

Contact Allergens in Oral Antihistamines

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Background: Excipients in various formulations of active drugs occasionally include known contact allergens. Their ingestion may trigger dermatitis or cause it to become widespread or refractory to therapy.

Objective: The aim of this study was to investigate the prevalence of common contact allergens among the excipients of oral antihistamines available in this country.

Methods: We gathered the complete ingredient lists of 2119 different preparations of 12 oral antihistamines from the National Library of Medicine data bank and entered them into an electronic database for analysis.

Results: More than half the formulations (55.0%) contained at least 1 member of the 10 allergen families assessed. Most brompheniramine and doxepin preparations included potentially allergenic excipients, whereas fexofenadine was most often free of them. Sorbitan group members, azo dyes, and propylene glycol were the allergens found most frequently in the antihistamines, each present in over 25% of the products. Elixirs, liquids, solutions, suspensions, and syrups were more likely than nonchewable caplets, capsules, and tablets to contain the allergens tabulated (100% vs 39.3%, respectively). Chewable pills frequently contained azo dyes.

Conclusions: Ingestion of antihistamines could precipitate a systemic contact dermatitis in a patient sensitized to an allergen present as an excipient in the medicine.

Oral antihistamines are widely used to manage a variety of clinical problems, from the common cold, to respiratory allergy, to pruritus from many causes, including atopic and allergic contact dermatitis. Many formulations of these agents, however, contain potential contact allergens among their listed inactive ingredients. Systemic administration of a contact allergen to a previously sensitized individual may produce any of a host of reactions, ranging from reactivation of the patch test site, to exacerbation of previous contact dermatitis, to the so-called baboon syndrome.¹ Food sources of several contact allergens were recently reviewed by Scheman et al.² Medication ingredients that could risk provoking a systemic contact dermatitis (SCD) have not been as well documented.

We were concerned to discover allergens present in several oral antihistamines during the course of caring for a patient in our clinic. A 9-year-old boy with atopy was found to have superimposed allergic contact dermatitis with a relevant positive patch test result to propylene glycol. His rash improved significantly after eliminating contact with the allergen by changing his topical corticosteroid. Later, his mother, curious about why his dermatitis flared annually when he developed seasonal rhinitis, discovered that the oral

antihistamine he used at that time contained propylene glycol. It was difficult to find an allergen-free alternative for him, but when the switch was made, the flare resolved.

We investigated the prevalence of several common contact allergens among the excipients in prescription and over-the-counter oral antihistamines available in the United States. The recognition of allergen presence and knowledge of products free of allergens would be useful to guide therapeutic recommendations to avoid precipitating SCD.

METHODS

We compiled complete ingredient lists for each formulation of the most commonly used oral antihistamines available in the United States. Data were obtained from the US National Library of Medicine data bank accessed through the Web site <http://dailymed.nlm.nih.gov/dailymed/about.cfm>, which provides complete package insert and labeling information for medications (through July 11, 2013). All data were entered into an electronic database (Microsoft Office Access 2007; Microsoft Corporation, Redmond, Wash), which allowed sorting by both active and inactive ingredients. The 12 oral antihistamines evaluated included traditional H1 receptor antagonists brompheniramine, cetirizine, chlorpheniramine, desloratadine, diphenhydramine, fexofenadine, hydroxyzine, levocetirizine, and loratadine; H2 receptor antagonists cimetidine and ranitidine; and doxepin, a tricyclic antidepressant with both H1 receptor and H2 receptor antagonistic effects. We excluded famotidine and nizatidine, 2 other H2 receptor antagonists, because they are only infrequently recommended for pruritus.

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Data were also collected on the leukotriene receptor antagonists, montelukast and zafirlukast, and zileuton, an inhibitor of leukotriene formation, which have recently been used primarily for respiratory symptoms in patients with atopy.

Products were evaluated to see if they contained any of the following contact allergens, most of which are present in the American Contact Dermatitis Society's list of core allergens³: aspartame (as a surrogate for formalin, which is produced as a metabolite), azo dyes, benzoic acid and benzoates (sodium, potassium, and calcium benzoate), carmine, gallates (octyl, lauryl or dodecyl, and propyl gallate), parabens (butylparaben, methylparaben, and propylparaben), propionates (propionic acid, sodium propionate, potassium propionate, calcium propionate), propolis, propylene glycol, and sorbitol, along with sorbates (sodium, potassium, calcium, and polysorbate), sorbitans (monostearate, tristearate, monolaurate, monooleate, and monopalmitate), polyoxylene sorbitans (monolaurate, monopalmitate, monostearate, tristearate, and monooleate), and Anidrisorb 85/70 (sorbitol-mannitol-hydrolyzed starch).

Although all listed excipients were logged, the labeling contained insufficient characterization of flavorings to correlate with patch test fragrance chemicals.⁴ Both soy and cornstarch were present in some items. They were not included in this analysis because they are primarily implicated in the aggravation of atopic dermatitis or excessive occupational protein exposure, and they show negative patch test results with positive prick and scratch test findings.⁵

RESULTS

In our database, we found a total of 2119 different preparations of the 12 oral antihistamines. Of this total, 1165 (55.0%) were found to contain at least 1 of the contact allergens designated for detection (Table 1). Brompheniramine was the oral antihistamine that most frequently contained a potential allergen among its ingredients (98/105, 93.3%), followed by doxepin (45/51, 88.2%). Fexofenadine preparations were least likely to contain such excipients (18/90, 20.0%).

The related allergens in the sorbitan group were the most prevalent in the 2119 oral preparations of antihistamines (in 563, 26.6%), nearly tied by azo dyes (in 562, 26.5%) (Table 2). The single, most frequently occurring contact allergen in the oral antihistamines was propylene glycol (in 554, 26.1%). Each of the selected contact allergens (or a member of the family, eg, potassium sorbate) was present in at least 1 antihistamine, except propolis, which was found in none (Table 2).

Table 3 shows the allergens most commonly present in the 502 antihistamine elixirs, liquids, solutions, suspensions, and syrups investigated. These were propylene glycol (74.9%), benzoic acid and benzoates (54.6%), sorbitan group (53.4%), azo dyes (50.8%), and parabens (40.6%). The 1563 nonchewable caplets, capsules, and tablets studied were most likely to harbor sorbitan group allergens (18.5%), azo dyes (17.7%), and propylene glycol (11.1%). Chewable caplets, capsules, and tablets were found to contain azo dyes (27.3%), carmine (18.2%), propylene glycol (18.2%), sorbitol (18.2%), and aspartame (9.1%).

TABLE 1. Allergens in Oral Antihistamine Products in Order of Prevalence

Active Ingredient	No. Products Studied	Products With 1 or More Allergens, n (%)
Brompheniramine*	105	98 (93.3)
Doxepin†	51	45 (88.2)
Cimetidine	37	27 (73.0)
Diphenhydramine‡	626	417 (66.6)
Hydroxyzine§	117	68 (58.1)
Loratadine	223	117 (52.5)
Chlorpheniramine	400	201 (50.3)
Cetirizine	230	106 (46.1)
Desloratadine	21	9 (42.9)
Levocetirizine	21	7 (33.3)
Ranitidine	198	52 (26.3)
Fexofenadine	90	18 (20.0)
Total¶	2119	1165 (55.0)

*Includes brompheniramine maleate and dexbrompheniramine maleate.

†Officially classified as a tricyclic antidepressant but included due to its potent antihistaminic activity.

‡Includes diphenhydramine citrate and diphenhydramine hydrochloride.

§Includes hydroxyzine hydrochloride and hydroxyzine pamoate.

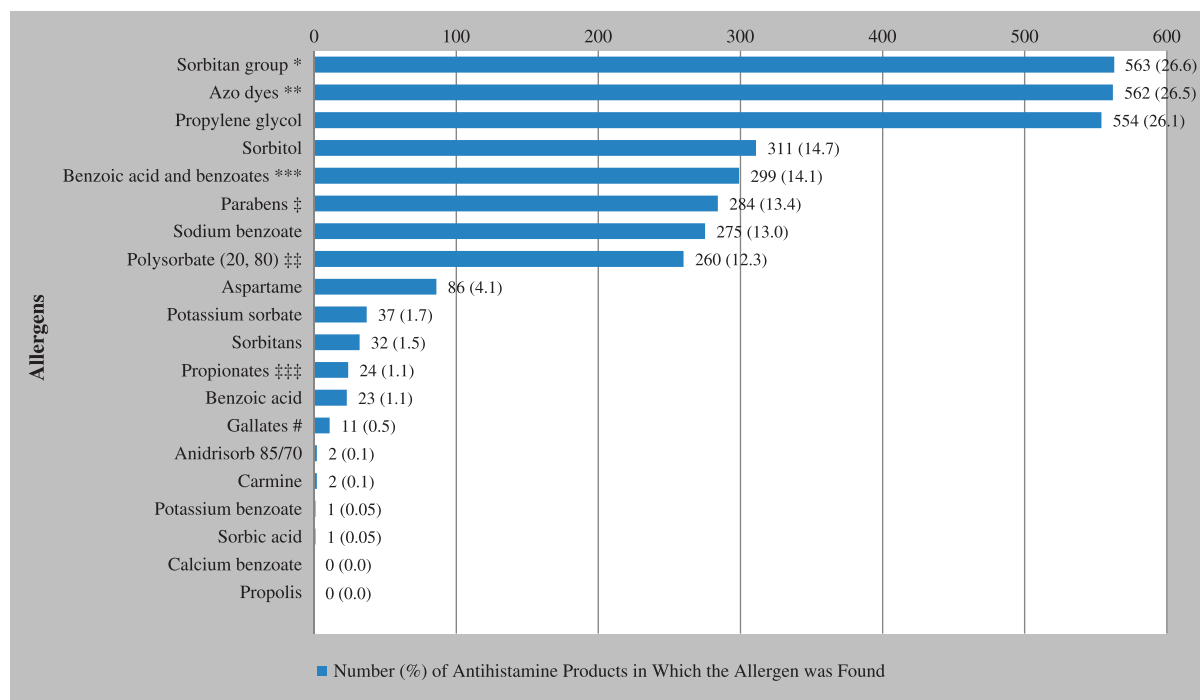
||Includes chlorpheniramine maleate, chlorpheniramine tannate, and dexchlorpheniramine maleate.

¶A manufacturer's product may be counted multiple times if the inactive ingredients varied with the dose of the active drug.

The type of formulation affected the frequency at which an allergen was found. Elixirs, liquids, solutions, suspensions, and syrups contained at least 1 allergen in 100% of the 502 products studied, whereas only 39.3% of the 1563 nonchewable caplets, capsules, and tablets contained at least 1 allergen. The liquid formulations were more likely than the nonchewable pills to contain propylene glycol (74.9% vs 11.1%, respectively) (Table 3). Benzoic acid and benzoates were more often present in liquid formulations (54.6%) than in nonchewables (1.5%) or chewables (0.0%). Sorbitan group allergens were also found more often in liquids (53.4%) than in pills (18.5%) or chewables (18.2%). Azo dyes appeared in 50.8% of the liquids, 17.7% of nonchewables, and 27.3% of chewables. Parabens followed a similar pattern, with liquid preparations (40.6%) dominating nonchewables (4.9%), but were absent from chewable formulations.

Certain antihistamines were more likely than others to contain a particular allergen (Table 4). Propylene glycol was found in 88.6% of all brompheniramine, 58.8% of doxepin, 38.7% of cetirizine, 38.1% of loratadine, and 35.9% of hydroxyzine products. Sorbitan group allergens were among the excipients in 79.0% of formulations of brompheniramine and 73.0% of cimetidine products. Azo dyes were present in over half the brompheniramine and doxepin formulations, and in 38.2% of diphenhydramine, 35.9% of hydroxyzine, and 33.0% of chlorpheniramine preparations. The paraben preservatives were found principally in formulations of cetirizine (37.0%). Benzoic acid or benzoates were found in over half the brompheniramine products.

Because the leukotriene inhibitors, montelukast sodium and zafirlukast, and the inhibitor of leukotriene production, zileuton,

TABLE 2. Allergen Presence in Oral Antihistamine Products (N = 2,119)

*Includes Anidrisorb 85/70, polysorbates, sorbates, sorbic acid, sorbitan, sorbitol.

**Includes FD&C Yellow #5, FD&C Yellow #6, FD&C Red #33, FD&C Red #40.

***Includes benzoic acid, calcium benzoate, potassium benzoate, sodium benzoate.

‡Includes butylparaben, methylparaben, propylparaben, methyl parahydroxybenzoate, propyl parahydroxybenzoate.

‡‡Includes polysorbate, polysorbate 20, polysorbate 80.

‡‡‡Only sodium propionate was found; no products contained calcium propionate or potassium propionate.

#Only propyl gallate was found; no products contained octyl or lauryl (dodecyl) gallate.

are being increasingly used in some of the same patients likely to receive antihistamines, we also surveyed their excipients. We found aspartame in 26/77 (33.8%) of the montelukast products studied (Table 4), most prevalent in the 5-mg chewable tablet. Zafirlukast is supplied in only 1 formulation, a film-coated tablet, and none of the 6 distributors incorporate any of the allergens assessed. Zileuton is sold by 1 company as a tablet or a film-coated extended release tablet, both of which contain propylene glycol.

Although we purposed to examine ingredients of commonly used oral preparations only, our data captured excipients of injectables as well. Of the 26 injectable formulations of antihistamines (2 cimetidine, 14 diphenhydramine, 3 hydroxyzine, and 7 ranitidine), all were free of the potentially allergenic excipients studied.

DISCUSSION

No large epidemiologic studies have been published to reveal how commonly systemic exposure to a contact allergen in a sensitized individual triggers a manifestation of SCD. Nickel ingestion is well described to provoke SCD. From a meta-analysis of prior studies, Jensen and colleagues⁶ estimated that 1% of nickel-sensitive

individuals may manifest SCD after ingestion of nickel at the low levels present in daily exposure (0.22-0.35 mg). An oral spice challenge given to 71 patients with positive patch test results to *Myroxylon pereirae* resulted in 10% with symptoms.⁷

There are thousands of oral antihistamines available in both over-the-counter and prescription preparations. They are widely used for symptoms of the common cold and allergic rhinoconjunctivitis. They are also recommended for itch secondary to urticaria, atopic dermatitis, allergic contact dermatitis, and a host of other pruritic maladies. Our investigation into these products revealed that more than half include a potential systemic contact allergen for sensitized individuals among their excipients.

Substances added to active ingredients for form, consistency, palatability, appearance, or flavor are listed as “inactive ingredients” on the label or package insert. These substances, more properly called “excipients,” are classified as inert, but the literature holds many case reports of adverse reactions to them.⁸ Excipients have been reported to trigger a variety of skin reactions, including the development of SCD when 1 of these ingredients is a known topical sensitizer.

In our study of oral antihistamines, the sorbitan group, azo dyes, and propylene glycol were the potential allergens found most

TABLE 3. Allergen Presence in Oral Antihistamine Products by Formulation Type*

Allergen	Elixirs, Liquids, Solutions, Suspensions, Syrups	Nonchewable Caplets, Capsules, Tablets	Chewable Caplets, Capsules, Tablets
	n (% of Formulation Type)	n (% of Formulation Type)	n (% of Formulation Type)
Aspartame	8 (1.6)	41 (2.6)	1 (9.1)
Azo dyes†	255 (50.8)	276 (17.7)	3 (27.3)
Benzoic acid and benzoates	274 (54.6)	24 (1.5)	0 (0.0)
Benzoic acid	20 (4.0)	3 (0.2)	0 (0.0)
Calcium benzoate	0 (0.0)	0 (0.0)	0 (0.0)
Potassium benzoate	1 (0.2)	0 (0.0)	0 (0.0)
Sodium benzoate	253 (50.4)	21 (1.3)	0 (0.0)
Carmines	0 (0.0)	0 (0.0)	2 (18.2)
Parabens‡	204 (40.6)	76 (4.9)	0 (0.0)
Propolis	0 (0.0)	0 (0.0)	0 (0.0)
Propyl gallate	10 (2.0)	1 (0.06)	0 (0.0)
Propylene glycol	376 (74.9)	173 (11.1)	2 (18.2)
Sodium propionate	0 (0.0)	24 (1.5)	0 (0.0)
Sorbitan group	268 (53.4)	289 (18.5)	2 (18.2)
Anidrisorb 85/70	0 (0.0)	2 (0.1)	0 (0.0)
Polysorbate§	31 (6.2)	229 (14.7)	0 (0.0)
Potassium sorbate	36 (7.2)	1 (0.06)	0 (0.0)
Sorbic acid	1 (0.2)	0 (0.0)	0 (0.0)
Sorbitans	0 (0.0)	32 (2.0)	0 (0.0)
Sorbitol	245 (48.8)	60 (3.8)	2 (18.2)
Total no. products in formulation type	502	1563	11

*Antihistamine products in the form of granules (effervescent, for solution), powder (for solution), and kits for mouthwash preparation were not included in this table (n = 43). A total of 83.7% of the products with this formulation type were found to contain aspartame, and 65.1% were found to contain azo dyes.

†Includes FD&C Yellow #5, FD&C Yellow #6, FD&C Red #33, FD&C Red #40.

‡Includes butylparaben, methylparaben, propylparaben, methyl parahydroxybenzoate, propyl parahydroxybenzoate.

§Includes polysorbate, polysorbate 20, polysorbate 80.

often. Sources of the many members of the sorbitan family are ubiquitous and include many foods.² We found these compounds in over a quarter of the antihistamine preparations studied. Several years ago, Hannuksela and Haahtela⁹ concluded that ingested sorbic acid had not been reported to cause or aggravate eczematous

dermatitis. More recently, however, both an adult¹⁰ and an infant¹¹ have been described whose dermatitis from sensitization to sorbic acid in a topical product failed to clear until after dietary avoidance of the allergen. It is possible that SCD due to the presence of sorbic acid or related preservatives in medications has gone unrecognized.

TABLE 4. Variation in Allergen Content by Medication Studied

Allergen	Brompheniramine	Chlorpheniramine	Diphenhydramine	Hydroxyzine	Cetirizine	Levocetirizine
	n = 105	n = 400	n = 626	n = 117	n = 230	n = 21
	%	%	%	%	%	%
Aspartame	5.7	2.5	5.1	0.0	0.0	0.0
Azo dyes	61.0	33.0	38.2	35.9	4.3	0.0
Benzoic acid and benzoates	57.1	19.8	14.4	6.0	1.3	0.0
Carmines	1.0	0.0	0.0	0.0	0.4	0.0
Gallates	0.0	0.5	1.4	0.0	0.0	0.0
Parabens	27.6	17.3	10.7	7.7	37.0	23.8
Propolis	0.0	0.0	0.0	0.0	0.0	0.0
Propionates	0.0	0.0	3.5	1.7	0.0	0.0
Propylene glycol	88.6	27.8	13.3	35.9	38.7	0.0
Sorbitan group	79.0	25.8	41.2	16.2	7.4	9.5

% = (total number of antihistamine products containing the indicated allergen/total number of products in the antihistamine category) × 100.*This leukotriene receptor antagonist is not an antihistamine; see text for comment on its inclusion here.

The prevalence of azo dyes in oral antihistamines was equally high (26.5%). Dyes added to medications have previously been associated with adverse cutaneous reactions. Among 11 patients reported by Swerlick and Campbell,¹² 1 patient developed a flare of dermatitis after ingesting doxepin containing azo dyes FD&C Red #40 (Allura Red) and FD&C Yellow #6 (Sunset Yellow), among other colorants. Rogkakou et al¹³ reported a former hairdresser with a severe reaction 24 hours after consuming a ferrous sulfate tablet containing Sunset Yellow. Her patch test results were strongly positive to both disperse orange #3 dye and paraphenylenediamine. The 27% prevalence of azo dyes in antihistamines raises concern, given the commonness of paraphenylenediamine allergy in the general population and the potential for cross-reactivity with azo dyes.

Propylene glycol was a listed ingredient in 26.1% of all antihistamines we studied. Fisher¹⁴ identified propylene glycol, an excipient in intravenous diazepam, as the causative agent of SCD in a previously sensitized patient. Hannuksela and Förström¹⁵ confirmed that an oral challenge dose of propylene glycol in an individual with cutaneous allergy would provoke a flare of prior dermatitis and reactivation of patch test sites. Propylene glycol ingestion in foods can also risk precipitating or aggravating dermatitis.² Its intake via an oral antihistamine was the apparent source of provocation of our patient's dermatitis, and its high prevalence (74.9%) in liquid formulations of antihistamines is of concern.

Of the benzoic acid–related preservatives, sodium benzoate was found in 13.0% of the antihistamine preparations. We found no literature clearly documenting SCD from exposure to this allergen, although Mori et al¹⁶ distinguished a cutaneous reaction to sodium benzoate preservative in an amoxicillin–clavulanic acid suspension from reactions to the antibiotic itself. In addition, urticaria has been successfully treated with dietary avoidance of sodium benzoate.⁹

We found paraben preservatives in 13.4% of the antihistamines. Patients with delayed-type hypersensitivity to paraben preservatives have been reported to flare not only after injected solutions preserved with methylparaben, such as lidocaine¹⁷ and intramuscular ampicillin,¹⁸ but also after ingested oral medications containing

these preservatives, such as haloperidol¹⁹ and a mucolytic.²⁰ With 284 paraben-containing antihistamines marketed, SCD might occasionally be seen.

In our study, aspartame was in 4.1% of the antihistamine preparations. Castanedo-Tardan et al²¹ reported a boy with atopy with positive patch test results to formaldehyde and many formaldehyde-releasing preservatives, who developed SCD from ingesting montelukast. The literature continues to add reports of a widespread dermatitis, usually involving the eyelids, that occurs in some formaldehyde-sensitive individuals after ingestion of aspartame-containing products.^{21–24} Physicians should be aware of this pattern of SCD in formaldehyde-sensitive patients taking montelukast or any of the 86 oral antihistamine preparations that contain aspartame.

Propionates, gallates, and carmine were each found in 1.1% or fewer of the medicines studied. None of these has previously, to our knowledge, been associated with SCD from either medication or food ingestion. Propolis has been reported to cause an SCD from ingestion of gummy vitamins.²³ It was not, however, an ingredient in any of the antihistamines we surveyed.

CONCLUSIONS

Systemic exposure of a sensitized individual to even a small amount of an allergen may stimulate a delayed hypersensitivity reaction, producing widespread or refractory dermatitis. Physicians should be alert to the possibility of SCD from excipients in oral antihistamines. This might be especially likely in pediatric patients because 100% of all elixir, liquid, solution, suspension, and syrup antihistamine formulations we studied contain at least 1 allergen. Physicians should inspect the excipients of medications consumed by their allergic patients. In addition, physicians should educate patients with known allergy to any of these excipients on how to examine complete ingredient lists, meticulously looking for their allergens to avoid incidental systemic exposure and precipitation or aggravation of contact dermatitis.

Loratadine n = 223	Desloratadine n = 21	Fexofenadine n = 90	Cimetidine n = 37	Ranitidine n = 198	Doxepin n = 51	Montelukast* n = 77
%	%	%	%	%	%	%
13.9	19.0	2.2	0.0	0.5	0.0	33.8
0.0	14.3	8.9	5.4	18.2	51.0	2.6
23.8	14.3	0.0	0.0	1.0	3.9	0.0
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.0	0.0	2.2	5.4	7.1	3.9	0.0
0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.0	0.0	0.0	0.0	0.0	0.0	0.0
38.1	14.3	4.4	5.4	6.1	58.8	0.0
13.0	23.8	5.6	73.0	6.6	3.9	0.0

Too little is currently known about the true prevalence of SCD, which specific contact sensitizers may trigger it, what the myriad sources and routes of exposure may be, and what are the uncommon and common manifestations of SCD. We recommend a national registry be established for these cases so that information can be gathered to facilitate assessment of the true risks and appropriate interventional measures.

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