

**Possible cross-reactivity
between *para*-
phenylenediamine and
sesquiterpene lactones**

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para-Phenylenediamine (PPD) is an aromatic *para*-substituted diamino compound with strongly sensitizing properties, especially well-known for causing hair dye contact dermatitis.

It cross-reacts with an array of other compounds substituted in the *para*-position such as, e.g. local anaesthetics, sulfonamides, anthraquinones, parabens, and aniline and azo dyes (1). Recent clinical observations suggest cross-reactivity to the large group of sesquiterpene lactone (SL) plant sensitizers.

Case Report 1

A 12-year-old schoolboy with asthma and a history of contact dermatitis from a henna tattoo was referred to our department with severe oedematous dermatitis of the scalp, ears, and periorbital area. The eczema developed within 24 hr after application of a black PPD-containing hair dye. Selected results of patch testing with our standard series, which contains parthenolide 0.1% pet. and the SL mix 0.1% pet., and the hairdresser series are shown in Table 1.

Case Report 2

A 35-year-old foreman of a fibreglass firm was referred to the Department of Dermatology because of contact dermatitis in the red-pigmented areas of 2 permanent tattoos. His past medical history included hay fever and urticaria in the pollen season. The patient was tattooed 10 and 9 years ago on the right arm and leg, respectively. Within the last year, he developed severe, itchy, oedematous

dermatitis confined to the red areas of the tattoos, first on the arm and later on the leg. Patch testing with our standard series and selected metals and dyes showed positive reactions to PPD, SL mix, potassium dichromate, and Dermovat® (Glaxo Smith Kline Pharma A/S, Brøndby, Denmark) cream that contains clobetasol propionate (Table 1).

Case Report 3

A 44-year-old woman with a medical history of childhood atopic dermatitis and current hay fever and possibly asthma was referred because of 2 episodes of skin reactions from hair dyeing. She had a 2+ reaction to SL mix (and alantolactone) on D3/4 of unknown relevance (Table 1). She had worked with marguerite daisies (*Argyranthemum frutescens*) from the Compositae family of plants 5 years previously but without any adverse effects. About 6 months later, she was tested with the Compositae mix 6% pet. and extracts of marguerite daisy as well as chrysanthemum (*Dendranthema*): apart from a doubtful positive reaction to Compositae mix on D3, the tests were negative and occupational plant allergy was ruled out.

Case Report 4

A 17-year-old schoolgirl with a history of contact dermatitis from

a black henna tattoo was referred to the Department of Dermatology because of recurrent dermatitis after a severe hair dye reaction 6 months previously. The results of patch testing are shown in Table 1.

On the basis of these case reports, we decided to evaluate the prevalence of SL sensitivity among PPD-allergic patients. Between January 1995 and March 2007, 115 tested positive to PPD and 15 of these (13%) were Compositae allergic as well. In 5 of the 15 patients, including the 4 cases presented here, the Compositae reactions were considered to be cross-reactions to PPD; in 6 persons, the 2 allergies were concomitantly appearing, while the remaining 4 subjects had relevant Compositae sensitization with PPD reactions of unknown relevance. The last-mentioned group may represent reciprocal cross-reactivity, which is rarely occurring because PPD is not among the top 10 allergens in our Compositae-sensitive patients (2).

Discussion

Contrary to the plant extract-based Compositae mix, SL mix rarely elicits false-positive reactions. The first patient had multiple strongly positive patch test reactions, but PPD, the SL mix, and the allergens of the hairdresser series were placed on 3 separate tapes, which makes a direct 'spillover' effect from adjacent strong reactions unlikely. Furthermore,

Table 1. Differences in reaction patterns to selected allergens of the standard and hairdresser series in 4 PPD-sensitive patients

Allergen	Case report no.			
	1	2	3	4
<i>para</i> -Phenylenediamine	+++	++	++	++
Sesquiterpene lactone mix	+ (D7)	+ (D7)	++ (D3 and D7)	–
Alantolactone	NT	NT	++ (D4)	NT
Parthenolide	–	0 (D2)	–	++ (D3 and D7)
Caine mix	++	0 (D2)	++	++
Black rubber mix	++	0 F.	–	++
<i>para</i> -Toluenediamine	+++	NT	+++	++
Hydroquinone	++	NT	+	++
Nitro- <i>p</i> -phenylenediamine	++	NT	++	–
Pyrogallol	++	NT	+	NT
3-Aminophenol	++	NT	++	+++
4-Aminophenol	++	NT	++	+++
4-Aminoazobenzene	+++	NT	++	NT
Amino- <i>m</i> -cresol	++	NT	NT	++
Disperse Blue 106	0	–	–	++
Disperse Blue 124	0	–	–	++
Disperse Orange 3	+++	0 F.	+++	NT
Ammonium thioglycolate	–	NT	–	+
Resorcinol	–	NT	0 F.	+

0, doubtful positive reaction; F., follicular reaction; NT, not tested.

positive reactions to SL mix rarely occur in this age group (3). Patient no. 2 had many doubtful positive reactions on D2 but eventually turned out to have 4 positive patch test reactions only. The similarity between the late-appearing weak SL mix reaction of unknown relevance and the strongly positive relevant PPD reaction, which were the only 2 reactions the 2 patients had in common, points to true cross-reactivity.

Likewise, patient no. 3 had positive reactions to SL mix but otherwise no evidence of plant allergy.

Patient no. 4 tested negative to SL mix but strongly positive to parthenolide from D3. The patient had dyed her hair regularly for a number of years, and her pattern of reaction was different from that of patient nos. 1 and 3.

From a chemical point of view, SLs contain an α,β -unsaturated lactone group fused to a carbocyclic skeleton typically consisting of 1 or 2 ring structures (4). Unlike PPD, the SLs do not contain aromatic ring structures in their basic carbocyclic skeleton and hence are not substituted in the *para* position. Although the chemical structures of PPD and SLs do not directly suggest cross-reactivity between these strong contact allergens, the question is whether some intermediate substance in the PPD metabolism, such as a quinone-imine, or even some compound cross-reacting with PPD has a molecular size, shape, and/or reactive functional group that makes cross-reactions with 1 or several SL structures possible.

The results of Picardo et al. (5) indicate that patch test reactivity to *para*-substituted compounds, including PPD, depends on the rate of oxidation on the skin and hence on the amount of reactive intermediates formed. Likewise, sensitization from azo dyes may be because of the dye itself or its degradation products (6). The well-known association between patch test positivity to PPD and Disperse Orange 3 (DO3) may, according to Goon et al., be because of either true cross-reactivity or degradation of DO3 to PPD in the skin (6, 7). The patients of cases 1 and 3 had many patch test reactions in common, including DO3, several allergens of the hairdresser series, and SL mix. Conversely, the patient of case 4, who was not tested with DO3, was positive to Disperse Blue 106, Disperse Blue 124, and partly

other allergens of the hairdresser series compared with cases 1 and 3. It is possible that this different pattern of sensitization has paved the way for a cross-reaction to parthenolide rather than the SL mix. Seidenari et al. (6) showed that only 16% of patients with positive patch test reactions to Disperse Blue 124 were co-sensitized to PPD, and they considered the association to be because of concomitant allergies.

Altogether, however, PPD was the only allergen that was common in all 4 cases, and cross-reactivity between PPD and SLs seems to be a possible, perhaps even likely, explanation. This suggests that cross-reactivity may occur between haptens of apparently unrelated chemical structures, which would add new insight to the molecular mechanisms behind cross-reactivity between strong contact allergens. The fact that a relatively small number of patients show evidence of this cross-reactivity may be because of genetic differences in skin metabolism.

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