

ALLERGEN

Focus



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NACDG Allergen: Benzyl Alcohol

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In 1997 the Food and Drug Administration granted an indication for the use of the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test Panels 1.1 and 2.1 as valuable, first-line screening tools in the diagnosis of allergic contact dermatitis (ACD). Many dermatologists utilize the T.R.U.E. test in their practices and refer to contact dermatitis referral centers when the T.R.U.E. test fails to identify a relevant allergen.

Specifically, the T.R.U.E. test screens for 44 distinct allergens and the Balsam of Peru (*myroxylon periereae*) mixture. The test is thought to adequately identify an allergen in approximately 24.5% of patients with ACD.¹ This being said, many relevant allergens are not detected by use of this screening tool alone and, for this reason, “Allergen Focus” has been expanded to cover the notorious Allergens of the Year and the North American Contact Dermatitis Standard Group (NACDG) Standard Allergens series.

“Allergen Focus” is a column designed to concentrate on common allergens and is intended to answer some of the most frequent questions relating to their origin and most common uses. This month, we highlight the naturally occurring, organic aromatic molecule, benzyl alcohol. This agent serves as a precursor to a variety of esters that are frequently used in topical and injectable medicaments and cosme-

ceuticals, as a preservative. It has just been added to the NACDG 2007 Standard 65 Allergen Screen.

CONTACT DERMATIDES

The contact dermatides include, irritant contact dermatitis, contact urticaria, and ACD. **Irritant contact dermatitis**, the most common form, accounts for approximately 80% of environmental-occupational based dermatoses. **Contact urticaria** (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis, the foremost example of this would be latex protein hypersensitivity. While this will be discussed in relation to allergy to benzyl alcohol, an in depth discussion is beyond the scope of this section. Because this form of hypersensitivity reaction may be severe and potentially fatal, we direct the reader to key reference sources.^{2,3}

ACD is an important disease with high impact both in terms of patient morbidity and economics. ACD represents a T helper cell Type 1 [Th1] dependent delayed-type (Type IV) hypersensitivity reaction. The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Daltons. On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated which includes cytokines (i.e., interleukin 2 [IL-2] and interferon gamma [IFN- γ]), T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD.

CLINICAL ILLUSTRATION

A patient presented to the University of Miami Contact Dermatitis Clinic for evaluation of generalized pruritus. She had been evaluated by the T.R.U.E. Test and found to be allergic to balsam of Peru and fragrance mix 1. Of note she was using a “fragrance-free” lotion.

THE ESSENTIAL COMPOSITION OF BOTANICALS

Essential oils are the highly concentrated volatile (rapidly evaporating) aromatic (exciting the sense of smell) substances extracted from various plants and trees. Because these oils were thought to represent the plant's essence of flavor and odor, they were named *essential*.⁴

Throughout the ages these oils have been highly valued for their healing properties and ability to uplift the spirit and body. The wide utility of these oils reflects the complex mixture of chemicals that may constitute one 'essential oil'.

Balsam of Peru, for example, is obtained by capturing the scarification exudate of the wounded *Myroxylon pereirae* tree which grows in El Salvador.

This exudate is known to contain a combination of the allergenic chemicals cinnamic aldehyde and alcohol, benzyl benzoate, benzoic acid, and vanillin.

Furthermore, at this time, it is believed that only 60% to 70% of the chemical constituents have been accurately identified.⁵

In addition, many of these chemical constituents naturally occur in seemingly unrelated botanicals. For example, many patients with known balsam of Peru allergy have reported that tomatoes triggered flares of their dermatitis. To put this issue to rest, in 2005, Srivastava et al performed a chemical analysis on tomatoes and found intense chemical peaks that were determined to be cinnamic alcohol (cinnamyl alcohol) and coniferyl alcohol.⁶ Of note, cinnamyl alcohol is indeed one of the more allergenic components of balsam of Peru.

Another important component of balsam of Peru is **benzyl alcohol** (also known as *phenylmethanol* or *phenylcarbinol*). This naturally occurring chemical constituent can also be found in a variety of other botanical essential oils including hyacinth, jasmine and ylang-ylang and is notable for its pharmaceutical importance and clinical relevance.

THE UTILITY OF BENZYL ALCOHOL

Early chemists noted that many compounds, especially botanicals, exhibited an aroma, and that as a group these compounds shared similar chemical features attributable to the benzene ring. Today, the term "aromatic" in organic chemistry refers to this benzene ring.



THE NATURALLY OCCURRING, ORGANIC, AROMATIC MOLECULE — **BENZYL ALCOHOL** — IS NOTABLE, BECAUSE IT SERVES AS A PRECURSOR TO A VARIETY OF ESTERS THAT ARE FREQUENTLY USED IN TOPICAL AND INJECTABLE MEDICAMENTS AND COSMECEUTICALS AS A PRESERVATIVE.

The naturally occurring, organic, aromatic molecule — **benzyl alcohol** — is notable, because it serves as a precursor to a variety of esters that are frequently used in topical and injectable medications and cosmeceuticals as a preservative. (See Table 1.)

Benzyl alcohol has antibacterial and fungicidal properties, and, at higher concentrations, is used as an antipruritic and anesthetic.⁷

In fact, one of the first described uses of benzyl alcohol was as a local anesthetic discovered accidentally by Macht in 1918.⁸ Upon tasting a sample of benzyl alcohol, he noticed his tongue becoming numb. He then went on to study its anesthetic properties.

A recent plastic surgery study suggested that benzyl alcohol might be a cheap alternative to other local anesthetics especially in patients who have had prior anesthetic allergies.⁹ (See Table 1.)

Benzyl alcohol is a naturally occurring compound found in grapes, and it is responsible for imparting the bitter almond taste to French wines as they age (and the wine gets metabolized by the enzyme benzyl alcohol oxidase).¹⁰ Thus, benzyl alcohol adds to the bouquet of wines, while also serving as a natural preservative.

ADVERSE EFFECTS OF BENZYL ALCOHOL

In the early 1980s, benzyl alcohol received a notorious reputation for its particular use as a preservative in saline flushes and medicaments.

It was responsible for many premature infant deaths associated with metabolic acidosis, respiratory compromise, and intraventricular hemorrhage, aka "gasping syndrome."^{11,12,13} As a result, benzyl alcohol is no longer used as a preservative in saline flushes for neonatal units. Furthermore, the cautious use of medications such as tinzaparin with benzyl alcohol preservation was advised in pregnant women.¹⁴

In addition to serious side effects caused by benzyl alcohol, it has been a culprit in causing allergic contact dermatitis.

INCIDENCE OF BENZYL ALCOHOL ALLERGY

Despite its widespread use in topical products, benzyl alcohol has been considered a rare contact allergen.

In 1986, De groot et al evaluated a series of 501 patients and found no one to be allergic to benzyl alcohol.¹⁵ This may reflect a lower number of benzyl alcohol-containing products at that time.

Fifteen years later, Guin et al reported a frequency of 0.9% for contact urticarial responses and 0.2% for delayed hypersensitivity in 404 patients who received intradermal tests of hydrocortisone in saline containing benzyl alcohol along with a control that only contained benzyl alcohol and saline.¹⁶ Out of 404 patients, four had either a urticarial or delayed hypersensitivity reaction to the control. This reaction was assumed to be due to benzyl alcohol.

HOW MOST CASES OCCUR

The majority of the cases of benzyl alcohol allergy have been reported to have occurred in patients who used topical antifungal and steroid creams for various dermatides, and sensitization may relate to the repeated application to dermatitic skin.^{7,17,18,19,20}

TABLE 1

EXAMPLES OF TOPICAL AND INJECTABLE MEDICAMENTS-COSMECEUTICALS CONTAINING BENZYL ALCOHOL AS A PRESERVATIVE.³²

TOPICALS

- Aloe-Cort Cream, Peter Thomas Roth
- Aloe Vera 98% Moisturizing Gel, Jason Natural Cosmetics
- Anusol-HC 2.5%, Salix Pharmaceuticals
- Bactroban Cream, GlaxoSmithKline
- Clotrimaderm (clotrimazole) 1% topical cream, Taro Pharmaceuticals
- Cortizone 10, Quick Shot (hydrocortisone 1%), Pfizer
- Elidel (pimecrolimus), Novartis
- Triamcinolone acetonide 0.1% Cream, E. Fougera and Co.

INJECTABLES

- A-hydroCort 250mg injectable, Hospira
- Solu-Cortef 250mg injectable, Pfizer
- Innohep (tinzaparin), Pharmion Corporation

UTILIZING REPEAT OPEN APPLICATION TESTING (R.O.A.T.)

This useful technique is frequently underutilized and proves to be helpful in discovering allergens that are not found on standard panels.

One can test products that are meant to be left on the skin, such as topical steroids, by applying a small quantity near the antecubital area twice or thrice daily for 7 days and then checking for a reaction.

This being said, benzyl alcohol has been the culprit allergen in various other products.

For example, Aguirre et al reported delayed-type hypersensitivity reactions in two patients using a commercial anesthetic spray which contained benzyl alcohol in the propellant vehicle.²¹ Both patients developed acute eczematous eruptions at the site of application and were found to be patch test positive to benzyl alcohol, as well as balsam of Peru and fragrance mix. This underscores the importance of recognizing the cross-component reactivity among these allergen components.

Furthermore, benzyl alcohol has also been reported to be a relevant allergen in hair dye. Recently, Carrascosa et al reported a patient who developed facial dermatitis after the application of a semi-permanent hair dye.²² This patient was found to be patch test positive to benzyl alcohol and paraben mix (which notably contains benzylparaben).

It is important to note that allergy to benzyl alcohol can also be a result of occupational exposure. Lodi et al reported two patients who developed an airborne contact dermatitis to benzyl alcohol after laying down parquet flooring using glue which contained benzyl alcohol.²³ Another case involved the use of benzyl alcohol containing cutting oils.²⁴

In addition to these cases of delayed hypersensitivity, benzyl alcohol has been reported to cause cases of contact and systemic urticaria, for example, in association with injectable substances such as gallium and vitamin B₁₂.^{25,26,27}

At times, benzyl alcohol has been found to be the culprit when other allergens were more suspect. For instance, Verecken et al reported a case of a patient who developed a diffuse urticarial response after the injection of betamethasone into the right shoulder for tendonitis.²⁸ The betamethasone was suspected to have caused the reaction in this patient; however, patch testing was negative and when intradermal testing was done, the patient developed a positive reaction to benzyl alcohol.

Importantly, these authors commented that a negative patch test reaction to benzyl alcohol does not exclude sensitization, especially in cases where patients develop Type I hypersensitivity reactions to benzyl alcohol.

And again, contact urticaria has been reported in patients using topical medicaments. In the Guin et al case, the patient was using benzyl alcohol-pre-

served saline soaks to treat her stasis dermatitis.¹⁶ Of interest, this patient self reported a history of allergy to multiple topical medicaments and antihistamines.

THE CONCOMITANT SENSITIVITY

It is not uncommon to see benzyl alcohol allergic patients react to other allergens. It has been commented that concomitant reactions to balsam of Peru are not cross-reactions per se, but rather that benzyl alcohol is a naturally occurring constituent in the aromatic mix and levels may be high enough to elicit a reaction upon patch testing.²⁰

In some cases, patients have been noted to react to paraben mix.¹⁷ This also is not considered a cross reaction but a consequence of the chemical breakdown of benzylparaben to benzyl alcohol. Notably, upon application of benzylparaben to the skin a hydrolytic reaction occurs which releases benzyl alcohol.¹⁷ This phenomena has been supported by cases where patients have reacted to both benzyl alcohol and paraben mix, and with further testing have been found to be nonreactive to the various other parabens, other than benzyl paraben.¹⁷ This is an unusual circumstance since paraben allergic patients commonly cross react to multiple paraben derivatives.¹⁷

WHEN TO SUSPECT BENZYL ALCOHOL

Although benzyl alcohol has been reported as a rare allergen, one should have a high suspicion in patients who report a history to multiple topical medicaments or in patients whose dermatides worsen with different and unrelated agents, such as antifungals and steroids.

THE ALL-IMPORTANT USE TEST

In many reported cases, the detection of benzyl alcohol has been discovered after the use of repeat open application tests (R.O.A.T.) using the patient's personal products.

This useful technique is frequently underutilized and proven helpful in discovering allergens that are not found on standard panels.

One can test products intended to be left on the skin, such as topical steroids, by applying a small quantity near the antecubital area, on clinically normal skin, twice or thrice daily for 7 days and then checking for a reaction.²⁹

TABLE 2

EXAMPLES OF PRODUCTS LABELED "FRAGRANCE-FREE" THAT CONTAIN BA

Moisturizing Cream Shave, Unscented, Alba Botanica

Aveeno Daily Moisturizing Lotion, Johnson & Johnson

Cetaphil Moisturizing Cream, Galderma Laboratories, Inc.

Jason Red Elements Gentle Gel Cleanser, Jason Natural Cosmetics

Olay Total Effect, Moisturizing Vitamin Complex, UV Protection, Fragrance-Free, Procter & Gamble

Any reaction should then be followed by comprehensive patch testing that includes ingredients found in the suspected product.

Since benzyl alcohol is not found in most commercially available standard panels, always maintain a high suspicion and *test to the patient's personal product whenever possible*.

TESTING FOR BENZYL ALCOHOL

The prevalence of allergy to benzyl alcohol is largely unknown, as until recently it was not routinely tested for on either the NACDG or European Standard. A Belgian study of common antimicrobial component allergens ranked benzyl alcohol as the twelfth most frequent allergen in antimicrobials; 25 (0.3%) of 8,521 patients had a positive patch-test reaction to benzyl alcohol.³⁰

Benzyl alcohol frequently reacts concomitantly with balsam of Peru, parabens (including benzylparabens), and benzyl cinnamate due to the constituent commonality.^{17,20}

Hausen reported three patients who were found to be allergic to balsam of Peru and benzyl alcohol by patch testing.³¹

"Benzyl alcohol was found to be one of the 20 constituents of balsam of Peru with which these individuals were tested. It was discovered that these patients were prone to eating large amounts of sweets, which seemed to correlate with dermatitis flares. It is possible that degradation products such as cinnamates and benzoates could also explain these reactions."^{31,32}

DISCLOSURES: Dr. Jacob has spoken for Connetics, Shire, Astellas and Coria. Dr. Militello has no conflicts of interest to disclose.

Benzyl alcohol 1% in petrolatum has been included on the North American Contact Dermatitis 2007 Standard 65 Allergen Screen. It can be purchased from Dormer (www.dormer.com) and Allergeze (www.allergeAZE.com).

THE VALUE OF THIS PATIENT CASE

This patient was patch tested with an extended vehicle tray and her personal hygiene products and was found to be allergic to benzyl alcohol and her "fragrance-free lotion." Because the benzyl alcohol had been added to her lotion for the indication of preservation, not fragrance, the product was labeled "fragrance-free." (See Table 2 on "fragrance-free" products containing benzyl alcohol).

This case highlights the importance of understanding the terminology behind "fragrance-free" and the value of comprehensive patch testing, including the patient's products.

Our patient was educated on **avoidance** and possible product substitutions and has been able to remain free from pruritus. ■

Dedication: This column is dedicated to master mentor in contact dermatitis Bruce Brod, M.D., for his inspiration and guidance to us both. Thank you.

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