

Allergic Contact Dermatitis Caused by Parabens: 2 Case Reports and A Review

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Parabens, methyl, ethyl, propyl, benzyl, and butyl, are the most common preservatives in use today. They are the alkyl esters of *p*-hydroxybenzoic acid and are used extensively because they are relatively nonirritating and nontoxic and offer good antimicrobial coverage. Testing for paraben allergen can be done by patch testing. Two cases of allergic contact dermatitis (ACD) to parabens are used to discuss the background of parabens, their allergenicity, patch testing issues, and several "paraben paradoxes." Although ACD to parabens has been reported, given the widespread use, it is relatively uncommon. Because of their low rate of allergenicity and their favorable preservative profile and efficacy, parabens remain the number one preservative in use.

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BM IS A 76-YEAR-OLD white woman with a long history of eczema that was generalized as a child and more limited to her face and neck as an adult. She presented with an exacerbation of the rash on her face and neck. She described this rash as very itchy and attributed the flare to a period in time when she was on vacation and using an increased number of products, many of them new, including lotions, shampoos, and sunscreens. The eruption improved with topical steroids except for 1 steroid lotion, Desowen (Galderma, Fort Worth, TX), that actually caused a flare of her eczema. On physical examination, she had areas of erythema with minimal scaling on her cheeks and neck bilaterally. She underwent patch testing to an expanded series including preservatives, vehicles, and corticosteroids. These were read at 48 hours and 96 hours and revealed a positive reaction to the paraben mix. Upon discontinuation of her paraben-containing cosmetic products and the Desowen lotion and the use of paraben-free products only, she cleared considerably.

BH is a 40-year-old woman with no significant medical history. She presents with a hand rash that has persisted for 2 years. Use of potent topical steroids resulted in improvement, but the rash would recur upon discontinuation of the topical medication. She was employed as a technician at

the hospital. She was on no medications and had no allergies to any medications. There was no personal or family history of atopic background. She described a baseline of dry, irritated, often cracked hands in the winter months that she attributed to frequent hand washing at work. Physical examination revealed diffuse involvement of both palmar and dorsal surfaces of the hands, with erythema, scale, and some vesiculation. The results of the test for potassium hydroxide (KOH) of her hands was negative. Her feet were clear. Extensive patch testing was performed and revealed a positive reaction to the paraben mix. After review of the products she was using, a moisturizer that contained parabens was found, and with discontinuation of the product and avoidance of paraben-containing moisturizers, her hands cleared. She was able to use paraben-containing cosmetics without difficulty.

Discussion

Preservatives are extensively used in the cosmetic, pharmaceutical, and industrial arenas to prolong product shelf life and prevent bacterial or fungal overgrowth. Numerous preservatives are commercially available but the ideal preservative is inexpensive, has a long shelf life with broad antimicrobial coverage, is compatible with other chemicals, and is not irritating or toxic.¹ Parabens meet many of these expectations and, therefore, have become the most commonly used preservative in cosmetic preparations and topical therapeutics.¹ In addition, many parenterally administered drugs con-

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tain parabens, such as antibiotics, corticosteroids, local anesthetics, and vitamins, to name a few. Over the past 10 years, the usage of parabens has continued to increase and is the number 1 reported preservative in use.² They are used so widely that methyl and ethyl parabens are second only to water as the most commonly used ingredient in cosmetic preparations.^{3,4} The term paraben is actually an abbreviation for *p*-hydroxybenzoic acid and the parabens (methyl, ethyl, propyl, benzyl, and butyl) are the alkyl esters of *p*-hydroxybenzoic acid with the substitution at the *para* position of the benzene ring. They are generally tested as a mix.

The antimicrobial effect of parabens and their use as a preservative was first established in 1924 by Sabalitschka.² The individual parabens have different antimicrobial profiles.³ Several parabens are frequently combined in a product because it has been shown that using them together provides a synergistic effect of the preservative activity.⁴ Propylene glycol also has been shown to potentiate paraben activity.⁵ In general, they are more effective against fungi than bacteria and more effective against gram-positive than gram-negative bacteria.⁴ To extend antimicrobial coverage, parabens often are used with another class of preservative.^{2,5} The antimicrobial effect combined with the low cost and low toxicity has led to the widespread usage of parabens as a preservative.

In the past, parabens have been used extensively in topical medicaments, often at a high concentration, 1% to 5%.⁶ Contact sensitivity became an issue, and their use in topical medicaments has decreased. In cosmetic preparations, parabens are used in lower concentrations, (0.1% to 0.8%) than what was typical of medicaments and are still the most widely used preservative in cosmetic products for several reasons.^{1,5,6} Parabens are not strong sensitizers, particularly in light of their widespread use. They are colorless, odorless, nontoxic, effective over a wide range of pH, and have a good antimicrobial and safety profile with low cost. Parabens have been extensively studied and (given their widespread usage) have been found to be safe. In animal testing, parabens have been found to be nontoxic when taken either acutely or chronically.⁴ Parabens do not accumulate in the body and are metabolized by the liver and kidney. Furthermore, they have no carcinogenic potential.

The North American Contact Dermatitis Group

has found 2.3% of their patients to have a positive patch test result.¹ The first case of paraben allergy was described in 1940 by Bonnevie and was caused by ethyl paraben in an antifungal preparation.⁷ Several individuals have reported allergic contact dermatitis (ACD) to parabens and also have raised concern about sensitivity to parabens.⁷⁻⁹ These reports often are associated with a paraben-containing product used on previously injured skin, such as in stasis dermatitis or eczematous dermatitis.¹⁰ Contact urticaria, bronchospasm, pruritus, and localized angioedema also have been described.^{2,11} In those exquisitely sensitive to parabens, systemic ACD has been seen after ingestion of paraben-containing foods or medications.^{2,12-14} Common paraben-containing foods include mayonnaise, water-based ice cream, preserved fish and vegetables, ketchup, mustard, marmalade, ciders, and candy. Despite these known reactions, several studies show the relatively low incidence of sensitization given the widespread use of parabens. Most studies report low rates of sensitization to parabens ranging from 0% to 4.2% with some isolated reports of up to 10.9%.²

Testing for paraben allergy is generally done with a paraben mix. Several paraben mixes are commercially available. The TRUE paraben mix contains equal parts of ethyl, methyl, propyl, butyl, and benzyl hydroxybenzoate. The Chemotechnique Diagnostics (Malano, Sweden) paraben mix contains 3% each methyl, ethyl, propyl, and butyl hydroxybenzoate, whereas the Trolab (Montreal, Quebec, Canada) paraben mix contains 4% methyl, ethyl, propyl, and butyl hydroxybenzoate. Cross-reactions among the parabens have been observed and may be caused by the common use of several parabens in 1 product because of the synergistic effect of multiple parabens.^{2,6} The least likely paraben to cause sensitivity is benzyl paraben, and this is most likely caused by its larger molecular weight.² Controversy surrounds the issue of testing for paraben sensitivity and arguments have been made that a paraben mix is not an appropriate way to test for paraben allergenicity. Citing several problems with mixes, including the low concentration of each individual paraben component as well as an overall concentration of the paraben mix near the irritation threshold, some have proposed testing for paraben sensitivity with a series of individual parabens rather than with a paraben mix.¹⁵ Permeability also varies among the parabens with methyl paraben being more highly

permeable than benzyl paraben.² Bioavailability of parabens has also been found to be greater in emulsions than in petrolatum. Some argue also that weak positive reactions should be interpreted cautiously as the mix used to do patch testing is near the irritation threshold, whereas others feel higher concentrations of the paraben mix could be used.² Given these concerns, further investigations need to be performed to determine optimal testing conditions for the parabens.

There are several issues regarding paraben usage and allergenicity that have been referred to as the "paraben paradoxes."^{3,16,17} One such paradox is seen in individuals who have had positive test results to parabens on patch testing and have a dermatitis on compromised skin, but can use paraben-containing products on other areas of the body that have intact, uninvolved skin.^{2,16} This may be the result of sensitization by a medicament that often has a higher concentration of parabens compared with the lower concentration of parabens contained in cosmetic products. Another explanation for this paradox may be the use of the topical medicament on diseased skin, which is compromised, allowing for easier penetration of the allergen versus the use of a paraben-containing product on intact skin, which is less easily penetrated.^{2,16} For example, contact sensitivity to parabens has been seen in stasis dermatitis caused by compression boots containing parabens, yet these same patients often can tolerate paraben-containing products on intact skin.^{8,9} Other paradoxes have been described by Fisher. Silver sulfadiazine contains 0.3% paraben as a preservative and is used extensively on burn patients. Given the first paradox (listed previously) stating that dermatitis may occur more easily when parabens are applied to altered or compromised skin but are simultaneously well tolerated on normal unaltered skin, one would expect a higher rate of sensitization to parabens caused by silvadene used on burns. Fisher explains this paradox by pointing out that Langerhans cells are needed to elicit ACD and that Langerhans cells are quickly destroyed when skin is burned.¹⁶ Furthermore, the seeming paradox that paraben-sensitive individuals can tolerate injected or oral medications that contain parabens may be explained by the route of entrance. Injections or oral medications bypass the Langerhans cells.¹⁶

Another paradox is the occasional false-nega-

tive patch test reaction of paraben-containing products tested on normal skin, in paraben-sensitive individuals, when these same products cause a dermatitis on compromised skin.² This false-negative patch test reaction, seen in sensitized individuals, caused by topical medicaments that contain sensitizers that have caused ACD in the patient is not unique to parabens. This observation may be attributable to several factors, such as the patch test being performed on normal, intact skin, whereas the actual product is used on compromised skin allowing easier penetration of the sensitizers. Furthermore, the product may contain a corticosteroid that could suppress a positive patch test reaction on normal skin but not on inflamed skin. Alternatively, the false-negative reaction observed could be caused by the inability of a low concentration of the paraben used in the topical preparation to cause ACD on normal skin but capable of causing a dermatitis on irritated skin.^{2,17}

Another issue surrounding parabens is the conflicting reports regarding cross-reactions among parabens and the so-called *para* group, which includes *p*-aminobenzoic (PABA) acid, the esters of this group form local anesthetics and *p*-phenylenediamine used in hair dyes. Some investigators include parabens in the *para* group, whereas others do not. Fisher points out that acids and their esters often behave differently and argues that, therefore, PABA does not cross-react with local anesthetics or *p*-phenylenediamine, but the esters of PABA could. For practical purposes, cross-reactions are not seen between parabens and *para* compounds, and ingestion of foods containing parabens rarely causes problems.^{2,17}

In summary, these cases show paraben sensitivity and provide an opportunity to review paraben allergy. Both cases show the probable sensitization of the individual to parabens through previously damaged skin that is then exposed to parabens by a topical preparation. The first patient could not tolerate paraben-containing products because the location of the initial problem was on the face. The second patient showed one of the paraben paradoxes and was able to use paraben-containing products on nonirritated skin. ACD to parabens is notably uncommon, given the widespread use of these preservatives. The potential for sensitivity to parabens is low. Therefore, the benefits of using parabens as preservatives appear to outweigh the

risk. Being one of the most innocuous preservatives available, they are the preservatives of choice for most cosmetic preparations. Several paradoxes exist, and these must be kept in mind when patch testing to the paraben mix.

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