

Immediate generalized reaction (anaphylactic type reaction but in which no IgE was demonstrated) induced by acetaminophen.

Clinical allergy-immunology rounds

Nearly fatal episodes of hypotension, flushing, and dyspnea in a 47-year-old woman

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HISTORY

The patient is a 47-year-old white woman who was well until three days before transferring to our hospital. She worked as a restaurant manager. While at work, she developed a headache and took two tablets of Anacin® Aspirin Free (Whitehall Laboratories Inc, New York, NY). Within 30 minutes, the patient developed lightheadedness, flushing, shortness of breath, and experienced a brief syncopal episode. Her blood pressure and pulse were 80/50 mm Hg and 120 beats/min. She was admitted to a nearby hospital to a telemetry unit with diagnoses of syncope and probable myocardial ischemia. Later that day, she experienced two more episodes of flushing, hypotension, and dyspnea. In one episode, her blood pressure dropped to 55/23 mm Hg with the pulse ranging from 121 to 150 beats/min on a cardiac monitor. She was immediately resuscitated with intravenous fluids and dopamine. A baseline arterial blood gas, drawn after the patient had improved, disclosed a pH of 7.42, PaCO_2 36 mm Hg and PaO_2 121 mm Hg on 32% oxygen. During a subsequent episode, the arterial blood gas changed to pH 7.40, PaCO_2 35

mm Hg and PaO_2 64 mm Hg while on 36% oxygen.

There were no proximate causes before these episodes except for eating navy bean soup on the morning of the first reaction. The patient stated she had eaten the same soup in the past without any symptoms and had no known food allergies. The only other external cause was ingestion of two tablets of acetaminophen [Tylenol® (McNeil Consumer Products Co, Fort Washington, PA), while in the hospital, and Anacin® Aspirin Free at work] before the episodes.

In between the episodes, during a 3-day hospitalization the patient was asymptomatic. In addition, she never developed urticaria, angioedema, or wheezing during these episodes when flushing, hypotension, and dyspnea occurred.

On the third hospital day, the patient was transferred to Northwestern Memorial Hospital, Chicago. While hospitalized she had no symptoms except for an occasional global headache.

PAST MEDICAL HISTORY

The patient had no known allergies to medications. She denied any aspirin sensitivity and had used aspirin and acetaminophen occasionally in the past, without any adverse reaction. During childhood, she had had tonsillectomy and several years ago, she underwent intrauterine polypectomy. She had had intermittent headaches for many years, which she attributed to stress.

PHYSICAL EXAMINATION

At our hospital, her physical examination was unremarkable aside

from anxiety concerning her recent onset reactions. Her blood pressure was 120/80 mm Hg, pulse 76 beats/min, and respirations 12/min. Her lungs were clear to auscultation and heart sounds were normal. There was no evidence of skin lesions, flushing, lymphadenopathy, thyromegaly, or hepatosplenomegaly.

LABORATORY EVALUATION

Complete blood count with differential, urinalysis, thyroid function tests, serum chemistries and serial CPK and LDH isoenzymes, were within normal limits. One electrocardiogram obtained after the first syncopal episode revealed diffuse ST segment abnormalities. Several repeated electrocardiograms were normal. In addition, chest roentgenograms, echocardiogram, 24-hour Holter monitor, ventilation-perfusion scan, Doppler ultrasound of the carotids and computed tomographic scan of the abdomen, obtained at the local hospital, were unremarkable.

QUESTIONS

1. Based on the history, physical examination, and laboratory results, what is the differential diagnosis?
2. Which other diagnostic or laboratory tests would not be appropriate?
 - A) 24-hour urine collection for vanillylmandelic acid, metanephrine, epinephrine, norepinephrine, and dopamine.
 - B) 24-hour urine collection for 5-hydroxyindoleacetic acid and serotonin.
 - C) Complements C3, C4, and CH50.

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- D) Skin testing to ingredients in the navy bean soup.
- E) Acetaminophen oral challenge.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of flushing associated with hypotension and dyspnea includes (1) systemic mastocytosis, (2) pheochromocytoma, (3) carcinoid syndrome, and anaphylaxis due to foods, medications, hidden allergens, or unknown cause. Flushing is a transient dilatation of the cutaneous blood vessels. Several vasoactive chemicals including histamine, kinins, and prostaglandins can cause flushing.¹

Some of the common symptoms suggesting systemic mastocytosis are flushing, dyspnea, and light-headedness associated with a fall in blood pressure.^{2,3} The disorder is characterized by a release of mast cell mediators such as histamine, prostaglandin D₂, heparin, and leukocyte chemotactic factors. The majority of lesions of mastocytosis are localized to the skin and the typical form is urticaria pigmentosa. In one series on systemic mast cell disease, urticaria pigmentosa was found in 53% of the cases.² Other extracutaneous clinical findings in systemic mastocytosis include hepatosplenomegaly, peptic ulcer, and lymphadenopathy. Bone and hematologic involvement are other manifestations of systemic mastocytosis.²⁻⁴ Our patient did not have any cutaneous lesions. Furthermore, she had normal complete blood counts, chest radiographs, and computed tomography of the abdomen.

Pheochromocytoma is a tumor of the chromaffin cells of the sympathoadrenal system. Most of the tumors are located in the adrenal medulla and secrete catecholamines.⁵ Hypertension is the presenting feature because pheochromocytomas usually secrete norepinephrine in higher amounts than epinephrine.¹ Rarely do pheochromocytomas secrete mainly epinephrine (which could cause hypotension), dopa, or

dopamine.^{1,5} The combination of elevation of urinary metanephrine and urinary catecholamines provides an excellent predictive value in diagnosing pheochromocytomas.⁵ To visualize the tumor, computed tomography is helpful. The diagnosis of pheochromocytoma is excluded in our patient, based on a normal computed tomography of the abdomen and 24-hour urinary vanillyl-mandelic acid, metanephrine, epinephrine, norepinephrine, and dopamine.

Another endocrine disorder associated with flushing is carcinoid syndrome. Carcinoid syndrome comprises the clinical manifestations of carcinoid tumors. They arise from the amine-precursor uptake decarboxylation system.³ The tumor cells are able to produce kallikrein, serotonin, substance P, histamine, dopamine, and other vasoactive substances.^{1,3} The cells are scattered throughout the gastrointestinal tract, lung, pancreas, ovary, thyroid, and other locations.^{4,6} Some of the common manifestations of the carcinoid syndrome are episodes of flushing, diarrhea, dyspnea, and right sided cardiac disease.⁴ Flushing from gut-derived carcinoid tumors is usually very brief (two to five minutes) and, uncommonly, associated with hypotension and tachycardia.⁴ Bronchial carcinoid tumors may cause flushing for hours or days.⁷ About 20% of the patients with carcinoid syndrome have evidence of cardiac disease and 70% of them have secretory diarrhea.^{1,4} The diagnosis of carcinoid syndrome is based on the clinical presentation and elevation of urinary 5-hydroxyindoleacetic acid, a metabolite of serotonin. The sensitivity of the test is 73% and the specificity is 100%.⁸ Some medications can interfere with the conversion of 5-hydroxytryptophan to serotonin but our patient had not taken any medications when the urine was collected. Further, the urinary 5-hydroxyindoleacetic acid and serotonin were normal. With a normal echocardi-

ogram, electrocardiograms, 24-hour Holter monitoring test, and normal urinary measurements, the diagnosis of carcinoid syndrome can be excluded.

Another possible diagnosis in this patient is anaphylaxis. Anaphylaxis implies a potentially fatal manifestation of immediate hypersensitivity. The clinical presentation can be mild urticaria, pruritus, flushing, and angioedema to hypotension, syncope, shock, and death.⁹ Some causes of anaphylaxis are listed in Table 1.¹⁰ Foods and medications are some of the agents responsible for systemic anaphylactic reactions. Our patient ingested navy bean soup on the day of her first symptoms. Working as a restaurant manager, she ate the same soup occasionally without any adverse reaction. To exclude foods as the cause of her symptoms, she was skin tested to the ingredients in the soup and similar ingredients (corn, garlic, pea, peanut, and soybean). The results were negative with a positive control for histamine.

A likely presumptive diagnosis was idiopathic anaphylaxis which refers to an immediate generalized reaction without an apparent external cause. The underlying pathophysiology is unknown.¹¹ The clinical features of idiopathic anaphylaxis are similar to other forms of anaphylaxis.¹¹ A classification of idiopathic anaphylaxis is presented in Table 2.¹¹ The diagnosis is suspected after a thorough evaluation with skin testing to foods, in some patients, laboratory tests and exclusion of medications or medical conditions.¹¹

Because of negative food skin tests and no history of prior food allergies, our working diagnosis was anaphylaxis, presumably idiopathic with classification of IA-generalized, frequent. With the history of ingesting acetaminophen, however, we undertook a stepwise challenge with Anacin® Aspirin Free. The Anacin® Aspirin Free tablet contained acetaminophen, croscarmellose so-

Table 1. Etiology and Classification of Immediate Generalized Reactions

IgE-Mediated	
<i>Chemicals and therapeutic agents</i>	
Penicillins (synthetic and semisynthetic)	Macrolides
Cephalosporins	Quinolones
Tetracyclines	Streptokinase
Sulfonamides	Thiopental
	Ethylene oxide (used to sterilize dialysis equipment)
<i>Foreign proteins</i>	
Heterologous (horse) serum	Fire ant venom
Blood products (rare IgA-deficient patient)	Antilymphocyte (horse) globulin
Insulin (animal and recombinant)	Protamine sulfate*
L-asparaginase	Allergen extracts
Chymopapain	Latex (in surgical gloves)
Hymenoptera venom	Monoclonal antibodies
<i>Foods</i>	
Shellfish	Fruits (such as kiwi and mango)
Nuts	Grains
Milk	Meats
Eggs	Seeds (including psyllium)
Legumes	
Immune Complex- and Complement-Mediated	
Cupraphane membranes	
Blood and blood products (including immunoglobulins and purified protein fractions)	
Direct Mediator Release	
Opiates	
Radiocontrast media	
Dextran	
Pentamidine	
Vancomycin	
Unknown Mechanisms	
Radiocontrast media	
Aspirin, other nonsteroidal anti-inflammatory agents	
Tartrazine†	
Idiopathic	

* Not all cases are IgE mediated.

† Tartrazine anaphylaxis appears to be exceedingly rare.

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Table 2. Classification of Idiopathic Anaphylaxis

Notation	Classification
IA-G-F	IA-Generalized, frequent*
IA-G-I	IA-Generalized, infrequent†
IA-A-F	IA-Angioedema (potentially life threatening), frequent
IA-A-I	IA-Angioedema (potentially life threatening), infrequent
IA-Q	IA-Questionable
CSD-IA	IA-Corticosteroid dependent
Malignant IA	CSD-IA in which high-dose prednisone does not suppress mast cell activation

* More than six episodes per year or two episodes within a 2-month period.

† Six or less episodes per year or consecutive episodes occurring at greater than 2-month intervals.

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dium, FD&C blue No 1 lake, hydroxypropyl methylcellulose, polyethyleneglycol, povidone, propylene glycol, starch, stearic acid, and titanium dioxide. The challenge was carried out 4 weeks after the hospitalization after she had been asymptomatic while on no medications. Before the challenge her blood pressure was 112/60 mm Hg and pulse was 76 beats/min. Spirometry revealed FVC of 100% and FEV₁ of 99% predicted. After placebo challenge at time 0, Anacin® Aspirin Free was administered as follows: 1, 2.5, 12.5, 50.0, and 125 mg at every 25 minutes. Blood pressure, pulse rate, spirometry, and symptoms were recorded before each dose. The patient was asymptomatic with normal vital signs and spirometry for the first two hours (having ingested a cumulative dose of 191 mg). Approximately 20 minutes after receiving the 125-mg test dose of Anacin® Aspirin Free, suddenly she developed diffuse erythema, dyspnea, dizziness, and abdominal cramps. Her blood pressure dropped from 120/70 to 86/50 mm Hg with the pulse rate increasing from 72 to 130 beats/min. The patient was treated with 0.3 mL of 1:1000 epinephrine solution by subcutaneous injection, intravenous normal saline, diphenhydramine 56 mg by intravenous injection, and hydrocortisone 200 mg by intravenous injection. Her symptoms improved rapidly and she was stabilized within 15 minutes. Figure 1 shows the systolic blood pressure and pulse with different dosages of Anacin® Aspirin Free.

Because of the severity of anaphylaxis, the patient was admitted for 24-hour observation. She remained asymptomatic and was discharged. Urinary histamine obtained one hour after the anaphylaxis and measured by the HRT ELISA (Miles Labs, West Haven, CT) was 165 ng/mL (0–10 ng/mL). Other tests including complete blood count, SMA20, serum salicylate concentration, complements C3,

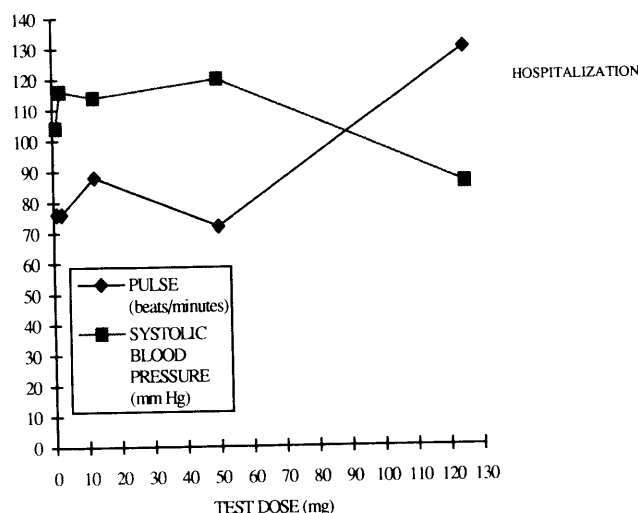


Figure 1. After placebo challenge at time 0, Anacin® Aspirin Free was administered as follows: 1, 2.5, 12.5, 50.0, and 125 mg at every 25 minutes. Darkened squares represent individual test doses of Anacin® Aspirin Free rather than the cumulative amount.

C4, CH50 were within normal limits. Currently, after 6 months of acetaminophen avoidance, the patient remains asymptomatic and is doing well without medications.

Because of the clinical history and the severity of the anaphylaxis during test dosing to Anacin® Aspirin Free, our final diagnosis is acetaminophen-induced anaphylactic shock. We do not suspect that the inactive ingredients in the Anacin® Aspirin Free tablet contributed to the patient's reaction. During further review of the patient's hospital record, the only medication she ingested before flushing, hypotension, and dyspnea was two tablets of Tylenol®, which contained acetaminophen, magnesium stearate, cellulose, sodium starch glycolate, and starch. Other than acetaminophen the common ingredients between Anacin® Aspirin Free and Tylenol® are stearate, starch and cellulose. None of these inactive ingredients has been reported to cause anaphylaxis.

DIAGNOSIS

Immediate generalized reaction (anaphylactic type reaction but in which no IgE was demonstrated) induced by acetaminophen.

DISCUSSION

Acetaminophen was introduced by Von Mering in 1893.¹² It is used internationally as an analgesic and antipyretic. In 1986, the estimated use of acetaminophen in the United States was 10,200,000,000 doses per year.¹³ The medication has a weak antiinflammatory effect and is a weak inhibitor of prostaglandin biosynthesis.¹⁴ Metabolized primarily by the hepatic microenzymes, the acetaminophen concentration in plasma reaches a peak in 30 to 60 minutes and its half life in plasma is two hours after a therapeutic dose.¹²

In therapeutic doses, some reported adverse effects of acetaminophen are listed in Table 3.^{12,15-21,23} In one report, the WHO Collaborating Centre for International Drug Monitoring had received 44 cases of "acute hypersensitivity" to paracetamol (acetaminophen).²¹ Two of the cases were reported as anaphylactic shock.²¹ One case was described as an "anaphylactic reaction" and the other was a reaction without description of the symptoms.²¹ Unfortunately, detailed descriptions of the reactions were not provided. In another report by the Netherlands Centre for Monitoring

of Adverse Reaction to Drugs, five cases of hypersensitivity to paracetamol preparations alone or in combination with caffeine were described.²¹ In these cases, symptoms occurred 15 minutes to one hour after ingestion of 500 mg or 1 g of paracetamol. Reactions consisted of bronchospasm, urticaria, hypotension, and tachycardia. One patient had a positive rechallenge with paracetamol but the description of the challenge was not provided.²¹ In addition to our case, another case of anaphylactic shock induced by acetaminophen was described and confirmed by rechallenge.²⁰

The pathophysiology of hypersensitivity to acetaminophen is unknown and speculative. Idiosyncrasy to the drug with nonimmunologic release of histamine is a possible explanation but is unlikely because of the infrequency of immediate generalized reactions. No evidence of IgE or IgG antibodies to acetaminophen or acetaminophen conjugated to albumin was found by immunoassay in our laboratory.

Another possible mechanism includes inhibition of prostaglandin synthesis. Acetaminophen can reduce cyclooxygenase activity in brain tissue, experimentally, with pharmacologic effects similar to other nonsteroidal antiinflammatory agents.²² In other tissues, acetaminophen is considered to be a weak inhibitor or has no effect on cyclooxygenase.²³ Aspirin inhibition of cyclooxygenase as a mechanism for causing anaphylaxis and bronchospasm is well known.²⁴ (The structure of aspirin as compared with acetaminophen is presented in Fig 2.)

There are reports of acetaminophen-induced increased airway obstruction in aspirin-sensitive patients.^{23,25} In one study, after ingestion of 1000 mg of acetaminophen, 28.6% of patients with aspirin idiosyncrasy developed a decrease of FEV₁ by a mean of 15.9%.²⁵ In addition, some patients developed rhinorrhea, facial flushing, nausea, ab-

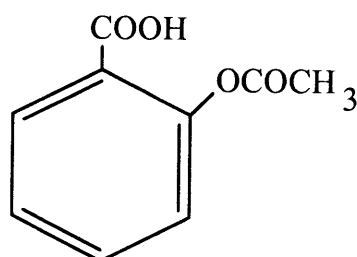
Table 3. Reported Adverse Effects of Acetaminophen in Therapeutic Doses

Skin	Anaphylactic Type Reaction*†	Hematologic	Respiratory	Cardio-vascular
Urticaria*		Neutropenia	Dyspnea*	Chest pain
Fixed drug eruption*		Thrombocytopenia	Bronchospasm*	Palpitations
Hypersensitivity syndrome resembling Kawasaki disease*		Pancytopenia	(500–1000 mg required in rare aspirin-sensitive patient)	
Vascular purpura*				
Angioedema				
Pruritus				
Flushing*				

* Reproducible with repeated exposure to acetaminophen.

† Occurred with subtherapeutic doses.

Aspirin



Acetaminophen

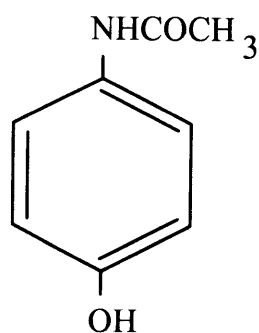


Figure 2. Chemical structures of aspirin and acetaminophen.

dominal pain, and diarrhea.²⁵ In another study, three asthmatic patients, with history of aspirin sensitivity and history of reactions to acetaminophen, reacted to 1000 mg of acetaminophen with a greater than 20% decrease in FEV₁.²³ How-

ever, clinical symptoms such as wheezing or urticaria did not occur.

In therapeutic doses, adverse reactions to acetaminophen are very rare but have been reported. In view of 10 billion doses of acetaminophen consumed annually and absence of reported cases of anaphylaxis from acetaminophen in the US, the rarity of the patient's reaction as a cause of repeated immediate generalized reactions is truly remarkable.

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