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Review

Contact Allergy to Hair Dyes

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Abstract: Many strong and extreme sensitizing chemicals, such as para-phenylenediamine (PPD), toluene-2,5-diamine (TDA) and other aromatic amines or cross-reacting substances, are ingredients in hair dye products. The chemistry of hair dyeing and the immunological reactions to the potent sensitizing hair dye components are complex and have not been fully clarified up until now. Recently 2-methoxymethyl-*p*-phenylenediamine (ME-PPD), a PPD derivate with moderate skin-sensitizing properties, was developed. Although developed for the prevention of sensitization, ME-PPD appears to be tolerated in some PPD/TDA-allergic individuals.

Keywords: contact allergy; allergic contact dermatitis; patch tests; hair dyes; *p*-phenylenediamine; 2,5-toluenediamine; 2-methoxymethyl-*p*-phenylenediamine

1. Introduction

Hair dye is a popular cosmetic product nowadays. A survey of the Danish adult population on hair dyeing habits showed a median age of first dyeing of 16 years [1]. A European cross-sectional study in the general population reported 50.9% of the individuals had used hair colorants at least once in their lifetime (78% female, 20% male), and 35% had used hair colorants during the last 12 months [2]. Among hair dye users, 11.7% reported a history of avoidance of hair dyes because of skin reactions. Hairdressers showed more frequent complaints of hand dermatitis, while complaints of the scalp and the face were more often reported by consumers [3].

2. Ingredients and Chemistry of Oxidative Hair Dyeing

Hair dyes can be divided into oxidative and non-oxidative dyes. Temporary and semi-permanent dyes are non-oxidative hair dyes. Their non-permanent appearance is based on the dye deposition; the dye only interacts with the hair cuticles and not with the inner shaft. These dyes will wash off over time. Oxidative hair dyes comprise 80% of the hair dye market in the European Union and include permanent, demi-permanent and auto-oxidative dyes [4]. Permanent hair dyes are oxidative hair dyes based on precursors, mostly colourless dye monomers. In order to create permanent staining, the chemicals need to penetrate deeply into the hairshaft. To achieve this, the cuticles should be opened. For this purpose usually an alkaline solution is used, e.g., ammonia. This alkaline solution not only opens the hair shaft, but also causes swelling of the shaft, making absorption of the dye easier. Subsequently, the monomers have to become polymerized by an oxidizing agent, such as hydrogen peroxide, and are coupled to the coupler chemicals. This results in the formation of colourful complexes that are too big to diffuse out of the hair shaft again [4]. Demi-permanent hair dyes consist of a mix of oxidation of dye precursors and semi-permanent chemicals. The combination of various hair dye precursors with different couplers is required to produce a wide variety of colours [4].

Many of the approved ingredients of oxidative hair dyes are strong or even extreme contact allergens [5]; for instance, *p*-Phenylenediamine (PPD, 1,4-diaminobenzene, CAS

no. 106-50-3), toluene-2,5-diamine (TDA, 1,4-diamino-2-methylbenzene, CAS no. 95-70-5; synonym *p*-toluenediamine, PTD) and *p*-aminophenol (CAS no. 123-30-8) are three important precursors or intermediates associated with hair dye-related allergic contact dermatitis [6].

Market surveys of the pattern of exposure to active components of oxidative hair dyes were performed in different countries. The prevalence of the presence of PPD in hair dye products was found to be very low in Germany (0.3%) and low in Sweden (16%) and Denmark (22%) [7–9]. In Germany, TDA was the most commonly used hair dye ingredient, appearing in 88% of all hair dye products [7]. This hair dye precursor was also frequently found in oxidative hair dyes according to market surveys in Sweden (80%) and Denmark (58%) [8,9]. In Spain, PPD (50%) is used as often as TDA (49%) in hair dyes [10]. In the US much more PPD (78%) than TDA (21%) is used in hair dyes [11]. Further, *p*-aminophenol was found in about 30% of the hair dye products in European countries, in contrast to the US where it was used much more frequently (60%) [7].

Thyssen et al. reported that PPD contact allergy was more prevalent in the central and southern European patch test centers than in the Scandinavian ones [12]. This difference could be explained by exposure to PPD but also to referral patterns of patients to patch test clinics.

3. Sensitization to Hair Dye Ingredients

PPD is the best-investigated hair dye precursor regarding adverse reactions and contact allergy. For several decades PPD has been tested as an indicator of allergy to hair colouring products in different baseline series. Studies on contact allergy are often based on patch testing of consecutive eczema patients. Data collected by the European Surveillance System on Contact Allergies (ESSCA) network between 2002 and 2012 from 12 European countries showed that the prevalence of contact allergy to PPD in consecutive eczema patients varied between the different countries from 2.3% to 5.8%. The overall prevalence of PPD sensitization in Europe was about 4%, which did not decline over time [13].

In the general population in five European countries, the prevalence of contact allergy to PPD was 0.8%. The prevalence was similar in men and women and in long-term users of hair colouring products and non-users [2]. Black henna tattoos appeared to be an important risk factor for PPD contact allergy, which can be explained by the high concentrations of PPD in black henna tattoos [2,14].

4. Cross-Reactivity

Cross-reactivity has been described as a contact allergic reaction to a molecularly similar chemical to which the individual has not yet been exposed. The immune system is not capable of differentiating between the sensitizing chemical and the almost similar new chemical [15]. Although it has hardly ever been clarified whether exposure to a cross-reacting chemical has occurred, it is assumed that PPD cross-reacts with TDA. Other cross-reacting substances include local ester anaesthetics, e.g., benzocaine, the rubber antioxidant *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine and azo colourants, including the textile dye Disperse Yellow 3 [16]. Many hair dye ingredients also have comparable molecular structures and can cross-react, although concomitant exposure frequently occurs. In these specific cases of hair dye allergy, it can be difficult to distinguish cross-reactivity from co-sensitization. Co-sensitization has been defined as a sensitization to two or more molecularly unrelated substances appearing simultaneously. PPD has been used as an indicator of contact allergy to hair dyes in the baseline series for many years. However, studies on contact allergy have shown that concomitant reactivity to PPD and TDA is only partial [17,18].

5. Metabolism

The metabolism of PPD is very complex and has not been completely elucidated. Research on this topic was initiated by Bandrowski and is still ongoing. Roughly, the skin metabolism of PPD comprises two major pathways, which are the oxidation pathway and the acetylation pathway.

During each hair dye procedure, most of the PPD oxidizes, due to contact with air oxygen or an oxidant (e.g., hydrogen peroxide), into monomeric, dimeric and trimeric oxidation products, such as *p*-benzoquinonediimine, benzoquinone or Bandrowski's base (BB) [19,20]. The presence of an adequate amount of couplers in permanent hair dye prevents auto-oxidation. Subsequently, it either prevents the formation of some of toxic auto-oxidation products, e.g., BB, or it enables the detoxification of others, e.g., benzoquinone diimine. However, despite an adequate amount of couplers, not all PPD is converted. The small amount of remaining PPD can still oxidize, especially under alkaline conditions and in the presence of a strong oxidant, as in hair dye products, hence causing sensitization [21].

Oxidation products of PPD were first studied for the production of azo dyes, which are synthetic colourants used to stain, e.g., clothing, plastics and leather. Later, the toxicological aspects of oxidation products of PPD gained attention [21–24].

Aeby et al. found that PPD was stable in the presence of air oxygen during 30 min [24]. After 30 min, a peak of PPD-derived monomers was detected. The initiator of the dye process is the PPD-derived monomer semibenzoquinone diimine radical (SBQDIR). This is one of the two possible pathways through which the highly protein reactive *p*-benzoquinone diimine (BQDI) can be formed. The other pathway through which BQDI is formed is via electron transfer. BQDI can be regarded as the central step in the oxidation of PPD and is one of the first-formed oxidation products. An important side step of this oxidation process is the formation of benzoquinone, another highly protein reactive oxidation product of PPD [21].

Trimeric oxidation products are formed from these PPD-derived monomers. The concept of the formation of dimeric reaction products has been controversial up to now, as no clear evidence for the existence of these products is present. The trimeric oxidation products include BB and azine, which is formed after the intramolecular rearrangement of BB. It has been suggested in various studies that those trimeric oxidation products of PPD are only formed in the absence of couplers, such as resorcinol or hydroquinone. Although BB is relatively stable, it is protein-reactive and a strong sensitizer [22]. The oxidation pathway of PPD is highly dependent on the concentration PPD, oxygen and the pH. The application of higher concentrations of PPD results in the formation of increased concentrations of oxidation products. These oxidation products cause a stronger activation of dendritic cells in vitro, suggesting that these oxidation products might be the culprit in PPD contact allergy [24–26].

Up until now it has been unclear whether PPD, its oxidation products or both are the main culprit in PPD contact allergy. Merk et al. suggested that PPD was recognized by the T cells through a processing-independent pathway, while the auto-oxidation products required metabolism [27].

The other metabolic pathway of PPD is the *N*-acetylation of this aromatic amine. During a hair dyeing procedure, less than 1% of the applied PPD will penetrate the stratum corneum of the skin. More than 80% of the PPD that enters the skin will be acetylated into monoacetyl-PPD (maPPD) and diacetyl-PPD (daPPD) [28]. The phase II enzyme responsible for this pathway is *N*-acetyltransferase 1 (NAT1). Unoxidized PPD can be acetylated into maPPD and subsequently converted into daPPD by NAT1 present in the stratum corneum. This acetylation pathway of PPD is also regarded as the detoxifying pathway, because these acetylation products are non-sensitizing or extremely weak sensitizers [29,30].

In several countries TDA is significantly more frequently used than PPD in hair dyes. Therefore, it would be interesting to know more about the metabolism of TDA; however, it is unknown.

6. New Hair Dye Ingredient: 2-Methoxymethyl-*p*-Phenylenediamine

PPD and TDA are being considered as major contact allergens among hair dye precursors. Because of the need to develop a precursor that would give similar color performance with reduced skin sensitization potency, 2-methoxymethyl-*p*-phenylenediamine (ME-PPD, CAS no. 337906-36-2) was recently developed. The introduction of a methoxy-methyl side chain into PPD resulted in a PPD derivate with good hair-colouring property. In vitro studies, identifying the skin-sensitizing potential, were indicative of lower skin-sensitizing properties compared to PPD and TDA [31]. In vivo studies,

such as the local lymph node assay (LLNA), showed that the skin sensitization induction potency of ME-PPD was weaker than that of PPD and TDA [31].

In vitro, ME-PPD was investigated for its protein reactivity and dendritic cell activation potential. Protein reactivity of ME-PPD, PPD and TDA was compared at different concentrations. Peptide depletion values for PPD and PTD increased to near maximal depletion (~80%) at the highest concentration of 200 μM, compared to ME-PPD, in which protein reactivity was low (<25% depletion) at all tested concentrations of 0.32 to 200 μM. CD86 expression of THP-1 cells, used as surrogate dendritic cells, was determined for different concentrations of ME-PPD and compared with PPD and TDA. For ME-PPD a higher concentration was needed to detect relevant increases in CD86 expression compared to PPD and TDA. Overall the CD86 up-regulation was much lower for ME-PPD than PPD and TDA [31]. In the local lymph node assay, the EC3 value (estimated concentration required to induce a stimulation index of three relative to concurrent vehicle-treated controls) of ME-PPD was 4.3% [31]. This indicated that ME-PPD has a moderate skin-sensitizing potency, compared to the EC3 values of 0.06% and 0.31% for PPD and TDA having extreme sensitizing potency [5]. According to a study in guinea pigs (modified guinea pig maximization test), TDA is an extremely potent skin sensitizer [32].

A study on the metabolic fate of ME-PPD indicated that the human skin was able to deactivate ME-PPD by *N*-acetylation. Differences in immune responses between ME-PPD and both PPD and TDA are unlikely based on *N*-acetylation [31].

PPD-sensitized individuals can cross-react to other chemically related (para-substituted benzene) components of hair dye products. In 30 PPD-allergic individuals, cross-elicitation to a ME-PPD-containing hair dye product was investigated under simulated hair dye use conditions on the forearm. Overall, cross-elicitation was shown in nine out of 30 (30%) subjects, while 70% were negative. Cross-elicitation was affected by the strength of the individual's sensitization status to PPD: two of four cases had a grade of +++, three of 10 had a grade of ++, and four of 16 had a grade of + [33].

ME-PPD has been developed for the prevention of sensitization in subjects who start colouring their hair and for those who colour their hair who have not been sensitized to other hair dye precursors, such as PPD or TDA, yet. ME-PPD-containing hair dye products were not developed to use in the case of a hair dye allergy. However, it is known that many subjects allergic to PPD or TDA continue dyeing their hair [34]. It is likely that they will consider the use of ME-PPD-containing hair dye products as an alternative. Recently, Kock et al. investigated whether PPD- and/or TDA-allergic individuals that did not respond to exposure to ME-PPD under simulated hair dye use conditions on the forearm would tolerate repeated and continued full hair colour treatments with ME-PPD-containing hair dye at their hairdresser [35]. Overall, 38 of 43 PPD-/TDA-allergic individuals did not show elicitation after testing with the ME-PPD-containing hair dye product on the forearm. Continued hair dying was tolerated by 29 of 43 (67%) PPD-/TDA-allergic subjects. Tolerance to ME-PPD-containing hair dye products was found in five subjects with a previous extremely strong (+++) positive diagnostic patch test reaction to PPD. A limitation of this study is that it was not disclosed how many of the participants were allergic to PPD, to TDA or to both. Also the grade of the patch test reaction to PPD/TDA was not always mentioned.

7. Conclusions

Hair dyeing is a popular part of fashion nowadays, as above 70% of all females and one-fifth of all males dye their hair at least once in their lifetime. In order to make the frequently used hair dye products have permanent properties, many extreme sensitizing ingredients are used, including PPD, TDA and other aromatic amines or cross-reacting substances, in combination with strong irritants, such as ammonia and hydrogen peroxide. Recently, ME-PPD was developed, a PPD derivate with moderate skin-sensitizing properties. Although developed for the prevention of sensitization, ME-PPD appears to be tolerated in some PPD-/TDA-allergic individuals. Nevertheless, the advice to PPD-/TDA-sensitized patients is not to dye with a ME-PPD-containing hair dye product. Also hairdressers and dermatologists should be aware of the risks involved.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

PPD	*p*-phenylenediamine
TDA	2,5-toluenediamine
BB	Bandrowski's base
SBQDIR	semibenzoquinone diimine radical
BQDI	*p*-benzoquinone diimine
maPPD	monoacetyl-PPD
daPPD	diacetyl-PPD
ME-PPD	2-methoxymethyl-*p*-phenylenediamine

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