

Hypersensitivity to antihistamines

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ABSTRACT

Antihistamines are the cornerstone of allergy therapy and are not expected to cause hypersensitivity reactions. We describe two cases, one had urticaria to multiple anti-H₁-preparations and the other had anaphylaxis to hydroxyzine. We also provide a review of the English literature on reported reactions regarding causative preparations and manifestations. The latter showed a wide range; most commonly urticaria/angioedema, contact dermatitis, anaphylaxis, and fixed drug eruption (FDE). Most reported cases were young to middle age adults, with apparent predilection to female subjects. The onset of reactions varied from a few minutes for anaphylaxis and urticaria/angioedema, several hours for maculopapular rashes, or longer for contact dermatitis and FDE. Almost all antihistamines have been reported as causing reactions; cetirizine was the most common oral preparation followed by its parent drug, hydroxyzine. Doxepin cream was the most commonly implicated topical preparation in causing contact dermatitis. A causal relationship is often difficult to recognize because the reaction may be similar to the disease being treated with that antihistamine preparation. Reactions to one preparation are likely to occur, but not always, to other members of the same class. Diagnosis is based on clinical suspicion and may be verified by challenge testing. Except for patch testing in contact dermatitis or fixed eruption, other tests have not shown optimal reliability. In most cases, challenge testing with multiple preparations would identify one or more preparations that can be tolerated. Although hypersensitivity to antihistamines seems to be very rare, awareness of the problem would reduce its misdiagnosis.

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Antihistamines are among the most used medications worldwide. They are considered the basic therapy for allergic disorders (H₁-antihistamines) and gastric hyperacidity (H₂-antihistamines). They are also ingredients in numerous widely used medications. Because antihistamines are primarily antiallergy medications, they are generally not suspected of causing hypersensitivity. However, there are several scattered reports of reactions to various antihistamine preparations that belong to almost all classes (Table 1). In this article, we present a summary of the literature and describe the cases of two patients we encountered over many years at a large allergy service.

CASE 1

A 44-year-old woman presented with urticaria for 5 years, rhinitis for many years, and past history of nasal polyps and asthma. The patient reported that each antihistamine she tried had triggered a flare of hives. The antihistamines were hydroxyzine, cyproheptadine, cimetidine, and doxepin.

At the initial visit, she had clear skin and no dermographism. Percutaneous testing with common indoor

and outdoor aeroallergens and food extracts showed positive reactions to corn, wheat, and multiple pollens. She consented to oral challenge testing, which was negative first to placebo capsules (sucrose) and then to corn flour. Because she ate wheat bread daily, a challenge was not performed. Challenges were then performed with several antihistamines on separate visits with standard adult single doses of brompheniramine, diphenhydramine, hydroxyzine, cyproheptadine, and promethazine. Mild-to-moderate urticaria developed to each of them within 30–90 minutes, without angioedema, hypotension, wheezing, or gastrointestinal symptoms. Prednisone for a few days was usually needed to relieve her symptoms.

CASE 2

A 47-year-old woman was referred for evaluation of angioedema to shellfish, allergic rhinitis, and eczema. Lately, within minutes after taking a hydroxyzine tablet at 25 mg, she developed shortness of breath and generalized pruritus that necessitated treatment in the emergency department.

Her physical examination was unremarkable except for mild eczema on her arms and hands and nasal mucosal edema. Her total IgE was 271 IU/mL and complete blood count showed eosinophilia of 910/ μ L. Aeroallergen skin prick testing (SPT) was positive to house dust mites and feather mix. Limited food allergy SPT was positive to shrimp, crab, and lobster, but negative to codfish and salmon.

She consented to a blinded oral challenge to hydroxyzine. On the day of challenge, she had normal

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Table 1 Classification of antihistamine preparations implicated in causing hypersensitivity

Antihistamine Class	Generation	Preparations
Piperazine	1st	Hydroxyzine
	2nd	Cetirizine; mebhydrolin
	3rd	Levocetirizine
Piperidine	1st	Ebastine; mizolastine
	2nd	Bepotastine; desloratadine; fexofenadine; loratadine olopatadine; rupatadine
Ethanolamine	1st	Diphenhydramine; dimenhydrinate; prophenpyridamine
Alkylamine	1st	Chlorpheniramine; dexchlorpheniramine; pheniramine
Other	1st	Doxepin; mequitazine
	2nd	Azelastine

vital signs, mild nasal mucosal edema, minimal eczema on arms, and clear lungs by auscultation. Spirometry showed moderate obstruction with forced expiratory volume in 1 second of 71% and forced expiratory volume in 1 second/forced vital capacity of 64% predicted. A placebo (5 mL of water sweetened with sugar), matching with hydroxyzine in color and taste, caused no reaction. Challenge with hydroxyzine syrup started with 1 mL (2 mg) and after 20 minutes 4 mg, which was followed within 3 minutes with generalized pruritus and severe bronchospasm. She had very little air movement on chest auscultation. She was treated with 0.3 mg of epinephrine i.m. and required oxygen at 5 L by nasal cannula to bring her O₂ saturation to 95%. She was subsequently treated with nebulized albuterol. Within 30 minutes she markedly improved. She was instructed to avoid hydroxyzine and its derivatives, cetirizine, and levocetirizine. She was prescribed fexofenadine for treatment of her allergic rhinitis and doxepin for itching from eczema, both of which she had tolerated well in the past.

At another visit, SPT was done with diphenhydramine (12.5 mg/5 mL), hydroxyzine (10 mg/mL), cetirizine (1 mg/mL), levocetirizine (2.5 mg/mL), fexofenadine (30 mg/mL), doxepin (10 mg/mL), and loratadine (5 mg/mL). Within a few minutes after application, she complained of pruritus, shortness of breath, and developed severe repetitive cough. The histamine site was positive but none of the antihistamine sites showed a reaction. Her vital signs showed blood pressure of 141/60 mmHg, heart rate of 96/min, and O₂ saturation of 100% on room air. Her oropharynx appeared normal, lungs were clear, and skin was clear except for marks of severe scratching. Because of the severity of her cough, she was given 0.3 mg of epinephrine i.m. and fexofenadine syrup at 30 mg for itching. Her symptoms significantly improved within 20 minutes. She was monitored for one more hour without any subjective symptoms or abnormal signs.

REPORTED HYPERSENSITIVITY TO ANTIHISTAMINES

Reported allergic reactions to antihistamines seem to be very rare, considering their extensive use worldwide. Our review of the English literature revealed 104 cases of allergy to H₁- and H₂-antihistamine preparations reported between 1949 and May 2013; most were reasonably proven. In most cases the patient was able to tolerate at least one other antihistamine, usually of another class. By far, most reported manifestations were cutaneous of various types and, very rarely, anaphylaxis.

Urticaria

Urticaria with or without angioedema was among the most commonly reported, with higher occurrence in adults and female subjects (Tables 2 and 3), and onset 30 minutes to 6 hours after intake. The first report was in 1949 on a woman who had urticaria to both diphenhydramine and prophenpyridamine, with negative SPT to both.¹ Antihistamines of all classes were implicated, with piperazine being the most common followed by piperidine.¹⁻¹³ Cetirizine was the most frequent preparation followed by hydroxyzine. The diagnosis of antihistamine-induced urticaria is often missed when the drug was taken for chronic urticaria.

It is generally believed that an individual who is allergic to an antihistamine is unlikely to tolerate another preparation from the same class. Tella *et al.* described a 32-year-old woman who developed hives to hydroxyzine (a first-generation piperazine) and its second-generation derivative, cetirizine.⁶ She was able to tolerate several piperidine members (mizolastine, loratadine, ebastine, and fexofenadine) and an alkylamine (dexchlorpheniramine). Kranke *et al.* also reported a patient who was confirmed to develop hives to two piperazines (cetirizine and levocetirizine), but tolerated a piperidine, loratadine.⁸ Another patient had

Table 2 Reported manifestations of hypersensitivity to antihistamine preparations during 1949–2013

Manifestation	Antihistamine Preparation (reported frequency)	No. of Reactions	No. of Patients
Cutaneous			
Urticaria/angioedema	Cetirizine (9), hydroxyzine (5), fexofenadine (4), loratadine (3), ebastine (3), dexchlorpheniramine (2), bepotastine, diphenhydramine, levocetirizine, mizolastine, propfenpyridamine, and ranitidine	32	17
Fixed eruption	Cetirizine (6), dimenhydrinate (6), diphenhydramine (2), levocetirizine (2), hydroxyzine, and loratadine	18	16
Generalized nonspecific rash	Hydroxyzine (8), cetirizine (3), azelastine, desloratadine, dexchlorpheniramine, diphenhydramine, ebastine, fexofenadine, levocetirizine, loratadine, mebhydrolin, mequitazine, mizolastine, ranitidine, and rupatadine,	24	12
Contact dermatitis	Doxepin (27), ranitidine (22), chlorpheniramine, diphenhydramine, olopatadine, and pheniramine	53	52
Photosensitive eruption	Diphenhydramine (4), chlorpheniramine, and ranitidine	6	4
Toxic epidermal necrolysis	Ranitidine (2)	2	2
Acute generalized exanthematous pustulosis	Ranitidine	1	1
Anaphylaxis	Ranitidine (18), mizolastine (4), dimenhydrinate (2), diphenhydramine (2), cimetidine, dexchlorpheniramine, famotidine, and nizatidine	30	28

hives to the piperidines ebastine and fexofenadine, but tolerated cetirizine.¹²

However, some patients reacted to antihistamines from different classes.^{9–11} For example, a patient who had reactions to three piperidines (ebastine, fexofenadine, and loratadine) developed hives on challenge with the piperazine cetirizine.⁹ Hypersensitivity to a particular class is not predictive of reactivity to any of the other classes. Conversely, another woman had urticaria to piperazine and piperidine classes, but tolerated chlorpheniramine, mequitazine, and azelastine, which are from different classes.¹⁰ A woman was allergic to hydroxyzine (a piperazine) and dexchlorpheniramine (an alkylamine), but tolerated loratadine (a piperidine).¹¹ Accordingly, it seems that patients allergic to one antihistamine preparation will probably react to most preparations in that class. Nevertheless, in a randomized double-blind placebo-controlled trial comparing the efficacy of cetirizine and levocetirizine in healthy adult volunteers, urticaria occurred in four patients who were on levocetirizine but in no patients who were on cetirizine.¹⁴

Isolated urticaria to H₂-antihistamines seems to be very rare. Ranitidine-induced urticaria with angioedema was reported in a 62-year-old woman for duodenal ulcer whose reaction was reproduced on challenge with ranitidine at 40 mg, but she tolerated cimetidine.¹⁵

Fixed Drug Eruption

There are a few reports of fixed drug eruption (FDE) to antihistamines, totaling 16 cases. FDE occurs as a late-type

reaction after a few hours to a couple of days. Most early reports were on diphenhydramine or dimenhydrinate and were based on the medical history.^{15–17} Overall, dimenhydrinate (an ethanolamine) and cetirizine (a piperazine) have been implicated the most.^{16–28} A 27-year-old man had bullous fixed eruption on the arms, back, and penis on two occasions a few hours after taking cetirizine but not loratadine.²⁰ Allergy patch test (APT) on previously involved skin areas was positive to cetirizine but negative to ethylenediamine.

As in cases of urticaria, there is some evidence of cross-reactivity between preparations from different generations of the same antihistamine class. In most cases where the culprit was cetirizine, both hydroxyzine and levocetirizine showed positive oral challenge or APT.^{25,26,29} However, in a patient who developed FDE to diphenhydramine (an ethanolamine), APT with nine antihistamines from various classes was only positive to diphenhydramine and negative to all others, including doxylamine (an ethanolamine).²¹ Adding to these inconsistent findings, there were multiple published cases of negative APT to implicated antihistamines that were proven by positive oral provocation.^{23,30,31}

Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) has been reported in many patients, with doxepin cream being the most commonly implicated.^{32–41} A postmarketing review of the Food and Drug Administration's experience with doxepin 5% cream between its approval in 1994 until

Table 3 Reported cases of urticaria/angioedema and anaphylaxis to H₁-antihistamines in the English literature (1949–2013)

No.	Author and Year	Ref #	Sex/Age (yr)	Implicated Drug	Reaction by History	SPT	ID Test	Challenge Result
1	Epstein <i>et al.</i> 1949	1	F/36	Diphenhydramine	Urticaria	–	ND	ND
				Propenpyridamine	Urticaria	–	ND	ND
2	Stingeni <i>et al.</i> 1997	2	F/70	Cetirizine	Urticaria	–	+	ND
3	Barranco <i>et al.</i> 1998	59	F/42	Diphenhydramine	Anaphylaxis	–	+	Anaphylaxis
				Dimenhydrinate	Anaphylaxis			ND
4	Karamfilov <i>et al.</i> 1999	3	F/29	Cetirizine	Urticaria	–	ND	Urticaria
5	Demoly <i>et al.</i> 2000	4	F/57	Dexchlorpheniramine	Urticaria	–	ND	ND
				Hydroxyzine	Urticaria	–	ND	ND
6	Calista <i>et al.</i> 2001	5	F/42	Cetirizine	Urticaria	–	–	Urticaria
7	Tella <i>et al.</i> 2002	6	F/32	Cetirizine	Urticaria	–	ND	Urticaria
				Hydroxyzine	Unknown	ND	ND	Urticaria
8	Schroter <i>et al.</i> 2002	7	F/36	Cetirizine	Urticaria/AE	+	ND	Urticaria/AE
9	Weidinger <i>et al.</i> 2004	61	F/47	Mizolastine	Anaphylaxis	–	ND	Anaphylaxis
11	Kranke <i>et al.</i> 2005	20	F/33	Cetirizine	Urticaria	–	ND	Urticaria
				Levocetirizine	Urticaria	–	ND	Urticaria
12	Gonzalez de Olano <i>et al.</i> 2006	9	F/30	Ebastine	Urticaria	–	ND	ND
				Loratadine	Urticaria	–	ND	ND
				Cetirizine	Unknown	–	ND	Urticaria
				Fexofenadine	Unknown	–	ND	Urticaria
13	Gonzalo-Garjio <i>et al.</i> 2006	58	M/26	Mizolastine	Anaphylaxis	–	ND	Anaphylaxis
14	Vythoulka <i>et al.</i> 2006	57	F/55	Mizolastine	Anaphylaxis	+	ND	ND
			F/30	Mizolastine	Anaphylaxis	+	ND	ND
15	Thurot-Guillou <i>et al.</i> 2007	62	F/63	Dexchlorpheniramine	Anaphylaxis	–	+	ND
16	Inomata <i>et al.</i> 2009	10	F/34	Fexofenadine	Urticaria	ND	ND	Urticaria
				Cetirizine	Urticaria	ND	ND	ND
				Hydroxyzine	Urticaria/emesis	ND	ND	ND
				Loratadine	Unknown	ND	ND	Urticaria
				Bepotastine	Unknown	ND	ND	Urticaria
17	Rodriguez del Rio <i>et al.</i> 2009	11	M/36	Hydroxyzine	Urticaria	ND	ND	MP rash
			F/20	Loratadine	Urticaria	–	ND	Urticaria
				Cetirizine	Urticaria	–	ND	Urticaria
			F/30	Dexchlorpheniramine	Urticaria	–	ND	Urticaria
				Hydroxyzine	Urticaria	–	ND	Urticaria
			M/57	Mequitazine	AE/MP rash	–	ND	AE/MP rash
				Ebastine	AE/MP rash	–	ND	AE/MP rash
18	Sanchez Morillas <i>et al.</i> 2011	12	F/45	Ebastine	Urticaria	–	ND	Urticaria
				Fexofenadine	Urticaria	–	ND	Urticaria
19	Lee <i>et al.</i> 2011	13	M/69	Fexofenadine	Urticaria	+	ND	Urticaria
20	Mur-Gemino <i>et al.</i> 2011	60	F/48	Dimenhydrinate	Anaphylaxis	–	ND	ND
				Diphenhydramine	Anaphylaxis	ND	–	Anaphylaxis

ND = not done; N/A = information not available; SPT = skin prick test; ID = intradermal; APT = allergy patch test; CU = chronic urticaria; AE = angioedema; MP = maculopapular; ARC = allergic rhinoconjunctivitis.

2003 revealed 26 cases of contact dermatitis.³² APT was positive in all 21 tested cases. In 65% of cases, contact dermatitis occurred after using the cream for durations that exceeded the recommended 8 days. Out of a series

of 97 patients with various dermatoses, doxepin APT was positive in 17, 13 of whom showed ACD on topical doxepin application and 2 had systemic contact dermatitis after oral doxepin intake.³³ Occupational ACD

to ranitidine was documented in several cases associated with pharmaceutical manufacturing.^{35–38}

Ophthalmic antihistamine preparations caused ACD in some patients. In a case of facial ACD to chlorpheniramine-containing eye drops, APT with chlorpheniramine maleate 5% was positive.³⁹ Another report of ACD was of bilateral conjunctivitis and eyelid dermatitis in a woman after using pheniramine (an alkylamine) eye drops.⁴⁰ APT was positive and showed cross-reactivity with two other alkylamines and diphenhydramine. Olopatadine was implicated by history in causing periorbital ACD in a patient.⁴¹

Photosensitive Dermatitis

Photosensitive contact dermatitis has been reported in several cases, either as photo toxic (dependent on a specific wavelength, no incubation period necessary) or photoallergic (not dependent on a specific wavelength, delay of 4–5 days).^{42–46} Both phototoxic and photoallergic reactions occurred in fraternal twin sisters to topical application of diphenhydramine and to oral intake in one.⁴² Contact photoallergy to diphenhydramine in a woman was indicated by positive patch testing with UVB light, but not with UVA light or diphenhydramine alone.⁴⁴ On the other hand, UVA light was needed to reproduce photoallergic contact dermatitis to diphenhydramine in a woman.⁴⁶ Two cases of photosensitive rashes were attributed to ranitidine but not to other H₂-antihistamines.^{46,47} One was reproduced by UVA photopatch testing, whereas the other was by UVB light and oral challenge. Topical promethazine was frequently responsible for multiple cases of photosensitive contact dermatitis and cross-reactivity with other phenothiazines.⁴⁸

Generalized Nonspecific Rashes

Nonspecific rashes are the most common cutaneous manifestations of adverse drug reactions in general. Among antihistamines, piperazines, particularly hydroxyzine, being the most frequent.^{11,49–52} The mechanism of these rashes has not been elucidated and neither SPT nor APT has shown optimal reliability. The rash may or may not recur on reexposure to the implicated preparation. In one patient, the rash was reproduced with seven different antihistamines.¹¹

Some believe that such rashes may represent systemic contact dermatitis after sensitization to cross-reacting contactants.^{43,50,52,53} There are several reports of generalized rashes that have occurred to oral cetirizine and hydroxyzine linked to positive APT to ethylenediamine or diethylenediamine, which are frequent excipients in many topical medications.^{51–53} A patient with a generalized rash to cetirizine had positive APT to cetirizine, ethylenediamine, and diethylenediamine.² However, three patients who had hy-

droxyzine sensitivity by oral challenge and positive APT showed negative APT to ethylenediamine and cetirizine.⁴⁹

Other Cutaneous Reactions

Toxic epidermal necrolysis, confirmed by biopsies, seemed to be attributed to ranitidine in two cases.^{54,55} However, a causal relationship would be difficult to prove because of the high risk of intentional challenge. A biopsy-confirmed acute generalized exanthematous pustulosis in a patient was attributed to ranitidine; APT 2 months after rash resolution caused local pustular eruption.⁵⁶

Anaphylaxis

Our literature search (1949–2013) revealed a total of nine anaphylactic reactions to H₁-antihistamines in seven patients reported between 1998 and 2011 (Table 3).^{57–62} Their ages were 26–63 years; six of the seven were women. The implicated H₁-antihistamines were mizolastine (4), dexchlorpheniramine (2), dimenhydrinate (2), and diphenhydramine (1). Oral challenge was positive in all four tested patients. As in the case of urticarial reactions, SPT was of suboptimal reliability. A woman had severe anaphylaxis minutes after taking a liquid cold medication containing diphenhydramine and a second episode after taking a tablet of dimenhydrinate, another ethanolamine.⁵⁹ She had negative SPT and APT, but positive intradermal (ID) test with diphenhydramine at 1 mg/mL. Subsequent single-blind challenge with diphenhydramine at 25 mg caused anaphylaxis within a few minutes. Challenges with terfenadine, cetirizine, loratadine, and dexchlorpheniramine were tolerated, indicating selective hypersensitivity to ethanolamines. Mur Gemino *et al.*⁶⁰ reported anaphylaxis in a woman 10 minutes after taking dimenhydrinate at 50 mg. She had negative SPT at 10 mg/mL, ID test at 5 mg/mL, and basophil activation test. Single-blind challenge with 12.5 mg caused severe anaphylaxis. SPT with several other antihistamines were negative and she tolerated loratadine.

Anaphylaxis has occurred to H₂-antihistamines as well. There were 21 cases reported between 1990 and 2013 (Table 4).^{62–80} Their ages were 18–80 years; 60% were female patients. Ranitidine was implicated in 18 subjects and nizatidine, famotidine, and cimetidine were involved in one each. The route was oral in 57% (12/21). In the other nine cases, where the route was i.v., anaphylaxis was severe, including one fatality.⁷¹ Oral challenge with the implicated drug was positive in all six tested subjects, five to ranitidine and one to nizatidine. In one patient, anaphylaxis was biphasic, with 6 hours in between.⁷⁶ Cross-reactivity was assessed by oral challenge with other H₂-antihistamines

Table 4 H₂-antihistamines reported causing anaphylaxis during 1990–2012 (18 ranitidine and 1 each to nizatidine, famotidine, and cimetidine)

No.	Author/Year	Ref #	Drug	Age (yr)/Sex	Route	SPT	ID Test	Challenge
1	Greer <i>et al.</i> 1990	63	Ranitidine	?/F	Oral	ND	ND	ND
2	Barry <i>et al.</i> 1992	64	Ranitidine	31/F	Oral	ND	ND	ND
3	Lazaro <i>et al.</i> 1993	65	Ranitidine	?/F	Oral	+	ND	+
4	Powell <i>et al.</i> 1993	66	Ranitidine	?/F	i.v.	?	+	ND
5	Kaneko <i>et al.</i> 2003	67	Ranitidine	30/F	i.v.	ND	ND	ND
6	Koh <i>et al.</i> 2006	68	Ranitidine	35/M	Oral	+	+	+
7	Demirkan <i>et al.</i> 2006	69	Ranitidine	49/M	Oral	–	+	ND
8	Demirkan <i>et al.</i> 2006	69	Ranitidine	49/F	i.v.	ND	ND	+
9	Thurot-Guillou <i>et al.</i> 2007	62	Ranitidine	63/F	i.v.	ND	+	ND
10	Rethnam <i>et al.</i> 2007	70	Ranitidine	56/F	i.v.	ND	ND	ND
11	Oliva <i>et al.</i> 2008	71	Ranitidine	51/M	i.v.	ND	ND	ND
12	Foti <i>et al.</i> 2009	72	Ranitidine	47/F	i.v.	–	+	ND
13	Castro <i>et al.</i> 2009	73	Ranitidine	36/F	Oral	+	ND	ND
14	Walker <i>et al.</i> 2010	74	Ranitidine	31/F	Oral	+	ND	+
15	Han <i>et al.</i> 2011	75	Ranitidine	25/M	Oral	+	ND	ND
16	Song <i>et al.</i> 2011	76	Ranitidine	42/F	Oral	ND	ND	+
17	Aouam <i>et al.</i> 2012	77	Ranitidine	36/M	i.v.	+	ND	ND
18	Antonicelli <i>et al.</i> 2012	78	Ranitidine	18/M	i.v.	+	ND	ND
19	Mira-Perceval <i>et al.</i> 1996	80	Nizatidine	59/F	Oral	–	+	+
20	Kim <i>et al.</i> 2010	79	Famotidine	23/M	Oral	–	+	ND
21	Song <i>et al.</i> 2011	76	Cimetidine	80/M	Oral	–	+	ND

SPT = skin prick test; ID = intradermal; ND = not done.

Table 5 Food ingredients incorporated in common commercial formulations of antihistamine preparations

Food Component*	Implicated Medication Formulations
Gelatin	Axid capsule, Benadryl Liqui-Gels, Benadryl Allergy Nighttime Liqui-Gels, Claritin Liqui-Gels, Claritin RediTabs, Hydroxyzine pamoate capsule (Sandoz, Teva), Sinequan capsule, and Vistaril capsule
Lactose	Atarax tablet, Claritin® tablet, Claritin-D tablet, Claritin RediTabs, Phenergan tablet, Zyrtec tablet, Zyrtec-D tablet, and Xyzal tablet
Starch (corn, potato, rice, or wheat)	Allegra tablet, Atarax tablet, Axid capsule, Allegra-D tablet, Benadryl® caplets, Clarinex tablet, Clarinex RediTabs, Claritin tablet, Claritin-D® tablet, Chlor-Trimeton tablet, Sinequan capsule, Sudafed PE Sinus and Allergy tablet, and Vistaril tablet
Cinnamon	Benadryl Liquid Elixir
Cocoa butter	Phenergan rectal suppository

*Source: Manufacturers' website, accessed May 2013.

(famotidine, cimetidine, and/or nizatidine) in four of these patients and three tolerated at least one other preparation, whereas one reacted to both ranitidine and famotidine.

PHARMACOLOGICALLY INACTIVE INGREDIENTS

Hypersensitivity drug reactions may not be to the pharmacologically active molecules, but rather to inactive ingredients, including food proteins (Table 5). Identifica-

tion of a culprit inactive ingredient is usually a very tedious process, primarily because of the difficulty in identifying or obtaining all ingredients. Challenge testing with different formulations (liquid, tablet, capsule, gel, or injectable) might be helpful. For example, Benadryl Liqui-Gels (Johnson & Johnson, New Brunswick, NJ) contain gelatin whereas the syrup contains cinnamon. Inactive ingredients of antihistamines have been used for testing (SPT, ID test, APT, or challenge) in various reports, but the yield was negligible.^{18,57,61,81}

DIAGNOSTIC APPROACH

The lack of understanding the mechanism of hypersensitivity to antihistamines makes the development of a diagnostic test difficult. Histamine has four receptors with different functions and organ distributions.⁸² Normally, histamine receptors are in equilibrium between active and inactive state, and histamine binding leads to the active conformation. Antihistamines exert their principal effect by acting as inverse agonists of histamine receptors and shifting their balance toward the inactive state. From our literature search, it seems that skin testing and *in vitro* testing are of limited value. The diagnosis should be primarily suspected by the medical history, and confirmation, if needed, should be by appropriately designed oral challenge.

Medical History

Being antiallergic medications, antihistamines are very rarely suspected of causing hypersensitivity reactions. For example, patients with chronic urticaria may present with refractory symptoms despite taking multiple antihistamines may report exacerbations minutes or hours after antihistamine intake. FDE onset may occur a few to several days after the offending drug initiation and recur in the same location on reexposure.

Role of Percutaneous Testing

Skin testing has not shown an optimal diagnostic reliability in identifying the causative antihistamine preparation. In our patient with hydroxyzine-induced anaphylaxis (case 2), SPT was negative to hydroxyzine and cetirizine, as well as to five others. Our literature search revealed that SPT was negative in 19 of 21 (90%) of challenge-proven acute urticaria cases. In a patient with urticaria, SPT with multiple antihistamines was negative to four challenge-proven preparations.⁹ Even in cases of H₁-antihistamine-induced anaphylaxis, five of seven (71%) had negative SPT (Table 3). In five cases with negative SPT, ID testing was positive in one of two patients with urticaria and in two of three anaphylaxis cases.

In the 21 subjects reported in the literature with anaphylaxis to H₂-antihistamines (Table 4), SPT was negative in 45%, including one of three challenge-proven patients. However, ID testing was positive in all eight cases suspected by history.

The low reliability of skin tests may be attributed to at least two factors. First, antihistamines, like most synthetic drugs, are of low molecular weight and act as haptens to induce a hypersensitivity reaction, and, hence, testing with the native drug may not be reliable. Second, testing reagents lack standardization.

Role of APT

APT seems to be helpful in cases of contact dermatitis and FDEs. Photo patch testing is needed to confirm

phototoxic or photoallergic reactions. APT may include suspected sensitizing excipients or additives, such as ethylenediamine and diethylenediamine. A limitation of APT with antihistamines is the lack of standardization.

Role of *In Vitro* Testing

A few *in vitro* tests have been tried in diagnosing hypersensitivity to antihistamines with conflicting results. Specific IgE was elevated in two patients who had anaphylaxis to ranitidine and had positive SPT.^{68,78} On the other hand, specific IgE antibodies could not be shown in multiple cases with anaphylaxis to antihistamines, even in those who had positive SPT.^{59–61,65} We are not aware of any currently available reliable specific IgE test for antihistamines hypersensitivity. Basophil activation test was attempted in a few cases, with a positive result in a patient with fexofenadine-induced urticaria¹³ but negative in another similar patient¹² and a patient with anaphylaxis to diphenhydramine.⁶⁰ *In vitro* histamine release was found to be negative in a patient with ranitidine-induced anaphylaxis with a positive SPT⁶⁵ as well as in a patient with urticaria to multiple antihistamines.⁹ Plasma histamine and leukotriene B₄ levels were elevated in a patient with urticaria to multiple antihistamines, reflecting mast cell or basophil degranulation.¹⁰

Challenge Testing

In general, the most definitive diagnostic procedure for drug or food allergy is well-designed oral challenge testing under supervision and with the availability of treatment of potential life-threatening reactions.⁸³ The starting dose varies depending on the severity of the previous reaction and the provoking dose. It can be 10% (or less) of the average dose, to be increased by 50–100% increments at 20- to 30-minute intervals until the total dose is administered. The patient then remains under observation for at least an hour to allow sufficient absorption. It is imperative to perform the procedure in a blind fashion, and a placebo test may be performed first. Multiple antihistamine preparations may be tested to ensure the safety of alternatives. It would be prudent to avoid challenge with the causative preparation, or other members of the same class, in patients who had a life-threatening reaction to a specific preparation.

CONCLUSION

Hypersensitivity to antihistamines seems to be very rare but may be underrecognized. We described two female patients, one had urticaria to multiple anti-H₁-preparations and the other had anaphylaxis to hydroxyzine. Reported reactions showed a wide range—most commonly, urticaria/angioedema, contact dermatitis, ana-

phylaxis, and FDE. A causal relationship is often difficult to identify because the reaction may be similar to the disease being treated. Most reported cases were young to middle-aged adults, with predilection to female patients. The onset of reactions was minutes for anaphylaxis and urticaria/angioedema, several hours for maculopapular rashes, and longer for contact dermatitis and FDE.

Almost all antihistamine preparations have been reported as causing reactions; cetirizine and hydroxyzine were the most common oral preparations. Reactions to one preparation are likely to occur to other members of the same class. Doxepin cream is the most commonly implicated in causing ACD. Diagnosis is based on clinical suspicion and can be verified by challenge testing. Except for APT in contact dermatitis or FDE, other tests have not shown optimal reliability. In most cases, challenge testing with multiple preparations would identify at least a safe one, usually of a different class. The underlying mechanism is not clear, particularly for type 1 (immediate) hypersensitivity reactions.

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