Patch testing with hydroxyethyl-\textit{p}-phenylenediamine sulfate – cross-reactivity with \textit{p}-phenylenediamine

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Summary

\textbf{Background.} Adverse reactions to permanent hair dyes are frequent, and primarily result from sensitization to \textit{p}-phenylenediamine (PPD).

\textbf{Objectives.} To investigate the degree of cross-reactivity to a chemically similar dye, hydroxyethyl-\textit{p}-phenylenediamine sulfate (HPPS), and whether this might be a dyeing alternative for patients who are sensitive to PPD.

\textbf{Method.} HPPS was patch tested in two concentrations in a total of 216 patients suspected of having contact dermatitis caused by hair dyes and/or hair cosmetics. A regular use test with a hair dye containing HPPS was suggested to every patient who had had an adverse reaction to a PPD hair dye in the past.

\textbf{Results.} Forty of 216 (19.9\%) patients reacted to 1\% PPD, whereas only 2/216 (0.9\%) showed a positive reaction to 1\% HPPS. Reactivity to 2\% HPPS was only slightly higher (5/216, 2.3\%). On the basis of the 43 PPD-positive patients, the reactivity to 2\% HPPS amounted to 12\%; the corresponding figure for toluene-2,5-diamine was 15\% (5/33). In a use test on two PPD-positive patients with a hair dye containing HPPS, no adverse reaction was seen, even after several years of regular dyeing.

\textbf{Conclusions.} HPPS may be an alternative hair dye for individuals not tolerating PPD-containing dyes. However, cross-reactivity with PPD and other aromatic amines may occur. HPPS is also a known sensitizer, and the risk of \textit{de novo} sensitization can only be assessed by a controlled study on a large panel and under regular use conditions.

\textbf{Key words:} hair dye allergy; hydroxyethyl-\textit{p}-phenylenediamine sulfate; patch testing; \textit{p}-phenylenediamine.

Hair dyeing is extremely common. A Danish population-based study showed that almost 75\% of women and 18\% of men had dyed their hair at some point in their lives (1). Hair dyeing is not only used by the elderly to cover grey hairs, but is increasingly used by teenagers for fashion reasons. Oxidative dyes are preferred, because of their permanent character and their ability to cover white or very grey hair. Typically, they contain \textit{p}-phenylenediamine (PPD) or toluene-2,5-diamine as precursors, and \textit{m}-aminophenol or resorcinol as coupling agents. Adverse reactions to hair dyes are common. In the Danish study, 5.3\% of users reported skin reactions compatible with an allergic origin (1). In a questionnaire study in the United Kingdom, eczematous reactions were reported with a frequency of 14\%, and features of angio-oedema with a frequency of 3\% (2). In a prospective study in Thailand, the prevalence of PPD
allergy in a normal adult population was found to be 2.7%. If this is projected to the adult Thai population, at least 1 million individuals could be allergic to PPD (3). Further information can be obtained from recent reviews and epidemiological studies (4–9).

Patients who have suffered from adverse reactions to hair dyes look for alternatives, and may not follow the dermatologist’s advice to refrain from dyeing; this is frequently the case if sensitization is slight as assessed by patch testing. Patients with a high degree of sensitization (+++ or ++++ reactions) are more likely to have a clear history of reacting to hair dyes, and are less likely to continue dyeing their hair, as shown by Ho et al. (4). Major manufacturers of hair dyes are therefore interested in screening new agents with less of a tendency to cause adverse effects. On the basis of the results of predictive tests, hydroxyethyl-\(p\)-phenylenediamine sulfate (HPPS; CAS 93841-25-9) was considered to be a possible candidate in the early 1990s. We therefore tested HPPS and PPD in patients with suspected sensitization to hair dyes and/or other hair cosmetics, in order to obtain information on the degree of cross-reactivity. Furthermore, a use test with a hair dye containing HPPS was offered to the patients.

Materials and Methods

Patch testing

Two case studies were conducted during two time periods, July 1991 to August 1995 (study period I) and February 1997 to March 2005 (study period II), in the department of dermatology of the Klinikum Dortmund. The interruption was caused by temporary lack of test material. The subjects were tested with HPPS, in addition to the baseline series and the hairdressers’ series of the German Contact Dermatitis Research Group (DKG). Patch test concentrations of HPPS were 1% and 2% in petrolatum (pet.). HPPS was obtained from Wella AG (Darmstadt, Germany). Patch test preparations were made at the hospital pharmacy and stored in the refrigerator. PPD 1% pet. (Hermal, Reinbek, Germany) was tested in parallel. The hairdressers’ series contained other aromatic amines, such as toluene-2,5-diamine, \(p\)-aminophenol, and \(m\)-aminophenol.

The inclusion criterion for testing with this series was suspected contact allergy to hair dye(s) including bleach or any type of hair cosmetic (shampoo, gel, etc.), or recalcitrant scalp dermatitis possibly caused by external agents.

Patch tests were performed with Finn Chambers®, according to International Contact Dermatitis Research Group and DKG guidelines. The patch test exposure time was 2 days. Readings were performed at D2 and D3, and, in some cases, additionally at D4. Retrospective data analysis was based on patch test reactions at D3, and performed with SAS® 9.1 software by the Information Network of Departments of Dermatology, University of Göttingen.

In study period I, 104 patients were patch tested with HPPS and PPD, and in study period II, 112 patients were tested. A description of the patients tested by use of the MOAHLFA index is given in Table 1. In addition, the proportions of (former or current) hairdressers, of patients tested because of suspected contact allergy to hair dyes, and of patients who had scalp dermatitis are given.

Use test with HPPS-containing hair dye

In a pilot project, Wella had provided, upon request, a black hair dye containing HPPS to individuals having reported adverse effects to PPD-containing dyes. This dye (Koleston 200 205/4) is not commercially available, and was sent to the patient’s hairdresser to ensure proper application with the usual precautions. This service was suggested to every patient in each study period who had shown a clinically relevant positive reaction to PPD and a negative or doubtful reaction to HPPS on patch testing.

Results

In study period I, only 1 patient reacted positively (+++) to HPPS 2% — the reaction was doubtful at 1% HPPS. This patient also reacted strongly to PPD (++++) and to her own hair dye. She was a 44-year-old Japanese non-atopic housewife suffering from scalp dermatitis. The reaction to PPD was considered to be clinically relevant. A use test with HPPS was suggested to her, but she was lost to follow-up.

<table>
<thead>
<tr>
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<th>Study period I (n = 104)</th>
<th>Study period II (n = 112)</th>
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<tr>
<td></td>
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<td>%</td>
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<td>Suspected contact allergy to hair dyes</td>
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<td>30.8</td>
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<tr>
<td>Scalp dermatitis</td>
<td>4</td>
<td>3.8</td>
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In study period II, 4 patients (3.6%) showed a positive reaction to 2% HPPS, 3 of them also reacting to PPD with a +++ reaction, and one of them reacting to PPD with a + reaction. Two of these 4 patients showed also a positive reaction to 1% HPPS; in 1 patient, the reaction was doubtful, and in another it was negative (Table 2). These patients were 4 women, aged 31, 43, 47 and 56 years, respectively. None of them was a hairdresser, and 2 were atopics. Two of them suffered from scalp dermatitis, and 1 each from periocular dermatitis and generalized dermatitis, respectively. In 3 patients, reactions to PPD were considered to be clinically relevant: dermatitis on the scalp and neck after hair dyeing in 2 patients, preceded in 1 of these by severe oedema of the eyelids; and severe dermatitis and oedema after dyeing of the eyebrows in the third patient.

In both study periods, high proportions of positive reactions to PPD were observed, namely 17/104 (16.3%) in study period I, and 26/112 (23.2%) in study period II (total 43/216, 19.9%). Details of the patch test reactions to HPPS and PPD and cross-reactivity are given in Tables 2–5.

The hairdressers’ series was tested in a total of 205 patients. Thirty-three patients were positive with toluene-2,5-diamine, 6 with m-aminophenol, and 7 with p-aminophenol. The 5 patients positive with 2% HPPS (studies I and II) were all also positive with toluene-2,5-diamine. There was also a high level of cross-reactivity with m-aminophenol (4/6) and p-aminophenol (4/7).

11.6% reacted to HPPS in the PPD positive group (95% confidence interval (CI) 4.0–25.0%) and 15.1% reacted to HPPS in the toluene-2,5-diamine positive group (95% CI 5.1–31.9%). This difference was not significant (Fisher’s exact test, p = 0.74).

Use test

Only one patient of study II accepted the offer of having her hair dyed by her hairdresser with the HPPS dye. The 56-year-old woman tolerated the HPPS dye for 5 years without any adverse effects (dyeing every 4–6 weeks). In the patch test study, she had reacted to PPD with a +++...
reaction, to 1% HPPS with a doubtful reaction, and to 2% HPPS with a + reaction.

Another patient, a 70-year-old woman, had used the HPPS dye without any side effects between 1997 and 2008 (dyeing every 6–8 weeks). She was not included in these two patch test series, because of an interruption interval between 1995 and 1997, owing to lack of HPPS material in the clinic. She was positive with 1% PPD (+ reaction) when patch tested in 1996, and gave a clear history of contact dermatitis caused by hair dyeing. In June 2008, she was patch tested with 1% HPPS, which produced a negative result.

**Discussion**

Higher proportions of positive reactions to PPD and HPPS in the second study period can be explained by the composition of the patient populations tested. In the second period, 56.2% of the patients tested had had dermatitis of the scalp or face, as compared with only 25.9% in the first study period. In addition, suspected contact allergy to hair dyes was far more frequent in the second study period (59.8%) than in the first one (30.8%). The reason is a change in the referral pattern of patients for patch testing. During the first time period, we had a relatively high number of hairdressers examined to validate for occupational hand eczema, referred to us by a major insurance institution. During the second study period, the indication for patch testing with this series focused more on patients with suspected adverse reactions to hair cosmetics of any type, including hair dyes.

Contact allergy to HPPS seems to be rare, according to the results of this study. Positive reactions were seen in only a small percentage of the patients tested, although they constituted a highly selected population. The latter can be seen not only from historical data, but also from the fact that 16.3% of the patients in study period I, and 23.2% of those in study period II, were sensitized to PPD. Allergic reactions to HPPS were seen only in patients who were highly sensitized to PPD. There was a clear dose–response relationship with the test concentration of HPPS; at 1% HPPS, we observed only 2 positive reactions, as compared with a total of 5 reactions ≥+ with 2% HPPS. The result of the use test in the first patient (patch testing ?+ with 1% HPPS, + with 2% HPPS, and +++ with 1% PPD) suggests that 1% may be the appropriate test concentration for this precursor. This assumption should be validated by a further study on a larger test population.

The results of predictive tests suggest that HPPS may have a slightly lower sensitizing potential than PPD (10). In the lymph node assay on mice, an EC3 value of 0.57 was calculated, which is indicative of a strong sensitiser (11).

Penetration studies on human skin showed lower rates than those for PPD (10). This may result in a lower sensitization rate among users. However, this has to be proven by epidemiological studies. Looking at the molecular structure of PPD and HPPS, it is not surprising that HPPS is a sensitizer that may cross-react with PPD (Fig. 1). As our data obtained with other aromatic amines show, there is also cross-reactivity with toluene-2,5-diamine, p-aminophenol, and m-aminophenol.

The main conclusion of this study is that HPPS does cross-react with PPD, although at a relatively low rate. Therefore, it may be an alternative for PPD-sensitive patients, if they wish to continue dying their hair with a strong, permanent hair dye. Wella and Procter & Gamble evaluated the use of an HPPS-containing dye in a large group of consumers who had a proven allergic reaction to PPD and/or toluene-2,5-diamine. The results of the use test were in line with the present findings of this study, and will be reported elsewhere (10). The Scientific Committee on Consumer Safety of the European Commission concluded in March 2010 that ‘based on the data submitted HPPS itself as an ingredient in oxidative hair dyes at a maximum concentration on-head of 2% does not pose a risk to the health of the consumer, apart from its strong sensitising potential’ (11).

So far, there is no commercial hair dye with HPPS available on the market. Furthermore, we are not aware

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**Fig. 1.** Chemical structure of hydroxyethyl-p-phenylenediamine (a) and p-phenylenediamine (b).
of any other product containing HPPS or any other substance cross-reacting with it (e.g. textile dyes). Thus, consumers may not have been exposed to HPPS. Therefore, a prospective controlled study on non-sensitized individuals who regularly dye their hair over a period of 6 months with an HPPS-containing dye should be performed, in order to obtain information about the sensitization risk under regular use conditions. The study design as described by White et al. (3) could serve as a model: they showed that, during a 6-month use period, the incidence of sensitization to PPD was 1.3% in the group of users with monthly application of a commercial dye, and substantially higher than in the control group (0.4%). Dose–response effects of HPPS should also be evaluated in humans and animals. With PPD, it has been demonstrated that intermittent exposure to low-concentration PPD can be equivalent to single, higher-dose exposure (12).

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**References**