

ORIGINAL ARTICLE

Skin testing of gallic acid-based hair dye in paraphenylenediamine/paratoluenediamine-reactive patients

Yunseok CHOI,¹ Joon Ho LEE,¹ Hyok Bu KWON,¹ Susun AN,² Ai-Young LEE¹

¹Department of Dermatology, Dongguk University Ilsan Hospital, Dongguk University Graduate School of Medicine, Goyang,

²AmorePacific Corporation, R&D Unit, Yongin, South Korea

ABSTRACT

Incidence of allergic contact dermatitis (ACD) to para-phenylenediamine (PPD)/paratoluenediamine (PTD) hair dyes is increasing. Hair dyes utilizing gallic acid (GA) may be a safe alternative. However, pretesting is recommended. We investigated the contact sensitivity to ingredients of a dye product; GA, monoethanolamine thioglycolate (MT), L-cystein and ferrous sulfate, and an appropriate pretest method in 31 patients reactive to PPD and/or PTD. An open test was performed with the test dye following the patch test. Subsequently, a use test was performed twice, with a 4-week interval. One subject showed a positive reaction to ferrous sulfate in the patch test. Another subject reacted to the first compound alone in the open test. Thirteen subjects manifesting cutaneous lesions from previous regular hair dyeing, showed reactions at the first use of the test dye; and six had reactions with reduced severity at the second test. GA and MT are safe for use in ACD patients reactive to PPD and/or PTD. For predicting contact allergy to hair dyes, the open test appeared to be a better pretest method than the patch test.

Key words: allergic contact dermatitis, gallic acid, monoethanolamine thioglycolate, paraphenylenediamine, paratoluenediamine.

INTRODUCTION

Contact allergy to paraphenylenediamine (PPD) and/or paratoluenediamine (PTD) has been a growing health concern as hair dyeing has grown in popularity among both young and old populations.^{1,2} Although tremendous effort has been put into developing a safe way to dye hair, no valid alternatives have been introduced. Gallic acid (GA) is an aromatic compound that is known for not causing contact allergy itself.³ However, people who have allergic contact dermatitis (ACD) to PPD and/or PTD may develop ACD to GA. Because aromatic compounds, such as PPD, PTD and GA, often show cross-reactivity to each other.⁴

Many hair dye manufacturers recommend pretesting of their products by applying some of the formulated compounds onto the bare skin (posterior auricular area or outer aspect of upper arm), to evaluate the development of erythematous reaction. This procedure is generally described as the “manufacturer’s open test” or “consumer’s open test”.⁵ While there are several methods of pretesting in use, no universally accepted method has been introduced to date.

A number of patients with ACD to PPD/PTD-based hair dyes seek medical counsel on the safety of permanent waving. There are no clear indications in scientific published work on whether waving caused ACD in patients allergic to hair dyes containing PPD and/or PTD. Monoethanolamine

thioglycolate (MT) has been frequently formulated in hair wave solutions.

We have presently investigated whether: (i) an aromatic compound hair dye product causes allergic reactions in patients with ACD to PPD and/or PTD by patch testing its individual ingredients, namely, GA, MT, L-cystein and ferrous sulfate; (ii) the manufacturer’s open test is more appropriate in a clinical setting, for predicting skin sensitivity versus the patch test; and (iii) permanent hair waving may be safely performed in patients with ACD to PPD and/or PTD by a patch test with MT.

METHODS

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the institutional review board of Dongguk University Ilsan Hospital. All the participants completed the informed consent forms.

Participants

Thirty-one subjects (aged >20 years), who were diagnosed with ACD to PPD and/or PTD by the patch test, were enrolled in the study. Exclusion criteria included pregnancy, breast-feeding, immunosuppressant medication within 1 week from enrollment in the study, malignancy, psychiatric disorders, alcohol abuse, or chronic or debilitating disease.

Correspondence: Ai-Young Lee, M.D., Ph.D., Department of Dermatology, Dongguk University Ilsan Hospital, Dongguk University Graduate School of Medicine, 27 Dongguk-ro, Ilsandong-gu, Goyang, Kyunggi-do 410-773, South Korea. Email: lay5604@naver.com

Received 30 May 2015; accepted 17 October 2015.

Hair dye product

The test product (Amore Pacific Corporation, Seoul, South Korea) used in the study consisted of two formulated compounds: (i) GA, MT and L-cystein hydrochloride comprised the first compound; and (ii) ferrous sulfate heptahydrate comprised the second compound.

Skin tests

Patch test. Based on the result from 20 healthy subjects, GA at 4%, MT at 2% and L-cystein at 1.5% in petrolatum (pet.) were determined as optimal concentrations for patch testing. Ferrous sulfate was prepared at 5% pet.⁶ Patch test results were evaluated according to International Contact Dermatitis Research Group criteria at 48 and 96 h from occlusion.

Open test. After the patch test, the four different test materials were applied to a 2 cm × 2 cm area on the upper back for 30 min, and then occluded with transparent waterproof adhesive tape: (i) the first compound alone; (ii) the second compound alone; (iii) sequential application of the first compound followed by the second compound (with a 15-min interval as instructed by the manufacturer); and (iv) mixture of the first and the second compounds. The reactions were read at 48 and 96 h post-application in a manner similar to the patch test.^{5,7}

Use test. One week after the open test, subjects were instructed to apply the hair dye to their whole hair as follows: (i) the first compound for 15–20 min; (ii) the second compound for another 15–20 min; and (iii) the hair was washed with water. It was performed twice with a 4-week interval. Subjects were followed up for 1 week after each use of the test hair dye for evaluation of cutaneous reactions in the head and neck region. The manifestations (items) of reactions assessed were erythema, excoriation, edema/papule, dryness/scale, oozing/crusting and vesicle/bulla. The assessment was based on a 4-point scale: none, 0; mild, 1; moderate, 2; and severe, 3.

RESULTS

Demographic data

Of the 31 included subjects, 11 were male and 20 female. The mean age was 53.1 years (range, 37–78). All subjects had been performing hair dyeing on a regular basis, namely, mostly once every 1–2 months, although they were well aware of their contact allergy to PPD and/or PTD.

Results of skin tests

One subject (3%) showed a weak positive reaction to ferrous sulfate in the patch test (Fig. 1a). This subject had a cutaneous reaction in the use test, namely, excoriation in the first use which turned to erythema (a milder form of reaction than excoriation) in the second test. The subject had no reactions to the open test. No subjects had reactions to GA and MT in the patch test (Table 1).

In the open test, one subject (3%) showed a positive reaction to the first compound alone (Fig. 1b). But this subject did

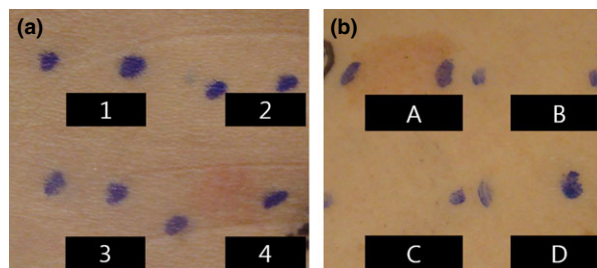


Figure 1. (a) Results of patch test of patient 2: 1+ to ferrous sulfate. (b) Open test of patient 1: 1+ to first compound alone. 1, gallic acid; 2, monoethanolamine thioglycolate; 3, L-cystein; 4, ferrous sulfate; A, first compound alone; B, second compound alone; C, sequential application of first and second compounds; D, mixture of both compounds.

not have reactions to other test materials in the open test, and had no reactions in the patch or use tests either (Table 1).

Assessment of use test

Thirteen subjects (42%), who carried cutaneous reactions from the previous use (prior to use test) of PPD and/or PTD-containing hair dyes, were found to have cutaneous reactions in the first use test. The number with cutaneous reactions decreased to six (19%) with severity being reduced after the second use test. All of these subjects were among the 13 subjects who reacted positively at the first use test. No subjects manifested aggravated reactions at the second use test. Various manifestations of cutaneous reactions appeared at the first use; however, erythema was the only reaction observed at the second use test except in one subject (no. 8) who showed edema and scale, in addition to erythema. Excoriation (reflecting itch) manifested at the first use in this subject but was not seen at the second use test (Table 1).

DISCUSSION

The chemistry of the test hair dye used in this study was based on mordant dyes. Mordant hair dyeing is different from the typical oxidation type that utilizes PPD or PTD as a coupler. It employs metal ions as a mordant to attach the low affinity dye onto the hair. In the test dye, ferrous sulfate and GA served as a mordant and dye substance, respectively.

Gallic acid, PPD and PTD are aromatic compounds. Our results suggested that GA did not cross-react with PPD and/or PTD, and hair dyeing utilizing GA could be safely performed, although further detailed studies are required to test the performance and safety of GA-based dyes to confirm the possibility as a safe alternative to PPD and/or PTD-based hair dyes. One patient showed a positive reaction to ferrous sulfate in the patch test (Fig. 1a). We believe the positive reaction might have been irrelevant to contact allergy to the test hair dye. While the subject had an erythematous reaction in the use test, more participants had eczematous lesions in the scalp prior to inclusion in the study due to repetitive use of hair dyes containing PPD and/or PTD until enrollment in the study. More-

Table 1. Results of skin (patch and open) tests and assessment of use test

Subject	Patch test				Open test				Use 1	Use 2
	Gallic acid	Monoethanolamine thioglycolate	L-cystein	Ferrous sulfate	A	B	C	D		
1					+					
2				+					Excoriation (mild)	Erythema (mild)
3									Erythema (mild)	Erythema (mild)
4									Erythema (moderate), scale (mild)	Erythema (mild)
5									Erythema/excoriation (mild)	Erythema (mild)
6									Oozing (mild)	Erythema (mild)
7									Erythema/edema/excoriation (mild)	Erythema/edema/scale (mild)
8									Erythema (mild)	
9									Erythema (mild)	
10									Erythema (mild)	
11									Edema (mild)	
12									Erythema/scale/excoriation (mild)	
13									Erythema/edema (mild)	
14									Erythema/excoriation (mild)	
15–31		No reactions observed								

Gallic acid, monoethanolamine thioglycolate and L-cystein were prepared in petrolatum at the same concentration as diluted in the product. Ferrous sulfate was prepared at 5% in petrolatum. A, first compound alone; B, second compound alone; C, sequential application of first and second compounds; D, mixture of both compounds; Use 1, hair dyeing as instructed by manufacturer; Use 2, repeat of hair dyeing after 4 weeks from Use 1. Blank spaces represent no reactions.

over, the severity of reactions in this subject improved as the use test was repeated. This subject did not show any reactions in the open test either. In keeping with our findings, an earlier study reported that ferrous sulfate may decrease contact allergy.⁸ MT is a substance that is frequently formulated in permanent waving products as a reducing agent. No subject had reactions to MT in the patch test suggesting that MT did not cross-react with PPD or PTD. Thus, permanent waving utilizing MT can be safely performed in subjects with ACD to PPD and/or PTD.

Studies on pretesting methods of hair dyes, particularly the open test, are scarce in the scientific published work.^{5,9,10} While, in a previous study, hair dyes were tested in the retroauricular area being kept *in situ* for 48 h, we applied the test hair dye to the upper back area. The relatively low epicutaneous penetration due to greater skin thickness of the upper back could be enhanced by occluding the test site. Although, according to the chemistry of mordant dyes,^{11,12} it may be assumed that the test material exists even after being wiped, we occluded the test site after wiping off the test materials once no hypersensitivity reaction was confirmed within the first 30 min of application. Only one subject showed a positive reaction to the first compound alone (Fig. 1b). This subject showed no reactions to other test materials in the open test, and had no reactions in either patch or use test; hence, we did not consider the event relevant to contact allergy. While the manufacturer's instructions indicate to apply the compounds on the skin for 30 min prior to use, it is suggested to read skin reactions in 48 h from applying to the skin.^{5,10} In accordance with our findings, previous reports and the manufacturer's

instructions, we suggest that it is convenient to perform an open test by wiping off the test materials after no hypersensitive reaction has been confirmed within the first 30 min and occluding the test site for 48 h.

The use test is performed to confirm the clinical relevance of allergen exposure identified in the prior patch test.^{7,13} Accordingly, we utilized the use test as a control with which we compared the results of corresponding patch and open tests. Typically, provocative use tests with the suspected agent are usually performed once on normal skin.⁷ However, the participants had cutaneous reactions from previous regular use of hair dyes. Therefore, we performed the use test twice with a 4-week interval. This allowed us to determine not only the occurrence of reactions but also the improvement/deterioration of existing reactions (e.g. participants with eczematous lesions). As shown in Table 1, the number of subjects who developed cutaneous reactions decreased at the second use test. Furthermore, the number of items of reaction and the severity of reactions also decreased at the second use test. This observation suggested that the cutaneous reactions observed at the use test might have not been due to the test products, but instead might have been attributed to the previous use of hair dyes containing PPD and/or PTD, namely, the remnants of chronic cutaneous lesions from previous hair dyeing.

In conclusion, those who have contact allergy to PPD and/or PTD-based hair dyes can safely perform hair dyeing utilizing GA. In addition, permanent hair wave products utilizing MT can also be safely used among them. Lastly, the results of epicutaneous tests and the clinical settings lead us likewise to suggest that it is preferable to open test the formulated compounds

than to patch test the ingredients of the compounds when pretesting for the skin sensitivity to hair dyes prior to use.

ACKNOWLEDGMENTS: This study was supported by the grant (13172MFDS987) from the Ministry of Food and Drug Safety.

CONFLICT OF INTEREST: None declared.

REFERENCES

- 1 Thyssen JP, White JML. Epidemiological data on consumer allergy to p-phenylenediamine. *Contact Dermatitis* 2008; **59**: 327–343.
- 2 McFadden JP, White IR, Frosch PJ, Sosted H, Johansen JD, Menne T. Allergy to hair dye. *BMJ* 2007; **334**: 220.
- 3 Housen BM, Beyer W. The sensitizing capacity of the antioxidants propyl, octyl, and dodecyl gallate and some related gallic acid esters. *Contact Dermatitis* 1992; **26**: 253–258.
- 4 Ramirez-Andreo A, Hernandez-Gil A, Brufau C, *et al.* Allergic contact dermatitis to temporary henna tattoos. *Actas Dermosifiliogr* 2007; **98** (2): 91–5.
- 5 Krasteva M, Cristaudo A, Hall B, *et al.* Contact sensitivity to hair dyes can be detected by the consumer open test. *Eur J Dermatol* 2002; **12**: 322–326.
- 6 De Groot AC, Frosch PJ. Patch test concentrations and vehicles for testing contact allergens. In: Frosch PJ, Menne T, Lepoittevin JP, eds. *Contact dermatitis*, 4th edn. New York: Springer, 2006; 907–928.
- 7 Devos SA, Van Der Valk PG. Epicutaneous patch testing. *Eur J Dermatol* 2002; **12** (5): 506–13.
- 8 Roto P, Sainio H, Reunala T, Laippala P. Addition of ferrous sulfate to cement and risk of chromium dermatitis among construction workers. *Contact Dermatitis* 1996; **34** (1): 43–50.
- 9 Krasteva M, Cottin M, Cristaudo A, *et al.* Sensitivity and specificity of the consumer open skin allergy test as a method of prediction of contact dermatitis to hair dyes. *Eur J Dermatol* 2005; **15** (1): 18–25.
- 10 Basketter DA, English J. Pre-testing in hair dye users: an assessment of the Colourstart system. *Eur J Dermatol* 2009; **19** (3): 232–7.
- 11 Cook DJ. Staining theory. In: Cook DJ, ed. *Cellular Pathology: An Introduction to Techniques and Applications*, 2nd edn. Oxfordshire: Scion Publishing Ltd, 2006; 67–104.
- 12 Samanta AK, Konar A. Dyeing of textiles with natural dyes. In: Akçakoca Kumbasar EP, eds. *Natural Dyes*. Rijeka: InTech, 2011; 29–56.
- 13 Nakada T, Hostynek JJ, Maibach HI. Use tests: ROAT (repeated open application test)/PUT (provocative use test): an overview. *Contact Dermatitis* 2000; **43** (1): 1–3.