FOCUS ON PROPYLENE GLYCOL

Personal care products and topical medicaments, especially topical corticosteroids, are the most common sources of PG allergy.

SUWIMON POOTONGKAM, MD, AND SUSAN T. NEDOROST, MD

Allergic contact dermatitis (ACD) is a significant health problem for many North American patients, affecting some 4.5 million persons each year.[1] The economic impact of this disease is high in terms of both patient morbidity and loss of income, school and work, not to mention significant expenditures for visits to healthcare providers and for medicaments.[1] A correct diagnosis of ACD will improve, prevent or "cure" the dermatitis and decrease overall costs to the healthcare system.[1] Once patch testing is performed and a culprit has been identified, education becomes the critical intervention to ensure adherence to an avoidance regimen. With allergen avoidance, remission of the dermatitis ensues. Quality of life is improved with correct identification of the offending allergen(s), especially when the dermatitis is present for less than 3 years.[1] If patients are unable to comply with the avoidance regimen, they become at risk for recurrent or sustained dermatitis or progression to a systematized presentation.[2,3]

Contact dermatitis is commonly separated into 2 categories based on the type of exposure – either irritant or allergic. Irritant contact dermatitis (ICD) is the most common cause of contact dermatitis and may occur in anyone who is exposed to the irritant with significant duration or in significant concentrations. Common irritants include chronic or frequent water exposure, abrasive cleansers, detergents and soaps. It is important to note that ICD can at times precede or be a concomitant diagnosis with ACD.[4,5] Unlike ACD, ICD is not immune mediated, but occurs secondary to contact with an irritating or abrasive substance. Contact urticaria (wheal and flare reaction), on the other hand, represents the least prevalent form of CD. It is important to note that it is an immune-mediated phenomenon whose hallmark is an IgE and mast cell-mediated immediate-type hypersensitivity reaction. We acknowledge this form of hypersensitivity due to the severity of the potential deleterious anaphylactic type reactions and direct the reader to key sources.[6,7]

The most common sites of ACD are also those with the most common contact with the allergen-containing topical products or source, such as the hands, face and scalp, though any body region may preferentially develop an ACD reaction, or ICD for that matter. At times, another primary dermatosis is present and the ACD is a secondary phenomenon due to symptomatic treatment with a myriad of topical products, as can occur with propylene glycol (PG).

Confirmatory diagnosis of ACD is through the use of the epicutaneous patch test procedure. Once a patient's spectrum of allergy is defined, education regarding their specific set of chemicals and products to avoid is of the utmost importance. Although ACD is not "curable," many individuals will achieve complete remission with assiduous avoidance. ICD, on the other hand, does not have a specific diagnostic procedure, but it is "curable" through complete avoidance of the inciting agent(s). Correct identifica-

tion of ACD and/or ICD is essential for successful long-term management of dermatitis. In this section focus, we highlight ACD and explore top relevant allergens, regional-based dermatitis presentations, topic-based dermatitis presentations and clinical tips and pearls for diagnosis and treatment.

HISTORY OF PG

Propylene glycol (PG) was described by Wurtz in 1859, and it was first considered for use in pharmaceutical preparations in 1932.[8,9] It was proposed to replace ethylene glycol as a solvent and vehicle for a bismuth product used in the treatment of syphilis. Short- and long-term toxicological studies have shown that PG has a low toxicity when used as a solvent in food and pharmaceuticals, compared to ethylene glycol which could potentially cause harmful effects and fatal outcomes.[10,11] PG, also called 1,2-propanediol or propane-1,2-diol, is a colorless, odorless, viscous liquid. It has a high degree of affinity for water and it is freely miscible with water, glycerol, methyl and ethyl alcohols, ether, chloroform and ethyl acetate. Overall, PG has all the excellent solvent properties of ethylene glycol.[8]

SOURCES OF PG

It is one of the most widely used ingredients in cosmetics, fragrances and various personal care products. PG functions as a solvent, emulsifier, preservative, vehicle, humectant and/or penetration enhancer. PG can be also found in food (as food additive eg, solvent for food colors or flavors), beverages, pharmaceutical preparations, electrocardiogram gels, household cleansers, pet foods, photographic chemicals, plasticizer and liquid cooling systems.[12] It was reported to the FDA as being used in 5,676 and 9,094 cosmetic formulations in 1984 and 2009, respectively.[13,14]

HOW IT IS USED

PG is used at concentrations up to 99%. The highest concentration is used in products that will be diluted and concentrations up to 73% are used in deodorants (which is notably the highest leave-on concentration currently in cosmetic products in the over-the-counter market). PG has been approved at concentrations up to 98.09% in topical drug products and 92% in oral solutions.[14,15]

In the US, PG is listed as generally recognized as safe for use in food. In the European Union, PG is not approved for use as a "general-purpose food grade product or direct food additive" but it may be used as a "carrier and carrier solvent in colors, emulsifiers, antioxidants and enzymes at a maximum content of 1 gram per kilogram of final foodstuff." The widespread use of products containing PG raises the concerns of sensitization and ACD.

Propylene glycol, also called 1,2-propanediol or propane-1,2-diol, is a colorless, odorless, viscous liquid. It has a high degree of affinity for water and it is freely miscible with water, glycerol, methyl and ethyl alcohols, ether, chloroform and ethyl acetate.

SENSITIZATION TO PG

The North American Contact Dermatitis [Research] Group (NACDG) reported 3.5% positive patch reactions to PG (30% aqueous) for the years 1996-2006 and 2.1% for 2007-2008 with 16.2% definite relevance.[16,17] Analysis of Information Network of Departments of Dermatology in Germany data of 45,138 patients who had been tested with 20% PG in water between 1992 and 2002 showed 2.3% positive reactions.[18] Occupation-related reactions were uncommon. The face was most commonly affected followed by a scattered or generalized pattern in patients with allergy to only PG.[16] Contact sensitization to PG may be more common in atopic patients (6.67% positive patch test to PG in patients with AD vs 3.95% in nonatopic patients).[19] In a study of contact sensitivity in patients with leg ulcerations, PG was one of the common allergens [14% (7/52)] and a wound care product with a high frequency of positive patch tests was hydrogel with PG [9% (5/54)].[20] It was proposed that the allergen in this product is PG because 60% (3/5) of patients allergic to this hydrogel were also allergic to PG. Impaired or disrupted barrier function and frequent exposure to PG in various products containing PG are considered as a potential risk of developing contact sensitization to PG. The frequency of cross-reaction to other PG derivatives remains unknown.

Of interest, PG shows negative results in the local lymph node assay. A study of the local lymph node assay for contact allergenic potency revealed no sensitization in a local lymph node assay with PG up to 100%.[21]

In terms of patch test concentrations and vehicles, the appropriate concentration of PG should be nonirritating but sensitive enough to elicit a reaction in the majority of allergic patients. In a study with healthy volunteers, 100% PG showed marginal irritant properties.[22] Twenty percent PG in water was suggested in a study.[23] The NACDG had tested initially using 10% PG aqueous (1992-1996) and then changed to 30% PG aqueous.[14]

ACD TO PG

There are many case reports of ACD to PG in a variety of topical medical preparations including acyclovir cream, ketoconazole cream, topical minoxidil, topical corticosteroids, topical rifamycin, calcipotriene ointment and 5-fluorouracil cream.[24-32] Reports of ACD also have been from ultrasonic gel and ECG electrode.[33,34] Patch testing was done with the products as is, their components and with a wide range of PG concentrations from 1 to 50% in petroleum or aqueous form.

PG has been associated with occupational contact dermatitis in the printing industry. A patient had been working as a press operator and he experienced a recurrence of a work-related eruption on his hands and forearms. It was found that the fountain solution used to ensure proper printing and an orange hand cleaner pumice lotion contained PG.[35]

Systemic contact dermatitis to PG following oral ingestion of foods, capsules and intravenous medication containing PG has been published.[36-40] One

Table 1. COMMON SOURCES OF PROPYLENE GLYCOL

Type of Product	Examples
Personal care products	Shampoos and conditioners, deodorants/antiperspirants, shaving creams, moisturizers, make-up (foundation, concealer, lipstick, lip balm, lip gloss, mascara, eyeliner), soap, body wash, hand sanitizer, hand cleaner, baby wipes, toothpaste, mouthwash, personal lubricant, sunscreen
Medications	
Oral medications	Ibuprofen, acetaminophen, coated aspirin, cetirizine, lozenges, vitamins, dietary supplements, clarithromycin, cyclosporine, dipyridamole, mycophenolate mofetil
Topical medications	Topical corticosteroids, antibacterials, antifungals, benzoyl peroxide preparations
Food	
Sauces	Steak sauce, horseradish, tartar sauce
Desserts/ snack foods	Cakes, cookies, cupcakes, cake mix, brownie mix, chocolate, sour creams
Prepared meals	Prepackaged meals, frozen pizza, prepackaged salads, prepackaged sandwiches
Condiments/dressings	Ketchup, mustard, salad dressings, sauces

case involved a woman with vulvitis after exposure to PG-containing lubricant that was used on her obstetrician's glove and after intravenous injection of a diazepam preparation containing 40% PG.[40] Hannuksela et al reported a perioral challenge test with 2-15 mL of PG in 38 patients with positive patch tests to PG.[38] Eight of 10 patients with a positive patch test reaction to 2% PG and 7 of 28 patients with a positive reaction to 10-100% PG developed an exanthem 3-16 hours after ingestion of PG. None of control subjects showed any dermatitis after ingesting PG. PG is one of the common allergens on standard screening trays that cause systemic contact dermatitis.[36] Flares at sites of previous contact dermatitis and recall flares of the positive patch test sites are clues for diagnosis for systemic contact dermatitis. As PG is not approved for use as a "general-purpose food grade product or direct food additive" in the European Union, a lack of reporting of systemic contact dermatitis from the European Union is expected given the lower exposure there.

IRRITATION TO PG

According to Cosmetic Ingredient Review, PG is generally nontoxic and noncarcinogenic as used in cosmetics in the present practice. The dermal irritation potentials of deodorant formulations containing 68.06% or 69.15% PG were evaluated in as single insult occlusive patch test that showed no more irritation than the reference control. Thirty-day use studies of deodorants containing 35%-73% PG did not report any potential for eliciting dermal irritation or sensitization.[14]

It is one of the most widely used ingredients in cosmetics, fragrances and various personal care products. PG functions as a solvent, emulsifier, preservative, vehicle, humectant and/or penetration enhancer. Propylene glycol can be also found in food, beverages, pharmaceutical preparations, electrocardiogram gels, household cleansers, pet foods, photographic chemicals, plasticizer and liquid cooling systems.

PEARLS/CAVEATS TO TESTING WITH PG

PG patch tests often produce weak reactions and may be difficult to distinguish from irritant reactions. Erythematous reactions with a sharp margin will favor irritant reactions. Reading day can also be helpful. Irritant reactions usually present early, within 24 hours after exposure. It is important to note that weak late (day 7) reactions may not necessarily be irritant in nature and may have clinical relevance.[41] Unlike irritant reactions which commonly cause "questionable" reactions at the early reading and are negative at the final reading, weak late (day 7) patch reactions to PG may indicate relevant allergy.[36] Reconsideration of even questionable day 3 or day 4 reaction and a negative reaction at day 7 (weak lost reactions) has been suggested in patients who do not clear with the avoidance of other identified allergens. Retests with serial dose dilutions and repeated open application tests/provocative use tests may be considered to help distinguish between irritant and allergic responses and also for clinical relevance.

SUMMARY

Personal care products and topical medicaments, especially topical corticosteroids, are the most common sources

of PG allergy. **Table 1** shows common sources of PG. PG can be found in topical corticosteroids, antibacterials, antifungals and emollients. PG was the most common allergen in topical corticosteroid vehicles, being present in 64% (106 of 166) of products.[42] ACD to PG should be considered if dermatitis worsens after use of a topical corticosteroid. Foods that commonly contain PG are salad dressings, sauces, sour cream, cake mixes and prepackaged meals. Reading labels and avoidance of foods in restaurants when ingredients cannot be verified should also be emphasized. Scheman et al reported data on several food additives extracted from a website that provides more than 75,000 food ingredients to help identify potential food sources eliciting systemic contact dermatitis. PG was found in 2,001 food products (~ 2.7%).[43] ■

Suwimon Pootongkam, MD, is a visiting research scholar at University Hospitals Case Medical Center, Department of Dermatology, Cleveland, OH.

Susan T. Nedorost, MD, is professor, department of dermatology, and director, Contact Dermatitis & Patch Test Clinic, at the University Hospitals Case Medical Center, Department of Dermatology, Cleveland, OH.

Disclosure: The authors have no conflicts of interest or financial disclosures to report.

References

1. Kim J, Lim H. Evaluation of the photosensitive patient. *Semin Cutan Med Surg*.1999;18(4):253-256.
2. European Multicentre Photopatch Test Study (EMCPPTS) Taskforce. A European multicentre photopatch test study. *Br J Dermatol*. 2012;166(5):1002-1009.
3. Canelas MM, Cardoso JC, Goncalo M, Figueiredo A. Photoallergic contact dermatitis from benzydamine presenting mainly as lip dermatitis. *Contact Dermatitis.* 2010;(63)2:85-88.
4. Ramírez A, Pérez-Pérez L, Fernández-Redondo V, Toribio J. Photoallergic dermatitis induced by diltiazem. *Contact Dermatitis*. 2007;56(2):118-119.
5. Greenspoon J, Ahluwalia R, Juma N, Rosen CF. Allergic and photoallergic contact dermatitis: A 10-year experience. *Dermatitis*. 2013;24(1):29-32.
6. Bryden AM, Moseley H, Ibbotson SH et al. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol*. 2006;155(4):737-747.
7. Goosens A. Photoallergic contact dermatitis. *Photodermatol Photoimmunol Photomed*. 2004. 20(3):121-125.
8. Seidenfeld MA, Hanzlik PJ. The general properties, actions and toxicity of propylene glycol. *J Pharmacol Exp Ther*. 1932;44(1):109-121.
9. Catanzaro JM, Smith JG Jr. Propylene glycol dermatitis. *J Am Acad Dermatol*. 1991;24(1):90-95.
10. Hanzlik PJ, Newman HW, Van Winkle W, Lehman AJ, Kennedy NK. Toxicity, fats and excretion of propylene glycol and some other glycols. *J Pharmacol Exp Ther*. 1939;67(1):101-113.
11. Ruddick JA. Toxicology, metabolism and biochemistry of 1,2-propanediol. *Toxicol Appl Pharmacol*. 1972;21(1):102-111.
12. Propylene glycol. Avaliable at: http://acdscamp.org/Narratives/20110103152837_~_ZZ%20PROPYLENE%20GLYCOL.pdf. Accessed April 1, 2013.
13. CIR (Cosmetic Ingredients Review Expert Panel). Final report on the safety assessment of propylene glycol and polypropylene glycols. *J Am Coll Toxicol*. 1994:13(6):437-491.
14. Fiume MM, Bergfeld WF, Belsito DV, et al. Safety assessment of propylene glycol, tripropylene glycol and PPGs as used in cosmetics. *Int J Toxicol*. 2012;31(5Suppl):245S-60S2.
15. Food and Drug Administration. Inactive ingredient search for approved drug products. Available at: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Accessed February 25, 2013.
16. Warshaw EM, Botto NC, Maibach HI, et al. Positive patch-test reactions to propylene glycol: a retrospective cross-sectional analysis from the North American Contact Dermatitis Group, 1996 to 2006. *Dermatitis*. 2009;20(1):14-20.
17. Fransway AF, Zug KA, Belsito DV, et al. North American Contact Dermatitis Group patch test results for 2007-2008. *Dermatitis*. 2013;24(1):10-21.
18. Lessmann H, Schnuch A, Geier J, Uter W. Skin-sensitizing and irritant properties of propylene glycol. *Contact Dermatitis*. 2005;53(5):247-259.
19. Nedorost ST, Babineau D. Patch testing in atopic dermatitis. *Dermatitis*. 2010;21(5):251-254.
20. Saap L, Fahim S, Arsenault E. et al. Contact sensitivity in patients with leg ulcerations: a North American study. *Arch Dermatol*. 2004;140(10):1241-1246.
21. Basketter DA, Blaikie L, Dearman J, et al. Use of the local lymph node assay for the estimation of relative contact allergenic potency. *Contact Dermatitis.* 2000;42(6):344-348.
22. Willis CM, Stephens JM, Wilkinson JD. Experimentally induced irritant contact dermatitis: determination of optimum irritant concentrations. *Contact Dermatitis*. 1988; 18(1):20-24.
23. Frosch P J, Pekar U, Enzmann H. Contact allergy to propylene glycol-do we use the appropriate test concentration. *Dermatol Clin*. 1990;8(1):111-113.
24. Corazza M, Virgili A, Mantovani L, La-Malfa W. Propylene glycol allergy from acyclovir cream with cross-reactivity to hydroxypropyl cellulose in a transdermal estradiol system? *Contact Dermatitis*. 1993;29(5):283-284.
25. Kim YJ, Kim JH. Allergic contact dermatitis from propylene glycol in Zovirax cream. *Contact Dermatitis*. 1994;30(2):119-120.
26. Bourezane Y, Girardin P, Aubin F et al. Allergic contact dermatitis to Zovirax cream. *Allergy*. 1996;51(10):755-756.
27. Eun HC, Kim YC. Propylene glycol allergy from ketoconazole cream. *Contact Dermatitis.* 1989;21(4):274-275.
28. Scheman AJ, West DP, Hordinksy MK, Osburn AH, West LE. Alternative formulation for patients with contact reactions to topical 2% and 5% minoxidil vehicle ingredients. *Contact Dermatitis*. 2000;42(4):241.
29. Fowler JF Jr. Contact allergy to propylene glycol in topical corticosteroids. *Am J Contact Dermat*. 1993;4(1):37-38.
30. El-Sayed F, Bayle-Lebey P, Marguery MC, Bazex J. Contact dermatitis from propylene glycol in Rifocine. *Contact Dermatitis*. 1995;33(2):127-128.
31. Fisher D A. Allergic contact dermatitis to propylene glycol in calcipotriene ointment. *Cutis*. 1997;60(1):43-44.
32. Farrar CW, Bell HK, King CM. Allergic contact dermatitis from propylene glycol in Efudix cream. *Contact Dermatitis*. 2003;48(6):345.
33. Connolly M, Buckley DA. Contact dermatitis from propylene glycol in ECG electrodes, complicated by medicament allergy. *Contact Dermatitis*. 2004;50(1):42.
34. Eguino P, Sanchez A, Agesta N, Lasa O, Raton JA, Diaz-Perez JL. Allergic contact dermatitis due to propylene glycol and parabens in an ultrasonic gel. *Contact Dermatitis*. 2003;48(5):290.
35. Noiles K, Kudla I, DeKoven J. Propylene glycol dermatitis in the printing industry: the fundamental role of a workplace visit. *Dermatitis*. 2010;21(1):E1-E4.
36. Lowther A, McCormick T, Nedorost S. Systemic contact dermatitis from propylene glycol. *Dermatitis*. 2008;19(2)105-108.
37. Fisher AA. Propylene glycol dermatitis. *Cutis*. 1978;21(2):166,170, 174-178.
38. Hannuksela M, Forstrom L. Reactions to peroral propylene glycol. *Contact Dermatitis*. 1978;4(1):41-45.
39. Fisher AA. The management of propylene glycol-sensitive patients. *Cutis*. 1980;25(1):24-26, 29-31, 44.
40. Fisher AA. Systemic contact dermatitis due to intravenous valium in a person sensitive to propylene glycol. *Cutis*. 1995;55(6):327-328.
41. Carlson S, Gipson K, Nedorost S. Relevance of doubtful ("equivocal") late patch-test readings. *Dermatitis*. 2010;21(2):102-108.
42. Coloe J, Zirwas MJ. Allergens in corticosteroid vehicles. *Dermatitis*. 2008;19(1):38-42.
43. Scheman A, Cha C, Jacob SE, Nedorost S. Food avoidance diets for systemic, lip, and oral contact allergy: an american contact alternatives group article. *Dermatitis*. 2012;23(6): 248-257.

Sharon E. Jacob, MD

Dr. Jacob, the Section Editor of Allergen Focus*, is Associate Clinical Professor of Medicine and Pediatrics WOS (Dermatology) at the University of California, San Diego.*

Disclosure: Dr. Jacob is an investigator for Smartchoice USA PREA-2 trial.