Dear Readers,

Patients with hand dermatitis frequently attribute their rash to the rubber in gloves—in particular, natural rubber latex. In fact, the most likely culprits in glove-related dermatitis are rubber accelerators. Read *Putting the Brakes on Accelerators* to find out why accelerators are added to gloves and to learn about “hypoallergenic” and “accelerator-free” gloves. We are happy to work “hand in glove” with you to provide solutions that work for your patients with glove-related hand dermatitis!

Our spring issue introduced the first of three individual markers for corticosteroid allergies, tixocortal-21-pivalate. In this issue we explore the second of these markers, budesonide. While patch testing with budesonide is useful in diagnosing allergic contact dermatitis related to Group B corticosteroids, it presents a particular risk to sensitized patients who are prescribed this drug in a wide range of topical medications and anti-inflammatory products. The table included in the article should be a valuable resource for you and your budesonide-sensitive patients.

We hope that these articles prove useful in your diagnostic process. We remain committed to helping you ensure that no patient suffering from allergic contact dermatitis goes without a diagnosis.

Kind Regards,

Dr. Curt Hamann
President and CEO, SmartPractice

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**Putting the Brakes on Accelerators**

Have you ever had patients, perhaps whose occupations involve health care, complain that their hand dermatitis is caused by gloves? They may have reached your attention because their numerous attempts at switching brands failed to resolve their dermatitis. If their dermatitis was severe enough, they may even have been considering abandoning their career. For example, a few years ago, a neurosurgical resident treated at our Contact Dermatitis Institute was seriously entertaining such thoughts—after 4 years of medical school and nearing the end of a 7-year residency. What a waste that would have been! Fortunately, patch testing identified this patient’s causative allergens, one of which turned out to be the rubber accelerator, carba mix, and a successful avoidance strategy was devised.

A common misperception among patients (and sometimes clinicians) is that gloves are responsible for their hand rash and that switching to another type of glove will solve their problem. They may even attribute the dermatitis to natural rubber latex (*Hevea brasiliensis*), can indeed be a potent Type I allergen associated with symptoms ranging from sneezing and urticaria to life-threatening anaphylactic reactions. However, it is rarely associated with Type IV allergic contact dermatitis. After manufacturing changes were instituted in response to the outbreak of latex allergies that followed the introduction of Universal Precautions in the 1980s, however, the prevalence of allergic reactions to latex proteins decreased significantly. In a Danish study, for example, the prevalence of NRL sensitization declined from 6.1% in 2002-2005 to 1.9% in 2006-2009 to 1.2% in 2010-2013. Furthermore, even if NRL is the culprit, switching gloves randomly may not help because latex proteins can be present in other types of gloves such as isoprene.

In fact, as was the case in our patient, the most likely cause of glove-related dermatitis is one or more rubber accelerators, which are sulfur-containing chemicals. Historically, the primary sensitizers, from most to least common, have been thiurams, dithiocarbamates, mercaptobenzothiazoles, thioureas, and guanidines. These chemicals can be present in both NRL and synthetic rubbers such as nitrile and chloroprene. In North America, the European Union, and Australia, the reported prevalence of allergies to rubber additives has ranged from 5 to 10%. In particular populations, rates as high as almost 20% and 32% have been found. If accelerators are bothersome enough to cause allergies,
Putting the Brakes on Accelerators…continued

why are they even added to gloves? The reality is that there are few economically viable alternatives for producing polymerized gloves, especially medical examination and surgical gloves, without accelerators.

What then are we to make of marketing claims such as “hypoallergenic” or “accelerator-free”? Goodier and colleagues recently explored this issue. They surveyed 11 glove manufacturers, of which 8 were included in the final analysis, about the accelerator content of a total of 190 gloves. The majority of the gloves (172/190, 90%) contained carbamates, which were the most common accelerators identified. Given that manufacturers attempted to reduce or eliminate thiurams in gloves—often by substituting carbamates—in response to their being the primary accelerator underlying glove allergies for so long, this finding is not entirely surprising. In fact, thiurams were only used in 11 (5.8%) of the gloves in the survey. Correspondingly, over time, the prevalence of thiuram allergy may well decrease while allergies to carbamates increase.

Interestingly, carbamates and thiurams are cross-reactive, which is often attributed to the reduction-oxidation relationship between the two allergens. Sensitization to carbamates has almost always been combined with thiuram sensitization, albeit not everyone who is sensitive to thiurams will also react to carbamates. Readers may find the extensive lists of the gloves surveyed and the accelerators used in their production, provided by Goodier and colleagues, to be helpful in identifying alternative products for patients with glove-related dermatitis that has been confirmed by patch testing to be elicited by accelerators. Readers, however, should be aware that such lists can rapidly become outdated as the availability of products changes.

And did Goodier and colleagues identify any accelerator-free brands of gloves? With newer manufacturing processes, rubber may be catalyzed with ultraviolet radiation or cross-linked with peroxide radicals. Altogether, four brands of surgical gloves (nonlatex neoprene) and eight brands of ex-linked with peroxide radicals. Altogether, four brands of surgical gloves (nitrile) were identified as being marketed as accelerator free. Two of the latter (Reflection® Sapphire™ nitrile gloves and Ultimate N-DEX® Free nitrile Powder Free Exam Glove), which are free of the accelerators surveyed in the Goodier study, are distributed by SmartPractice. If you have questions, we are always happy to help you identify the best products to keep you or your patients dermatitis free!

Von Hintzenstern J, Heese A, Koch HU, et al. Frequency, spectrum and occupational relevance of type IV allergic contact dermatitis in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels.


Putting the Brakes on Accelerators…continued

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INDICATIONS AND USAGE:
T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis in persons 6 years of age and older whose history suggests sensitivity to one or more of the 35 substances included of the T.R.U.E. TEST panels.

CONTRAINDICATIONS
• Do not apply to skin of patients with a history of severe allergic reaction (systemic and/or local) to any of the allergen components or inactive substances of T.R.U.E. TEST.
• Do not apply to skin that is injured or inflamed.

WARNINGS AND PRECAUTIONS
• Acute allergic reactions, including anaphylaxis, may occur.
• Sensitization to one or more of the allergens may occur with initial or repeat testing.
• Extreme positive reactions, excited skin syndrome, tape reactions, irritant contact dermatitis, persistent reactions, and late reactions at the test site may occur.

ADVERSE REACTIONS
• The most common adverse reactions (occurring in more than 1% of the study population) were burning, tape irritation, persistent reactions, erythema, and hyper/hypo pigmentation.

Suggested Readings
Goodier MC, Rokkanen SD, Hylva SA. Rubber accelerators in medical examination and surgical gloves. Dermatitis 2018;29(2):66-76
This second article in our series on corticosteroid markers considers budesonide, a potent triamcinolone acetonide type of corticosteroid. Budesonide is an ingredient of topical medicinal and anti-inflammatory products. In the Coopman Classification (see the September 2017 issue), budesonide is considered a Class B corticosteroid for which it serves as a patch test marker. Depending on the concentration used for patch testing and the patch test population, the prevalence of budesonide allergy has ranged from about 0.8 to 1.8% in North America and from as low as about 0.6% in Finland to as high as 2.4% in northern Italy.

Patients who are allergic to budesonide typically have local reactions involving the area of skin to which the allergen has been applied. However, distant ipsilateral flares of toxicoderma-like reactions have erupted on the torso in patients who had budesonide applied to their arm. Allergic patients who inhaled budesonide have developed flares at the sites of previous patch tests and distant skin lesions. Sensitization to budesonide can also be considered in the differential diagnosis of patients with chronic leg ulcers who develop contact dermatitis. In a Danish study, however, duration of disease and the presence of leg dermatitis were not significantly associated with budesonide allergy. Instead, the variables significantly associated with budesonide allergy were age (older than 40 years), occupational dermatitis, and atopic dermatitis.

Patch testing with budesonide can be used to help diagnose allergic contact dermatitis related to Group B corticosteroids as well as to certain esters in Group D (which will be discussed in an upcoming article), based on a classification of topical corticosteroids by cross-reactivity. Budesonide is available in petrolatum and may be patch tested at both 0.1% (preferred in North America and Britain) and 0.01% (preferred in Europe). Not surprisingly, however, some budesonide-sensitized patients exhibit a reverse-dose relationship. That is, they may have a stronger reaction to the lower dose of the allergen and a weaker reaction to the higher dose. As with other corticosteroids, the effect is attributed to the intrinsic anti-inflammatory and hence suppressive effect of the drug itself when applied in high doses. Patch tests with budesonide have also been associated with the “edge effect” (i.e., a positive ring around a negative center where the chamber was placed).

Where are patients likely to encounter budesonide? In work environments, especially healthcare, patients may encounter budesonide in anti-inflammatory agents found in topical medications; in creams, lotions, ointments, and powders; in inhalation drugs, tablets, and injectables; and in rectal suspensions. For the treatment of various skin conditions and other local inflammations, patients may be prescribed any of these anti-inflammatory medications containing budesonide. Budesonide is also used in ear, nose, and eye drops for the treatment of rhinitis, otitis, and conjunctivitis. In inhalational drugs, tablets, and injectables, budesonide is used to treat asthma and other allergy-related lung diseases. In rectal suspensions, budesonide is used for the treatment of colitis and related diseases. It is available as a suspension, powder, solution, aerosol powder, and aerosol liquid.

Continued on next page
Corticosteroid Markers: Part II. Budesonide... continued

Sensitized patients should avoid products with the ingredients and medications listed in Table 1. Budesonide may also be referred to by lengthy chemical names such as (11-β,16-α)-16,17(butylidenedioxy)-11,21-dihydroxyprogna-1,4-diene-3,20-dione; (RS)-11β, 16α,17,21-tetrahydroxyprogna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde; or 16-α,17-α-butyldenedioxy-11-β, 21-dihydroxy-1,4-pregnadiene-3, 20-dione. Budesonide-sensitive patients also may have cross-reactions to other corticosteroids such as hydrocortisone-17-butyrate, hydrocortisone-17-acepionate, hydrocortisone buteprate, methylprednisolone acepionate (Class D2), and prednicarbate. Consequently, patients who are sensitive to budesonide must inform their health care providers about their allergy and request products free from budesonide and related compounds and cross-reacting corticosteroids.

Table 1: Medications and Ingredients Budesonide-Sensitive Patients Should Avoid

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ingredient</th>
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<tbody>
<tr>
<td>Aminonide</td>
<td>Lidex</td>
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<tr>
<td>Bidien</td>
<td>Lidex-E</td>
</tr>
<tr>
<td>Budeson</td>
<td>Micronyl</td>
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<tr>
<td>CortiVent</td>
<td>Preferid</td>
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<tr>
<td>Desonide</td>
<td>Pulmicort Respules®</td>
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<tr>
<td>Desowen</td>
<td>Rhinocort®</td>
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<tr>
<td>Entocort®</td>
<td>Rhinocort® alpha</td>
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<td>Esonide</td>
<td>Rhinocort aqua®</td>
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<tr>
<td>Flunisolide</td>
<td>Spirocort®</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Symbicort®</td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>Synalar</td>
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<tr>
<td>Fluoxonide-E</td>
<td>Tridesilon</td>
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<tr>
<td>Halcinonide (Halog®)</td>
<td>Vanos</td>
</tr>
</tbody>
</table>

Suggested Readings
Vind-Kazunovic D, Johansen JD, Carlens BC. Prevalence of and factors influencing sennitization to corticosteroids in a Danish patch test population. Contact Dermatitis 2011;64:325-329
Isaksson M, Brunz M. Repetitive usage testing with budesonide in experimental nickel-allergic contact dermatitis in individuals hypersensitive to budesonide. Br J Dermatol 2001;145:36-44
Isaksson M, PERSION LM. Contact allergy to hydrocortisone and systemic dermatitis from prednisolone with tolerance of betamethasone. Am J Contact Dermatol 1998;9:136-138