

Medication Dyes as a Source of Drug Allergy

Robert A. Swerlick MD[a] and Caren F. Campbell MD[b]

[a]Department of Dermatology, Emory University School of Medicine, Atlanta, GA
[b]Department of Dermatology, Jefferson Medical College, Philadelphia, PA

ABSTRACT

Excipients are defined as inert substances added to a drug or food to confer a suitable consistency, appearance, or form. They may be added for bulk, to change dissolution or the kinetics of absorption, to improve stability, to influence palatability, or to create a distinctive appearance. The last function may depend heavily on the use of coloring agents, especially when there are multiple dosages (such as with warfarin), and dose confusion may result in profound complications. While described as inert, excipients have been associated with triggering immunological reactions, although this is almost never considered in common practice when patients have reactions to medications, even when they appear to react to many different and distinct drugs. We have found a cohort of 11 patients with chronic, unexplained pruritic skin disorders that have responded to medication changes centered around avoidance of coloring agents, particularly FD&C Blue No. 1 (bright blue) and Blue No. 2 (indigo carmine). We believe that reactions to agents that color medications and foods may be more common than previously appreciated and that recognition of this phenomenon may provide therapeutic alternatives to patients with intractable pruritic disorders.

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INTRODUCTION

Excipients are defined as inert substances added to a drug or food to confer a suitable consistency, appearance, or form. They may be added for bulk, to change dissolution or the kinetics of absorption, to improve stability, to influence palatability, or to create a distinctive appearance. The last function may depend heavily on the use of coloring agents, especially when there are multiple dosages (such as with warfarin or L-thyroxine), and dose confusion may result in profound complications. More often than not, excipients account for the majority of the weight or volume of a medication. While described as inert, excipients have been associated with triggering various skin reactions. This is rarely and inconsistently considered in common practice when patients have reactions to medications, even when they appear to react to many different and distinct drugs. We have found a cohort of 11 patients over the past 5 years with chronic, unexplained pruritic skin disorders that have responded to medication changes centered around avoidance of coloring agents. We believe that reactions to agents that color medications and foods may be more common than previously appreciated, and recognition of this phenomenon may provide therapeutic alternatives to patients with intractable pruritic disorders.

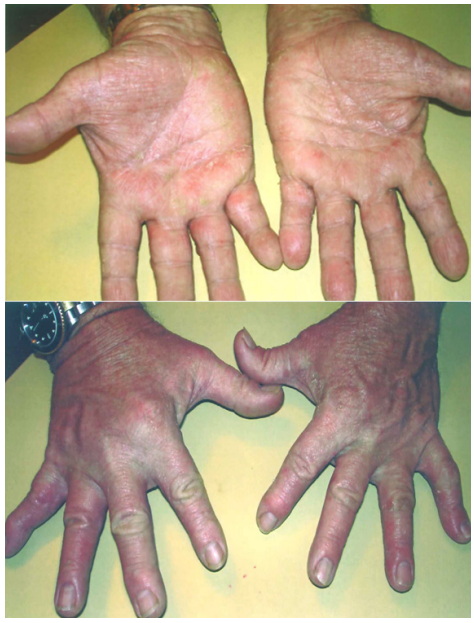
Cases

Case 1: The index case was a 61-year-old white male with a multiyear history of chronic, low-grade hand dermatitis. The patient noticed an explosive flare in hand dermatitis after changing the manufacturer of glyburide/metformin (5 mg/500 mg) mix (Figure 1). He was aware of the change because he noted the appearance of the new tablet was markedly different from what he had previous received, going from a "light-colored" tablet to one he described as being almost black in color. When therapy was switched back to the lighter-colored tablets, the dermatitis promptly resolved. Review of the ingredients of the 2 forms demonstrated that the only difference was that the dark tablets contained FD&C Blue No. 2. He did not report any previous sulfonamide allergy but did report a similar eruption when placed on hydrochlorothiazide at some point in the past.

Case 2: A 16-year-old white female presented with a severe flare of long-standing atopic eczema whose worsening skin symptoms could only be controlled by the concurrent administration of prednisone 30 mg/day, azathioprine 225 mg/day, cyclosporine 300 mg/day, cetirizine 10 mg twice a day, zafirlukast 20 mg twice a day, and doxepin 50 mg every night at bedtime. All attempts to taper the prednisone dose below 30 mg/day were accompanied by generalized itching and dermatitis. At one point during the course of her disease, the patient became aware of repeated and acute worsening of itching within an hour after taking her nighttime doses of doxepin. Further investigation into the inactive ingredients in doxepin led to the discovery that her medication was colored with multiple coloring agents, including FD&C Blue No. 1, FD&C Blue No. 2, D&C Yellow No. 10, D&C Yellow No. 6, and FD&C Red No. 40. The patient was switched from the dye-containing pills to a dye-free liquid form of doxepin. In addition, she also noted that particular prepared foods (eg, candy, breakfast cereals, breakfast bars, yogurt) she consumed also contained these same dyes. We eliminated medications with possible offending dyes and prepared foods containing food coloring, particularly FD&C Blue No. 2, from her diet. Her long-standing eczema persisted, but within 1 month, the prednisone and cyclosporine were discontinued, and the azathioprine dose was ultimately decreased to 100 mg/day. Her eczema has been stable over the intervening 5 years.

Case 3: A 73-year-old white male with a complex medical history presented with generalized dermatitis and pruritus. He had a history of inflammatory bowel disease treated with small bowel resection, which left him with short bowel syndrome. He had documented gluten sensitivity and markedly elevated immunoglobulin E levels

FIGURE 1. Explosive hand dermatitis in case 1 after exposure to a preparation of glyburide/metformin (5 mg/500 mg) that contained FD&C Blue No. 2.



above 10,000 IU. Skin biopsy demonstrated modest perivascular lymphohistiocytic infiltration with eosinophils, consistent with a hypersensitivity reaction. Direct immunofluorescence was negative for features of dermatitis herpetiformis or other blistering skin disease. Treatment with aggressive topical steroids resulted in marked clearance of the dermatitis. However, the pruritus persisted.

Over the subsequent 5 years, the patient was treated with systemic corticosteroids, azathioprine, mycophenolic acid, omalizumab, and rituximab, all in conjunction with aggressive anti-H1, anti-H_2, and antileukotriene therapy. Pruritus was tolerable with systemic corticosteroid treatment, but response to the other agents was minimal, especially related to corticosteroid-sparing agents. Ultimately, systemic corticosteroid treatment was complicated by iatrogenic Addison's disease and severe osteoporosis.

This patient used over-the-counter (OTC) diphenhydramine for acute severe itching. He routinely purchased the dye-free liquid, but at one point during his course, when he began to use a dye containing diphenhydramine product (D&C Red No. 27), he noted acute worsening of his pruritus within 1 hour of taking a dose. At that point, he also noted that the hard candy he bought in bulk to provide the calories required to maintain weight because of short bowel syndrome also triggered attacks of itching.

We subsequently reviewed all his medications and found dye-free substitutes for all except tamsulosin, which contained FD&C Blue No. 2. Upon substitution, his itching ceased except for transient itching when he took tamsulosin. Once a dye-free alternative was located, his itching ceased altogether, but when the dye-containing tamsulosin was reintroduced, his itching returned and resolved again when the dye-free form was substituted.

Case 4: A 61-year-old African American female was referred for evaluation of recurrent angioedema associated with bouts of generalized pruritus for 3 years. She was suspected to have an allergy to yellow dyes and an aspirin allergy, given the presence of nasal polyps and chronic urticaria. She had no history of asthma. However, avoidance of these triggers failed to alleviate her itching and angioedema. Control of hypertension was a major problem, with apparent flares of her skin problem with every regimen of oral agents tried. While oral clonidine induced angioedema and generalized pruritus, clonidine patches were tolerated and resulted in improved but not optimal blood pressure control. When evaluated in the dermatology department, her most recent oral regimen, consisting of metoprolol, hydrochlorothiazide, and amlodipine, was found to contain medication dyes, including FD&C Blue No. 1 and No. 2, FD&C Yellow No. 6 and No. 10, and FD&C Red No. 28 dyes. Based on the suspicion of excipients allergy, we recommended strict use of dye-free oral medications. In the intervening year, she has had only rare episodes of angioedema and itching, some of which were clearly attributable to inadvertent ingestion of offending dyes. In particular, she noted an episode of angioedema initiated by ingestion of OTC cetirizine that contained FD&C Blue No. 1.

Case 5: A 42-year-old white male with 9-month history of axillary, perianal, and waist itching with subtle urticarial eruption was initially unable to identify any specific triggers. The itch improved but did not completely resolve with oral H_1 antihistamines. Paradoxically, he noted acute worsening with OTC cetirizine. His presentation suggested systematized allergic dermatitis, perhaps to FD&C Blue No. 1 in the cetirizine, but no additional source could be identified. Over the subsequent year, the symptoms waxed and waned without apparent triggers, with improvement but not resolution on treatment with fexofenadine and zafirlukast. In August 2011, he noted complete resolution of his itching when he traveled and forgot his usual personal care items. Of note, the only major change in products was substitution for Sensodyne Iso-Active Whitening Gel toothpaste (GlaxoSmithKline, Lewisburg, PA), which contains FD&C Blue No. 1.

Clinical Summary of Remainder of Patients

A total of 11 patients (5 men, 6 women) were identified where there was a high index of suspicion for a potential dye trigger. Their average age was 54.5 ± 19 years. The universal presenting symptom was pruritus with all but one patient presenting with generalized itching. Three patients presented with urticaria and/or angioedema. None of the patients reported wheezing or other respiratory symptoms. The duration of symptoms before initial presentation ranged from as short as 1 week to as long as 20 years. Seven of the 11 patients experienced continuous symptoms for more than 1 year before diagnosis.

All patients had complete blood count with differential blood testing and comprehensive metabolic panels, which showed no consistent or relevant abnormalities. Only 2 patients demonstrated any evidence of peripheral eosinophilia during their disease course. Seven patients underwent biopsy by hematoxylin and eosin (H&E) staining, and 3 for direct immunofluorescence. H&E staining demonstrated nonspecific findings with perivascular infiltrates with eosinophils. Six patients reported a history of sulfonamide allergy, and 3 reported aspirin allergy. Six of the patients reported multiple drug allergies, including 2 patients who reported 8 and 10 drug allergies, respectively. All patients experienced suboptimal to no responses to topical corticosteroids or generic oral antipruritics, including antihistamines (both sedating and nonsedating) and antileukotrienes. When dye allergy was suspected, identification of dye-free alternatives was accomplished using the National Institutes of Health–based DailyMed database (http://dailymed.nlm.nih.gov/dailymed/about.cfm). Three patients appeared to be sensitive to more than one dye based on reactions observed upon inadvertent rechallenge.

DISCUSSION

We have identified a small cohort of patients whose history is strongly suggestive of medication dyes as a trigger for itching and dermatitis. This has been an area of interest for a number of years,[1] although little has been written recently in the dermatology literature.[2] Most of what has been reported is in the form of single case reports or small case series.[3-5] FD&C Yellow No. 5 (tartrazine) has been the most frequently implicated in adverse reactions, including asthma, urticaria, worsening of atopic eczema, eosinophilia, and angioedema. Tartrazine reactions have been purported to be most relevant in aspirin-intolerant individuals.[4,6] The proposed mechanism for these reactions is dose-related histamine release from mast cells.

There are multiple single case reports focusing on what appeared to be reactions to dyes other than tartrazine, including FD&C Yellow No. 6, Yellow No. 10, and Red No. 40,[7] which was extensively reviewed more than 10 years ago.[8] Intravenous or local injections of other dyes used for diagnostic purposes are well-known to sporadically induce anaphylaxis in patients.[9,10] Similarly, use of FD&C Blue No. 2 has been reported to cause reactions as severe as anaphylaxis during cystoscopy in patients with sulfa allergies.[9,10] The reaction of the index case (case 1) to the very distinctive blue/black tablets prompted us to consider whether this might be a much more common phenomenon than initially appreciated.

While there are few reports implicating blue dyes, we had at least 3 patients whose pruritus and dermatitis appeared to be aggravated by blue dyes. Blue No. 1 and Blue No. 2 are 2 of 7 certified color additives that can be used in food, drug, and cosmetic products in both the United States and the European Union. FD&C Blue No. 1 is used in beverages, dairy products, powders, jellies, confections, condiments, icing, syrups, and extracts, while FD&C Blue No. 2 is used in baked goods, cereals, snack foods, ice cream, confections, and cherries. In the pharmaceutical industry, FD&C Blue No. 1 is used as a bluing agent in white tablets to confer their brightness, while FD&C Blue No. 2 is used as a dye for drug capsules, and in urologic, gastrointestinal, gynecologic, and obstetrical procedures, including amniotic fluid leaks.

"Simply being aware that dyes in medications and other ingested products may trigger generalized pruritus, with or without typical urticaria or dermatitis, may prompt alternative management strategies."

Literature linking FD&C Blue No. 1 and Blue No. 2 to allergic reactions is essentially anecdotal, with a very limited number of reports. In a study of 43 children with a history of angioedema/urticaria who responded to an additive-free diet, 19 were challenged with FD&C Blue No. 2 (indigo carmine), and 3 "reacted." Interestingly, these 3 patients did not have positive skin tests to common allergens, including dogs, cats, and eggs.[11]

One study reported that adverse reactions to food additives, including dyes, were very rare in the general population (0.01%-0.23%), but higher in atopic individuals (2%-7%).[12] Given the difficulty in undertaking these studies, we must accept that these numbers are at best crude estimates. However, given the ubiquitous nature of exposure in medications, supplements, and foods, even a small percentage may mean that substantial numbers of patients could be affected. Using the lower bound of these estimates (0.01%) would suggest that up to 30,000 people could be affected in the United States alone. One has to wonder how many patients who report multiple drug allergies may simply be allergic to a color additive or other drug excipients.

Unfortunately, the real incidence of reactions to any additives is essentially unknown because of the lack robust and readily deployable tools required to accomplish vigorously controlled studies. First, there is an inherent problem in challenging patients with chronic urticaria or other potentially serious adverse reactions.[13] Even though our cohort of patients did not report airway issues, there are still substantial logistical problems associated with these evaluations. One cannot assume that challenge will not be accompanied by anaphylaxis or other severe reactions. Most of the studies looking at reactions to medication excipients and food additives examined either airway reactivity or objective changes to skin observed within 24 hours of challenge. Given the major complaint in our cohort was pruritus, often experienced without objective findings, this represents a particular challenge to consistently measure. While double-blind challenges are held as the

gold standard for diagnosis, the lack of clearly defined objective end points limits the utility of even this diagnostic tool.

Despite the inconsistent evidence supporting the role for specific excipients in adverse drug reactions, the possibility that dyes in foods and medications may induce reactions should not be considered implausible. Many of the dyes used to color medications were historically referred to as *coal tar colors*, based on the fact that their original synthesis was from coal tar. It is interesting to note that the origins of the modern chemical and pharmaceutical industry are from that same source. Synthetic dye manufacture served as the genesis for the modern German chemical industry in the mid-19th century. The dyes that were deployed initially to dye clothing were retasked in medicine, first to dye tissue for histology and then as the backbones for many modern pharmaceuticals.[14,15]

It is not contested that virtually all medications are potential sources of reactions, particularly allergic reactions. Reactions to specific medications are taken as a given, supported generally only by a temporal relationship between administration and development of objective findings or symptoms. Because of the lack of a gold-standard test to confirm specific drug allergy other than rechallenge, we accept most diagnoses of drug allergy based on less stringent diagnostic criteria.[16] Rarely, if ever, does the claim of drug allergy require a double-blind challenge with the suspected offending agent.

Despite their similar origins and common elements of chemical structure, there is limited consensus on whether medical and food dyes can induce similar reactions. However, there is nothing chemically distinct about the classes of agents used as dyes that would predict immunological responses any different from agents designated as drugs. Consistent with this perspective is a study showed that FD&C Blue No. 2 (indigo carmine) behaved like a drug in that it interacted with the cytochrome P450 system, inhibiting CYP2A6 in a noncompetitive manner.[17] We would anticipate a low frequency of hypersensitivity reactions in both groups of compounds. The major difference is in the realm of exposure, which regarding dyes is almost ubiquitous, being found in many prescription drugs, OTC, drugs, foods, and personal care products.

Simply being aware that dyes in medications and other ingested products may trigger generalized pruritus, with or without typical urticaria or dermatitis, may prompt alternative management strategies. A given excipient may be avoided by simply switching to a different manufacturer, a different strength of the preparation, or a different formulation, as shown in case 2, where the patient switched from a doxepin pills/capsules to a dye-free liquid formation.

An invaluable resource in managing patients with suspect excipient allergy is the US National Library of Medicine Web site (http://dailymed.nlm.nih.gov), which provides medication package inserts that are brand-specific and dose-specific. While certified color additives are typically listed under inactive ingredients in OTC and prescription medications, this is strictly voluntary for all certified color additives with the exception of FD&C Yellow No. 5 and Yellow No. 6.[18] It is important to know that drug manufacturers are allowed to change any of the excipients, without informing anyone, as long as US Food and Drug Administration–approved ingredients are GRAS (generally recognized as safe).[19]

In summary, we have identified a cadre of patients with pruritic dermatoses, many of long standing, whose skin symptoms appear to be triggered by dyes in medications. Substitution of different preparations of the same medications resulted in clearance or improvement of pruritus and dermatitis. Further study is warranted to better define patients who are affected and to develop diagnostic approaches.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Robert A. Swerlick MD

E-mail:.....rswerli@emory.edu