levels were reduced by 50% over 5 months. We conclude that patients with a confirmed diagnosis of IA who manifest phobic responses to beneficial medications should be reassured of the diagnosis promptly by their physician. When reassurance fails and the medication is essential to the patient's health, test dose challenges may be conducted to reintroduce the drug to the patient's regimen. (Allergy and Asthma Proc 22:303–309, 2001)

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Idiopathic anaphylaxis (IA) is a well-defined condition in which anaphylaxis occurs in the absence of a clearly identifiable, exogenous precipitant and was first described in the late 1970s.¹ Like other presentations of anaphylaxis to known precipitants, IA is an acute, immediate reaction that is spontaneous and life threatening. However, it is endogenous (internal) in origin and attempts to determine the underlying pathophysiology are in progress.² The syndrome

consists of angioedema or urticaria (or both) with at least one of the following: hypotension, syncope, bronchospasm, or gastrointestinal manifestations of pain or acute diarrhea.³ The diagnosis is one of exclusion and is confirmed once an extensive evaluation has been made to rule out other common or suspected causes of anaphylaxis (Tables I and II). Once the diagnosis of IA has been established, patients can be further classified based on symptom presentation, frequency, and response to therapy (Table III). Many cases of IA have been reported by our department in the medical literature⁴⁻⁹ and successful algorithms have been proposed to guide physicians in the management of this condition.^{10,11}

Despite education and reassurance from physicians experienced in diagnosing and treating IA, a number of highly

anxious patients will find it difficult to accept the fact that the disorder is not the result of some external agent such as a food or medication. The severe anxiety experienced by these patients is understandable given the life-threatening nature of anaphylaxis and identifying an external cause allows the patient to gain a sense of control over the disorder and lessens the fear of experiencing a similar attack in the future. Medications that have been well tolerated and taken consistently for years may be targeted by these patients because they provide an easy, although often false, explanation for the reaction. When patients become fearful of essential medications and avoid necessary therapy despite adverse health consequences, they may meet the criteria for a phobic disorder.

Phobias are relatively common in the general population and in community samples, a 1-year prevalence rate of ~9% with a lifetime rate of 10–11.3% has been reported.¹² Fortunately, the majority of phobias are benign in nature and do not adversely affect the mental or physical well-being of the patient. However, a phobia that is severe enough to result in sufficient impairment or distress may become pathological in nature and often is referred to as a “specific phobia” (Table IV). Medication phobia, also defined as “pharmacophobia,” is an unfounded, marked fear to a specific drug or class of drugs and may meet the criteria for a specific phobia if, despite adequate education and insight, the patient avoids essential medications to the detriment of his/her health. Pharmacophobia has been encountered by our service with regards to prednisone use¹³ and a Canadian study has likewise reported a high prevalence of misconception and fear to inhaled corticosteroids among patients with asthma recruited from the general population.¹⁴

Phobias to essential, preexisting medications are common in anxious patients diagnosed with IA and present a difficult scenario for the managing physician. Reassurance typically fails to convince these patients to resume crucial medications and prophylactic therapy for IA may likewise be avoided. This presents a very serious problem because preexisting disorders are inadequately treated and deaths from IA have been reported in the medical literature.^{15,16} The following case illustrates many of these concepts and shows how to reintroduce safely, essential medications to patients with drug phobias by using test dose challenging.

CASE REPORT

Our case involves a 49-year-old white female who presented to our service on October 31, 1994. Her medical history included perennial allergic rhinitis, moderate-persistent asthma and familial hypercholesterolemia. Her mother had coronary artery disease that required a coronary-artery-bypass graft at a relatively early age. The patient had been taking lovastatin on a daily basis for >3 years with no adverse reactions in addition to inhaled triamcinolone acetonide and albuterol. Her asthma occasion-

TABLE I

Differential Diagnosis of Idiopathic Anaphylaxis

- I. Known causes of immediate generalized reactions
 - A. IgE mediated
 1. Foods
 2. Medications
 - a. Penicillins
 - b. Cephalosporins
 3. Food supplements
 - a. Psyllium
 - b. Bee Pollen
 - B. Exercise-induced anaphylaxis
 - C. Food plus exercise-induced anaphylaxis
 - D. Medication-induced reactions
 1. Aspirin
 2. Nonsteroidal anti-inflammatory drugs
 3. Angiotensin-converting enzyme inhibitors
 4. Opiates
 - E. Radiographic contrast media reactions
- II. Hereditary angioedema
 - A. Classical form
 1. Absent C1 inhibitor
 2. Dysfunctional C1 inhibitor
 - B. Acquired form
 1. B cell lymphoproliferative disorder
 2. Autoantibodies to C1 inhibitor
- III. Systemic mastocytosis
- IV. Asthma masquerading as anaphylaxis
- V. Munchausen's stridor
- VI. Munchausen's anaphylaxis
- VII. Undifferentiated somatoform IA
 - A. Prevarication anaphylaxis
 - B. Simulated anaphylaxis
- VIII. Miscellaneous diagnoses
 - A. Panic attacks
 - B. Globus hystericus
 - C. Histamine-rich food induced flushing
 - D. Carcinoid syndrome
 - E. Pheochromocytoma

Source: Ref. 2.

TABLE II

Diagnostic Tests to Consider for a Patient with Unexplained Anaphylaxis

Procedure	Comment
Urine histamine	To help confirm mast cell activation to secure the diagnosis
Serum tryptase	Supportive if elevated
Immediate skin testing for foods*	May help to confirm or exclude food allergies as etiologic
Immediate skin testing for spices	To exclude a falsely implicated additive
Immediate skin testing for penicillin	To confirm that penicillin was responsible for the anaphylaxis
Immediate skin testing for lasix	May masquerade as idiopathic or food-induced anaphylaxis
Test dosing with NSAIDs	To demonstrate or exclude these as possible agents
Test dosing with a medication or food additive (bee pollen)	To demonstrate or exclude these as causes for anaphylaxis
Complement determinations	To confirm or exclude C1 inhibitor: deficiency/dysfunction C4, CH50
Bone marrow biopsy, skin biopsy, bone scan, and liver scan	To exclude or confirm systemic mastocytosis or urticaria pigmentosa
Diagnostic therapeutic trial with prednisone for 2–3 mon	IA is prednisone responsive

* In vitro testing by RAST or ELISA is less sensitive and can be less specific. Positive skin tests demonstrate IgE antibodies, which may be related to episodes of anaphylaxis. However, they may occur in patients with IA and not make a diagnosis of an external cause for anaphylaxis.

NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: Ref. 2.

ally flared and required short bursts of prednisone, which were administered by another physician. She had no history of a food or medication allergy and no personal or family history of urticaria, angioedema, or anaphylaxis.

Approximately 4 days before our evaluation, the patient had consumed an evening dinner of salmon with a vegetable salad and red wine. She had eaten these foods in the past with no adverse consequences. The patient was not on prednisone therapy at the time and took only inhaled triamcinolone acetonide in the evening before going to bed. On awakening the next morning, over 10 hours later, she felt that her asthma was a bit worse and took two inhalations of albuterol with minimal relief. She took no other medications at that time, including lovastatin or nonsteroidal anti-inflammatory agents and consumed only one cup of coffee. She admittedly was involved in an argument with her son that morning and said that within minutes of this episode she developed diffuse flushing; urticaria; pruritus; dyspnea; throat tightness; and swelling of her hands, lips, face, and ocular and intranasal areas. The patient called 911 and was transported to a local emergency room where she was treated with nebulized albuterol, intravenous (iv) diphenhydramine, and epinephrine. She responded well to the therapy and recovered within a few hours of symptom onset. A presumptive diagnosis of IA was made and the patient was discharged home on prednisone, 60 mg by mouth daily, with instructions to follow up with our service as soon as possible.

We evaluated the patient in our clinic and a thorough history and physical examination failed to reveal an obvious precipitant for the anaphylactic episode. Skin-prick tests to salmon, fish mix, shellfish mix, cereal grain mix, nuts (almond, Brazil nut, cashew, chestnut, fiber nut, peanut, and walnut), egg white, cow's milk, soybean, and wheat gluten (Allergy Laboratories of Ohio, Inc., Columbus, OH) were negative. Urine and blood analysis (CBC with differential, chemistry/hepatic profile, erythrocyte sedimentation rate and complements: C3, C4, and CH50) also were unremarkable. The patient was diagnosed as having IA-generalized (G) and placed on our service's IA treatment protocol.^{10–11} She complied with the protocol and did well without return of anaphylaxis, urticaria, or angioedema and was tapered off of prednisone. She experienced no recurrent attacks over the next year and her final diagnosis was IA-G, single episode, in remission.

However, on follow-up with her primary care physician shortly after the incident the patient had expressed a strong fear that her lovastatin was responsible for the anaphylactic episode. Despite earlier reassurance from our service to the contrary, she remained anxious when advised to resume the medication and persuaded her physician to discontinue it. She was fearful of all statin agents in general and refused to take any medications in this class. Although alternative agents such as nicotinic acid and bile acid sequestrants were used, the patient had difficulty tolerating them and her total cholesterol and low-density lipoprotein (LDL) levels re-

TABLE III	
Classification of IA	
	Symptoms/Definition
Disease	
Generalized (G)	Urticaria or angioedema with bronchospasm, hypotension, and syncope
Angioedema (A)	Angioedema with upper airway compromise (laryngeal, pharyngeal, and tongue).
Frequency	
Infrequent (I)	Less than six episodes a year.
Frequent (F)	More than six episodes a year.
Summary of Diagnoses	IA-G-F, IA-G-I, IA-A-F, IA-A-I.
Variations of IA	
Corticosteroid dependent (CSD-IA)	Controlled with prednisone but with recurrent episodes below a threshold dose of prednisone.
Malignant IA (M-IA)	Requires high doses of prednisone to control IA (>60–30 mg daily or every other day).
Questionable IA (IA-Q)	Patient has possible IA but documentation of objective findings are unsuccessful and diagnosis is uncertain.
Variant IA (IA-V)	Applied when symptoms of IA vary from classic IA. IA-V may subsequently be classified as IA-A, IA-G, IA-Q or USIA.
Undifferentiated somatoform IA (USIA)	Symptoms mimic IA but no objective findings are documented and the symptoms are not responsive to the regimen for IA
<i>Source: Ref. 4.</i>	

TABLE IV
DSM-IV Criteria for Specific Phobia
A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation.
B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or predisposed panic attack.
C. The person recognizes that the fear is excessive or unreasonable (feature may be absent in children).
D. The phobic situation is avoided or otherwise endured with intense anxiety or distress.
E. The avoidance, anxious anticipation, or distress in the feared situation interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships or there is marked distress about having the phobia.
F. In individuals under 18 years of age, the duration is at least 6 mon.
G. The anxiety, panic attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder.
<i>Adapted from Ref. 12.</i>

mained elevated 5 years later at 422 and 317 mg/dL, respectively. She was subsequently referred to a new cardiologist who promptly informed us of the situation and asked us to evaluate her for the perceived “statin allergy” because he determined that this class of medication was essential to the patient’s health.

Atorvastatin was the cardiologist’s drug of choice and we informed the patient that we could test dose her to this agent under close observation in our clinic. We reassured the patient that an allergic reaction to this class of medication would be very unlikely given her history and the rarity of such incidents reported in the medical literature.^{17,18} After a thorough discussion of the risks and benefits, the patient finally agreed to the test and our laboratory prepared a 1/100, 1/10, and full dose of atorvastatin in gelatin capsules for oral administration. After providing informed consent, she was given oral challenges of atorvastatin at 0.1, 1.0, and 10.0 mg (full dose) at 30-minute intervals. Emergency therapy for anaphylaxis was available at the testing site and included iv fluid, epinephrine (1:1000 solution), hydroxyzine, DepoMedrol (Pharmacia & Upjohn, Kalamazoo, MI), and oxygen. Vital signs and a directed physical examination of the skin and cardiopulmonary system were conducted before each test dose and at 1 and 2 hours after the full dose had been administered. The patient was observed by a physician for the duration of the test. As anticipated, she tolerated the medication well, followed up with cardiology later that afternoon, and was started on atorvastatin therapy.

Approximately 1 month after initiating the atorvastatin regimen, the patient’s total cholesterol decreased to 285

mg/dL and her LDL value fell to 188 mg/dL. The effect was sustained at 5 months as her total cholesterol and LDL values diminished further to 258 and 158 mg/dL, respectively. She has continued to tolerate the atorvastatin well with no episodes of anaphylaxis and with normal hepatic function tests. In addition, she has no remaining anxiety to this class of medication and has continued to follow up with us for the management of her asthma.

DISCUSSION

As this case illustrates, pharmacophobia may be present in patients with a diagnosis of IA. Given the magnitude and life-threatening nature of anaphylaxis, some degree of anxiety is to be expected and it is not surprising that medications are viewed with suspicion because they offer an easy explanation and can be avoided in the future. This was the case with our patient who attributed the episode of anaphylaxis to her only oral medication lovastatin. However, our service felt that this agent was not responsible for the reaction given the long, asymptomatic duration of use (>3 years) and the fact that the patient had last taken the drug ~24 hours before the onset of her attack. There was no obvious cause for anaphylaxis in either the history or physical examination and our laboratory investigations likewise failed to identify an obvious etiology for the attack.

Once the diagnosis of IA has been confirmed, patients should be encouraged to resume essential medications. With education and reassurance, most patients will gain a reasonable insight into their diagnosis and renew their previous regimen. Others, although apparently comprehending the nature of the disorder, will remain fixated in the belief that their particular medication was responsible for the reaction. This unfounded, phobic response meets the criteria for a pathological, specific phobia when the needless avoidance of an essential medication compromises the health of the patient. Our patient met many of the diagnostic criteria for a specific phobia and avoiding statin agents led to an increased risk of death or disability from a cardiovascular event given her history of familial hypercholesterolemia and failed control on alternative agents.

Approaching these highly anxious patients and convincing them to resume essential medications may be an extremely difficult task for the managing physician. Our case shows the effectiveness of test dose challenging as a means to safely reintroduce crucial, feared medications when attempts at reassurance and education have failed. This approach is similar to other forms of therapy for phobias in which the dreaded object or situation is presented to the patient along with extensive reassurance and education. The exposure, coupled with positive reinforcement, often serves to minimize or stop the specific phobia in question. Test dose drug challenges have been used to assess and reassure patients when the clinical suspicion for a life-threatening, anaphylactic response is low and the method can be used effectively for patients with IA and pharmacophobia.

However, test dosing should be used only in specific circumstances with clearly defined limitations (Table V). It is not practical, for instance, to test for every feared medication because this would be time-consuming, expensive, and yield little valuable information. Such an approach also might reinforce the erroneous notion that a search for additional suspected culprits must continue indefinitely. Furthermore, frequent, unnecessary testing will inevitably yield numerous false positive results and may precipitate hysterical reactions that will heighten preexisting anxiety and impede effective therapy. Only medications that are essential to the patient's health should be chosen for testing and the patient should be informed of the urgent need to resume these specific agents. When alternative medications are available for the agent in question, an attempt should first be made to use these secondary drugs. In addition, for medical-legal reasons, it is preferable that the physician performing the test is not the physician determining that the medication is required. If this is the case, then consultation should first be obtained to establish that the drug feared by the patient is indeed essential to his/her health.¹⁹ Our case effectively illustrates these principles. Although lovastatin was not suspected as a cause for anaphylaxis, alternative agents were used first in light of the patient's persistent anxiety. Only after these secondary medications failed and only after an independent physician determined that a statin drug was essential to the patient's care did our department proceed with test dosing for atorvastatin.

TABLE V	
Indications/Conditions for Test Dose Challenging	
I.	Should be used only for drugs essential to the patient's health that are considered low risk for causing an anaphylactic reaction.
II.	An independent physician (not performing the challenge) has determined or confirmed that the drug in question is essential for the patient's health.
III.	No alternative agents are available for the essential medication or alternative agents have been used with unacceptable results.
IV.	Patient understands purpose of the challenge and provides informed consent.
V.	Emergency therapy for anaphylaxis is available at site of test and physician monitors patient before, during, and after the protocol.
VI.	No premedication is administered before test dose challenging.
VII.	Published/accepted protocols for challenge are used when available, otherwise test dose is initiated at 1/1000 or 1/100 of full dose and administered in increasing concentrations of 10 at 30-min intervals.
VIII.	Physician performing challenge is experienced with this approach and prepared to respond appropriately to hysterical responses.

Care must always be taken to obtain informed consent from the patient and backup emergency therapy should be available in the unlikely event that a true anaphylactic reaction should occur. A focused physical examination emphasizing vital signs, skin, oral mucous membrane, and cardiopulmonary systems should be conducted before the testing is initiated and repeated at set intervals (usually 30 minutes to 1 hour) between challenges. Asthmatics with peak expiratory flows or spirometry measurements significantly below their baseline status should have testing deferred until a greater degree of control is acquired.

For most foods and for a very few specific medications, skin testing can be administered to assess for an immediate immunoglobulin E (IgE) response to the suspected agent. When skin testing has no published, approved protocol (as is the case with the majority of drugs), then test dose challenges by an iv, intramuscular, or oral route can be administered. This approach was necessary in our patient because no reliable skin tests for atorvastatin have been approved and the interpretation of this method (*i.e.*, irritant versus anaphylactoid versus true IgE-mediated response) would have been questionable. Effective test dosing for the more commonly implicated drugs may be done by using well-established test protocols, many of which are documented in the medical literature.¹⁹ In general, the medication in question can be given orally or iv starting with $1/1000$ or $1/100$ dilutions of the final desired dose. Each dose typically is increased by factors of 10 every 30 minutes until the full dose is finally administered.^{20,21} When the feared outcome is anaphylaxis, symptoms in response to a test dose should be expected to occur within approximately 30 minutes of the challenge. Thus, test doses can be given at this interval and the entire procedure usually can be completed within 3–5 hours.^{19–21} Prophylaxis with either steroids or antihistamines is not warranted in these situations given the small risk of masking a less severe reaction to a lower concentration of the agent.^{19,20}

Hysterical reactions may occur during the testing and are not uncommon in IA patients with pharmacophobia. The responses are variable and can range from mild (*i.e.*, light-headedness, headaches, and flushing) to more extreme presentations (choking, dyspnea, vocal cord dysfunction with stridor, fainting, etc.). The examining physician must know how to respond appropriately to these types of reactions and careful documentation of objective physical findings (*i.e.*, the lack thereof) is very important. If at all possible, test dosing should be continued in these situations given the extreme necessity to resume the essential medication and the patient should be reassured that the reaction is not allergic in nature. Often, testing simply cannot be resumed in light of the high anxiety expressed by the patient. In these situations, a double-blind, placebo-controlled challenge could be proposed but in most cases psychiatric referral should be considered. We were very fortunate that a hys-

terical reaction did not occur with our patient and our attempts had a successful outcome because the patient was reassured and able to initiate therapy with atorvastatin. As mentioned, she showed a very favorable response with no return of anaphylaxis.

In conclusion, our case shows an effective method of reintroducing essential medications to anxious patients with IA and coexisting drug phobias. Anxiety surrounding the diagnosis of IA is not uncommon and many physicians are faced with patients who are similar to the one described in our report. Once the diagnosis of IA has been confirmed, these patients should be encouraged to stop worrying or searching for external causes and be provided with literature on IA. They should be reassured that the feared medication is safe and informed of the more realistic hazards to their health that will result from discontinuing a crucial medication. When these attempts fail and alternative agents are unacceptable, test dose challenges to the essential drug should be considered. Our approach for test dosing with atorvastatin can be replicated successfully and adapted for use with other medications in similar clinical circumstances.

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