Dear Reader,

Hair dye, of course, is a classic source of exposure to para-phenylenediamine (PPD). Now a new cosmetic trend is poised to increase the risk of sensitization to this highly sensitizing chemical. Read In the Blink of an Eye to discover the novel link between eyelid dermatitis and PPD.

Speaking of PPD, the sensitizing potential of PPD has even elicited concerns about its safety for use in patch testing—at least at the 1% concentration currently considered by many as standard. But is 1% PPD in petrolatum safe, or is it actively sensitizing patients? And if it is not safe, are there any alternatives? Explore this topic in Concentration, Volume, and Dose in PPD Patch Testing.

This issue concludes our series on patch testing with corticosteroids by focusing on hydrocortisone-17-butyrate. The marker for Group D2 corticosteroids, H-17-B can manifest signs of sensitization similar to those of the other corticosteroids while presenting diagnostic challenges of its own.

As always, we remain committed to our mission of helping you provide an accurate diagnosis to your patients. If you have questions, we are just a phone call away!

Kind Regards,
Dr. Curt Hamann
President and CEO, SmartPractice

The Last of the Corticosteroid Markers: Hydrocortisone-17-Butyrate and Beyond

Hydrocortisone-17-butyrate (H-17-B) is a midstrength (methylprednisolone aceponate type) corticosteroid (see the September 2017 issue), most often used to treat inflammatory skin diseases and psoriasis. H-17-B, which is a Coopman Group D2 steroid and may be the third most sensitizing corticosteroid after tixocortol pivalate (see the March 2018 issue) and budesonide (see the June 2018 issue), is the patch test marker for D2 steroids. Of the 2% of patients who exhibited a corticosteroid allergy in a large Danish study, the overall rate of positive reactions to H-17-B was 1%. In North America, the prevalence of positive reactions to H-17-B has been slightly lower, ranging from about 0.1 to 0.7%. Positive reactions to H-17-B, however, tend to have high clinical relevance—almost 80% in one study from the North American Contact Dermatitis Group (NACDG).

Patients may be exposed to H-17-B in many over-the-counter and prescription pharmaceuticals. In the work environment, it may be encountered in a variety of medicaments formulated in creams, lotions, ointments, and powders. At home, patients may be exposed to H-17-B in the same formulations used to treat eczema and other localized skin inflammations; in ear, nose, and eye drops; and in rectal suspensions. Skin-to-skin transfer of the allergen can also elicit a dermatitic outbreak (i.e., consort dermatitis) if a spouse, children, or other individuals with whom patients have close contact use such topical preparations.

Corticosteroid hypersensitivity, both in general and specifically to H-17-B, tends to be a treatment-related contact allergy. Factors found to be associated with allergy to H-17-B have included occupational dermatitis, age older than 40 years, and, most significantly, duration of dermatitis. Like tixocortol pivalate, H-17-B is a popular topical medicament. In contrast to tixocortol, however, which is associated with both atopic dermatitis and leg dermatitis (for example, from its use to treat stasis dermatitis or leg ulcers, particularly in the elderly), no association has been found between sensitization to H-17-B and these conditions.

As with other corticosteroids, diagnosing sensitization to H-17-B can be challenging. Failure of a skin condition to improve or one that worsens when treated with H-17-B can be a symptom of sensitization. Improvement of a patient’s dermatitis when treatment is stopped can also signal an allergy to H-17-B. A rare manifestation of allergic contact dermatitis (ACD) related to H-17-B is a skin eruption that mimics acute generalized exanthematous pustulosis, and ACD involving the face has mimicked papular rosacea in at least one reported case.

Continued on next page

The Last of the Corticosteroid Markers: Hydrocortisone-17-Butyrate and Beyond
For patch testing, some clinicians have recommended using H-17-B in ethanol (allergEAZE NA69), which is thought to enhance penetration of the allergen. The timing of readings is another consideration. Delayed readings (i.e., at day 7) are often recommended for corticosteroids, including H-17-B. Reactions to H-17-B, however, can disappear relatively rapidly, a phenomenon that may be related to the metabolism of the allergen in the skin. Therefore, reading H-17-B only at day 7 may be associated with an unacceptably high rate of false-negative reactions. Clinicians must remember that patients can have a negative patch test reaction to any corticosteroid, including H-17-B, even when they are truly sensitized; the response reflects the inherent immunosuppressant property of the drugs.

Metabolically, H-17-B is first converted to hydrocortisone-21-butyrate and then to hydrocortisone, a Group A steroid. Consequently, cross-reactivity between H-17-B and Group A steroids can occur. Patients allergic to H-17-B may need to avoid steroids in both Group D2 and Group A. Concomitant reactions between H-17-B and the Group B steroid budesonide have also been reported. Sensitized patients should check all anti-inflammatory preparations (prescription and nonprescription) for H-17-B as well as for related corticosteroids and should ask their pharmacist if they are uncertain whether a medication contains the allergen. Patients must inform their health care providers and ask them to use or prescribe products that are free from H-17-B and related corticosteroids. Sensitized patients should avoid products that list the following ingredients: h.17b, Laticort, locoid, h(sub 17), Alfason, Cortisol 17-butyrate, Plancol, and Hydrocortisone butyrate as well as to those listed in Table 1.

Markers for corticosteroids in groups C and D1 are also available: clobetasol-17-propionate for the former and desoximetasone for the latter. Overall, sensitization to these corticosteroids appears to be rare. For example, as of the year 2000 only four cases of ACD to clobetasone butyrate had been reported, and, based on a recent analysis, desoximetasone, at least in a topical spray formulation, appears to have little potential for sensitization (or irritation). Based on NACDG data, the prevalence of positive patch test reactions to clobetasol has ranged from 0.3 to 0.7% while that of desoximetasone has been 0.2% or less.

When H-17-B is combined with the other major markers for corticosteroid allergy, tixocortol pivalate and budesonide, 80% of patients who are allergic will be identified. These three markers are included on T.R.U.E. TEST® to make screening for corticosteroid allergies easy and are, of course, also available from allergEAZE in petrolatum. Continued on next page
formulations. Desoximetasone (NA68) is available in a petrolatum formulation while Clobetasol-17-propionate is offered in both ethanol (CS998) and petrolatum (CS492, NA20) formulations. Corticosteroids and their role in ACD are complicated. So, if you still have questions about which products would best serve the needs of your practice, our friendly sales representatives are available to answer your questions at 1-800-878-3838.

Table 1: Products that May Cause Reactions in Patients Sensitized to H-17-B

<table>
<thead>
<tr>
<th>Amincine</th>
<th>Hydrocortisone acetate</th>
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<tbody>
<tr>
<td>Budesonide</td>
<td>Hydrocortisone butyrate</td>
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<tr>
<td>Cloprednol</td>
<td>Hydrocortisone valerate</td>
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<tr>
<td>Cortifoam cortisol</td>
<td>Hydrocortisone valerarne</td>
</tr>
<tr>
<td>Cortril</td>
<td>Incortin-H Kendall’s compound F</td>
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<tr>
<td>Desonide</td>
<td>Methylprednisolone</td>
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<tr>
<td>Efcorlin</td>
<td>Micronized fluocinonide</td>
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<tr>
<td>Efcortelin</td>
<td>Prednicarbate</td>
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<td>Elocrin</td>
<td>Prednisolone</td>
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<tr>
<td>Fluocortison acetate</td>
<td>Prednisolone acetate</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Proctosert</td>
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<tr>
<td>Fluocinonide</td>
<td>Rectoid</td>
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<tr>
<td>Flurandrenolide</td>
<td>Steroids: Group B &amp; Group D2</td>
</tr>
<tr>
<td>Halcinonide</td>
<td>Triamcinolone</td>
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<tr>
<td>Hydrocortisone</td>
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In the Blink of an Eye…

Moreover, her medical history revealed that she had previously developed an itchy rash after getting a temporary black henna tattoo on vacation. Conclusion? Having been sensitized by the tattoo, the patient was ripe for elicitation of allergic contact dermatitis by the PPD-containing eyelash dye.

Because allergens are easily transferred to the eyes by the hands, other causes of eyelid dermatitis, such as sensitization to gold, fragrance mix, balsam of Peru, nickel, and neomycin, are well established. Other classic causes of eyelid dermatitis include sulfonamide formaldehyde resin in nail polish, acrylates in artificial nails, and rubber in makeup sponges and eyelash curlers. In fact, in some studies, fragrance and moisturizers in cosmetics and beauty products have been identified as the leading sources of eyelid dermatitis. In the case of eyelash dying, products containing potentially allergenic preservatives, fragrances, or emulsifiers such as cleansing wipes, lotions, and oils are used in pre- and post-dyeing treatment. Moreover, both eyelash dyes and dye developers contain other known sensitizers, such as cetearyl alcohol, ethylenediamine-tetraacetic acid (EDTA), propylene glycol, resorcinol, m-aminophenol, and p-aminophenol. Additionally, m-aminophenol and toluene-2,5 diamine (TDA) have been reported to cause eyebrow allergic contact dermatitis after probable sensitization from PPD in a temporary black henna tattoo.

Eyelid dermatitis is a complex area of allergic contact dermatitis, and obtaining an accurate diagnosis can be challenging. Patients are most likely to be women, who are affected far more often than men. The involvement of the eyelids themselves offers some clues to the diagnosis. Bilateral disease may point to allergic contact dermatitis, atopic dermatitis, or irritant dermatitis. Unilateral eyelid dermatitis, however, has been associated with allergic contact dermatitis exclusively. Involvement of all four eyelids may be another major risk factor for allergic contact dermatitis. Nonetheless, eyelid dermatitis is not always restricted to the eyelids. The head and neck may be involved in almost a third of cases, and other parts of the body may be affected in almost half the cases.

The risk of developing eyelid dermatitis is far from restricted to the presence of PPD in the products used to dye eyelashes and eyebrows—or in the many other beauty and hair care products on the market. However, PPD is recognized as a highly sensitizing allergen. In fact, PPD is so sensitizing that concerns about its use even in patch testing have recently emerged, as explored in the next article, Concentration, Volume, and Dose in PPD Patch Testing.

SUGGESTED READINGS
Lareb A, Ghaffar SA. Standard practices and awareness concerning p-phenylenediamine among salons that provide eyelash dyeing services (letter). Contact Dermatitis 2018;78:433-434
Vogel TA, Conraads PJ, Schuttelaar ML. Allergic contact dermatitis presenting as severe and persistent blepharoconjunctivitis and centrofacial oedema after dyeing of eyelashes. Contact Dermatitis 2014;71:303-317
Concentration, Volume, and Dose in PPD Patch Testing

In 1961, the Consumer Product Safety Commission identified the blue-black aniline dye p-phenylenediamine (PPD) as one of five “strong sensitizers” in the United States. Historically, the primary route of sensitization to this allergen has been through hair dyes. However, exposure from temporary henna tattoos for-}

with two precisely measured volumes and concentrations of PPD:

cept by patch testing 17 subjects with a known sensitivity to PPD

can deliver the same dose per unit area. This distinction is important because

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governs the production and licensing of allergens is extremely

titig Society to name PPD as the 2006 Contact Allergen of the Year.

PPD and its derivatives and considering global median prevalenc-

es of sensitization to PPD (ranging from 2% to > 6%), the allergen

was, until recently, included in all major baseline series.

That is, until concerns about the risks of active sensitization from

patch testing with 1% PPD in petrolatum (pet) led the German Contact Dermatitis Research Group [Deutsche Kontaktallergie-Gruppe (DKG)] to remove this allergen from their baseline series in 2005. Backed by a study by Hillen et al., the DKG found that

patch testing with this formulation elicited late reactions (on Day 7 or beyond) in 1.5% of patients tested. They interpreted the finding to mean that patch testing with a 1% concentration of PPD might be actively sensitizing patients. In a subsequent study, the DKG found that using a 0.35% concentration of PPD for patch testing was both safe and effective. Based on this and other studies, the Information Network of Departments of Dermatology and the DKG recommended replacing PPD 1% with PPD 0.3% pet in the German baseline series.

PPD is an allergen of global importance, and it makes sense for manufacturers of contact allergens to offer PPD at the lower recom-

mended concentration. However, the regulatory process that
govens the production and licensing of allergens is extremely
time consuming. In 2018, more than a decade after the DKG re-

leased its findings, a 0.3% PPD formulation has yet to be licensed in Germany (or anywhere else). The lack of a commercially available 0.3% PPD formulation has effectively eliminated patch testing with this important allergen in Germany. A recent article [An-

dersen F, Hamann C, Andersen K, et al. Different concentrations and volumes of p-phenylenediamine in pet. (equivalent doses) are

associated with similar patch test outcomes: a pilot study. Contact Dermatitis 2018;78:335-340], however, suggests an alternative solution to this dilemma based on using a precise definition of dose.

Dose is often conflated with concentration (percentage) of an allergen. However, dose is a function of the concentration and the amount of allergen dispensed in a patch test chamber of a given size. This distinction is important because dose per unit area is the critical factor underlying both sensitization and elicitation of contact allergy. In mathematical terms, the concept of dose per unit area implies that different volumes of the same concentration of PPD can deliver the same dose per unit area.

Andersen and coworkers demonstrated the validity of this con-

cept by patch testing 17 subjects with a known sensitivity to PPD

with two precisely measured volumes and concentrations of PPD:

6 mg of PPD 1% and 20 mg of PPD 0.3%.

The investigators used the full diameter of the Finn Chamber® (9.5 mm), not just the 8-mm diameter of the inner chamber depres-

sion, to account for spreading of the allergen to the edges of the chamber (resulting in an effective area of 71 mm). The frequency of reactions was recorded for both formulations of PPD. Based on the following equation for calculating dose, the two test volumes effectively produced the same dose per unit area.

Amount of allergen dispensed (mg x allergen concentration (%)/patch test chamber area (cm²) = dose (mg)/unit area (cm²).

Overall, 13 of the 17 subjects had a positive reaction to at least one of the allergen formulations. Two subjects had a positive reaction to one formulation each. The overall agreement between the two formulations was 88.2% (95% confidence interval: 63.6 –98.5%).

What is the implication of the finding that the two different volumes and concentrations of PPD, which delivered the same dose per unit area, elicited similar outcomes? Certainly, as a short-term solution to the absence of a licensed PPD 0.3% formulation in Germany, patch testing could be conducted with a smaller amount (6 µl) of the currently available concentration of 1% pet rather than with the amount widely accepted as standard (20 µl).

In general terms, however, the finding underscores the importance of discussing patch test allergens in terms of dose/unit area. And although other allergens were not tested, this finding may well be generalizable. It may then be reasonable to modify the dose of highly sensitizing allergens when desired allergen concentrations are unavailable. Furthermore, the amount of allergen dispensed can vary widely depending on the experience of the person pushing the plunger of an allergen syringe. To reduce the dose of allergen as described in this article, a calibrated micropipette must be used. But for clinicians striving for greater precision in dispensing allergens at the standard doses of 20 µl, TruVol® precision allergen dispenser can eliminate concerns about unwanted variation. A quick phone call (1-800-878-3838) can help you find out how to take this step toward standardizing your patch test practice.

SUGGESTED READINGS

Politzer PM, Kamers AJ. Hazardous substances and articles: administration and enforcement regulations: notice of proposed rulemaking: revisions to supplemental definition of ‘strong’ sanititizer. Consumer Prod-


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