

Late reactions to patch test preparations with reduced concentrations of *p*-phenylenediamine: a multicentre investigation of the German Contact Dermatitis Research Group

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Summary

Background. *p*-Phenylenediamine (PPD) 1% in petrolatum has been shown in a prospective study to elicit late reactions in 1.5% of routine patch tests, which may be indicative of patch test sensitization.

Objectives. To assess the frequency of late reactions to reduced PPD patch test concentrations.

Methods. In 1838 patients, PPD was tested at three concentrations (0.5% pet., group I; 0.4% pet., group II; and 0.35% pet., group III). Patch tests were read on D1 (D2) to D3 (D4); additional late readings were performed on D7, D14, and D21. Patients who were not able to return for all scheduled late readings were telephoned on D7, D14, and D21, and questioned about a reaction at the patch test sites.

Results. Data of 1666 patients (1069 women and 597 men) were eligible. Late reactions were observed in 9 patients, 3 in group I (0.49%) and 5 in group II (0.63%). In 7 of 8 of the patients with late reactions, patch tests were applied for 48 hr. On retesting, 4 of 5 patients became positive at D2 or D3.

Conclusions. The occurrence of late reactions to PPD may be influenced by patch test concentration and duration. PPD 0.4–0.5% pet. may cause late reactions indicative of active sensitization.

Key words: active sensitization; allergy; baseline series; contact dermatitis; late reaction; patch test sensitization; PPD; *p*-phenylenediamine.

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p-Phenylenediamine (PPD) is an important contact allergen. The predominant cause of PPD allergy is exposure to hair dyes, but PPD allergy or cross-sensitization may also result from exposure to so-called temporary henna tattoos, leather (e.g. shoes), fur, textiles, or industrial rubber products (1–3). Hair dyeing is popular. A survey in Denmark revealed that 18.4% of the male respondents and 74.9% of the female respondents had, at some point, dyed their hair (4). The use of hair

dyes is increasing among young people, and adverse skin reactions compatible with allergic contact dermatitis have been reported by a significant number of those dyeing their hair (5, 6). PPD allergy is frequent. The median prevalence in dermatitis patients is 4.3% in Asia, 4.0% in Europe, and 6.2% in North America (3). Recently, an increasing frequency of sensitization to PPD was observed in London, possibly resulting from increasing use of hair dyes (7). In a prospective multicentre investigation of the German Contact Dermatitis Research Group [Deutsche Kontaktallergie-Gruppe (DKG)], it was recently shown that 1% PPD in petrolatum elicited late reactions in 1.5% of routine patch tests, which may be indicative of patch test sensitization (8). There is no doubt that PPD fulfils the criteria to be an allergen of the baseline series. Nevertheless, the DKG removed PPD 1% pet. from the German baseline series because the risk of active sensitization was considered to be too high. Because PPD is indispensable in diagnostic patch testing, patch testing with reduced PPD concentrations was performed by 10 centres of the DKG. The results are presented here.

Patients and Methods

In the participating centres, patients in whom patch testing with the baseline series was indicated were informed that PPD 1% pet. had been removed from the DKG baseline series because of the higher risk of patch test sensitization than with other baseline allergens. In addition, they were informed that PPD is an important allergen that is internationally tested in the baseline series, and they were offered the opportunity of having a patch test with a reduced patch test concentration of PPD. For this purpose, PPD (CAS 106-50-3, PPD-base, 1% pet.; Almirall Hermal, Reinbek, Germany) was diluted with pet. (Almirall Hermal) by the respective hospital pharmacist. According to the actual patch test concentrations used in the different centres, three groups of patients were defined (Table 1): group I, PPD 0.5% pet. (range 0.45–0.5% pet.); group II, 0.4% pet. (range 0.36–0.44% pet.); and

group III, 0.35% pet. (range 0.33–0.35% pet.). Samples of the patch test preparations applied in the different centres were analysed at the quality laboratory of Almirall Hermal.

Patch tests with the diluted PPD preparations were applied on the medial side of the left upper arm, with the exception of one centre, where the patch tests were applied on the right side of the upper back (near the shoulder). Patch tests were placed so that the patients themselves were able to observe the patch test site. Eight-millimetre Finn Chambers® on Scanpor® tape (Epitest, Tuusula, Finland) were used by all participating centres.

Centres were allowed to apply patch test substances either for 24 hr or for 48 hr, according to their usual practice. Patch tests were read on D1 to D3 (D4) and D2 to D3 (D4), respectively; additional late readings were performed on D7, D14, and D21. Patients who were not able to return for all scheduled late readings were telephoned on D7, D14, and D21, and questioned about reactions at the patch test sites. Patients were instructed to perform daily self-examination from D4 onwards, and to return immediately to the clinic if a reaction became visible.

Patch test results were considered to be positive if at least a + reaction according to the criteria of the International Contact Dermatitis Research Group and the DKG (9, 10) was observed at D3 and/or D4 or at one of the late readings. Patch test reactions occurring 7 days after patch test application or later are, in this study, defined as late reactions. Late reactions that occurred at D10 or later and then became early positive [up to D3 (D4)] at retesting were considered to be active sensitizations. Among the late reactions, data analysis of early patch test reactions was based on reactions at D3. In 6 cases, reactions at D4 (altogether, D4 readings were performed in 126 patients) were analysed instead of the D3 readings [4 PPD-negative patients not read at D3, and 2 patients with positive reactions (+ and ++, respectively) at D4, but negative at D3].

If the D3 reading was missing and no reading was performed at D4, or if one of the late readings was not available, unless an unequivocal positive reaction had occurred, data were discarded from evaluation.

Patch test results and clinical history data were documented, anonymized, and then recorded in the database of the Information Network of Departments of Dermatology (IVDK, Göttingen).

Data analysis was performed with SAS™ software (version 9.2; SAS Institute, Cary, NC, USA).

Differences in proportions of disjunct subgroups of patients were tested for statistical significance with Fisher's exact test or chi-square test, where appropriate. A *p*-value of 0.05 was regarded to be significant.

Table 1. *p*-Phenylenediamine patch test concentrations and exposure time

Group	Patch test concentration (%)	Number of patients tested (%)		Σ
		Exposure time of 24 hr	Exposure time of 48 hr	
I	0.5	274 (16.4)	333 (20.0)	607 (36.4)
II	0.4	251 (15.1)	548 (32.9)	799 (48.0)
III	0.35	67 (4.0)	193 (11.6)	260 (15.6)
Σ		592 (35.5)	1074 (64.5)	1666 (100)

Table 2. Positive patch test reactions to different *p*-phenylenediamine (PPD) patch test concentrations with different exposure times on D3/D4

Patch test results	Group I (PPD 0.5% pet.), no. (%)			Group II (PPD 0.4% pet.), no. (%)			Group III (PPD 0.35% pet.), no. (%)			All patients, no. (%)
	24 hr	48 hr	Σ	24 hr	48 hr	Σ	24 hr	48 hr	Σ	24 or 48 hr
Negative	269 (98.2)	325 (97.6)	594 (97.9)	249 (99.2)	53 (97.1)	781 (97.7)	61 (91.0)	185 (95.9)	246 (94.6)	1621 (97.3)
?	0	1 (0.3)	1 (0.2)	0	4 (0.7)	4 (0.5)	0	1 (0.5)	1 (0.4)	6 (0.4)
+	4 (1.5)	1 (0.3)	5 (0.8)	1 (0.4)	5 (0.9)	6 (0.8)	5 (7.5)	2 (1.0)	7 (2.7)	18 (1.1)
++	1 (0.4)	3 (0.9)	4 (0.7)	1 (0.4)	2 (0.4)	3 (0.4)	1 (1.5)	1 (0.5)	2 (0.8)	9 (0.5)
+++	0	2 (0.6)	2 (0.3)	0	5 (0.9)	5 (0.5)	0	4 (2.1)	4 (1.5)	11 (0.7)
ir	0	1 (0.3)	1 (0.2)	0	0	0	0	0	0	1 (0.1)
Σ	274 (100)	333 (100)	607 (100)	251 (100)	548 (100)	799 (100)	67 (100)	193 (100)	260 (100)	1666 (100)
Σ (+, ++, +++)	5 (1.8)	6 (1.8)	11 (1.8)	2 (0.8)	12 (2.2)	14 (1.8)	6 (9.0)	7 (3.6)	13 (5.0)	38 (2.3)

ir, irritant reaction.

All patients in whom the standard series was applied, 1838 altogether, were included; data of 172 patients (9.4%) had to be discarded from the evaluation. All participating patients gave informed consent prior to inclusion. The study was reviewed and approved by the recognized Ethics Review Committee.

Results

Description of subgroups

Data of 1666 patients [1069 women (64.2%) and 597 men (35.8%)] were evaluable. Subgroups of patients selected for data analysis according to the actual PPD concentration were as follows: group I comprised 607 patients [387 women (63.8%) and 220 men (36.2%)] group II comprised 799 patients [508 women (63.6%) and 291 men (36.4%)] and group III comprised 260 patients [174 women (66.9%) and 86 men (33.1%)]. Patch tests were applied for 24 hr in 45.1%, 31.4%, and 25.8%, and for 48 hr in 54.9%, 68.6%, and 74.2%, of the patients in groups I, II, and III, respectively. The proportions of females and males did not differ significantly between the subgroups ($p = 0.60$), whereas there was a significant difference in the proportions of exposure times ($p < 0.0001$). Table 1 gives an overview of the exposure time distribution in the three subgroups of patients with different PPD patch test concentrations.

Early positive reactions [D3 (D4) readings]

PPD elicited positive patch test reactions in 38 patients (2.3% of 1666 patients): 13 reactions were observed in patients who had a 24-hr patch test exposure time (2.2% of 593 patients), and 25 in patients with a 48-hr exposure

time (2.3% of 1074 patients). The proportion of positive reactions did not differ significantly between these two groups ($p = 0.86$).

Significantly more positive reactions occurred in patients who were tested with the lowest concentration of PPD ($p = 0.005$) than in the other two subgroups of patients. In group III, 13 early positive patch test reactions occurred in 260 patients tested [5.0%; 95% confidence interval (CI) 2.7–8.4%]; in group I and group II, 11 of 607 (1.8%; 95% CI 0.9–3.2%) and 14 of 799 patients (1.8%; 95% CI 1.0–2.9%), respectively, had an early positive reaction to PPD. In none of the three groups did the proportion of early positive reactions to PPD differ significantly between the respective subgroups with different exposure times (Table 2). In groups I–III, the reaction index ranged from 0.55 to 0.86, and the positivity ratio from 43 to 54% (data not shown in detail). However, owing to the limited numbers of non-negative reactions in the separate subgroups, the significance of these data is limited.

Late positive reactions (D7 readings and beyond)

In 8 patients, positive patch test reactions did not appear before the late readings (Table 3). Late reactions were observed in 3 of 607 patients of group I (0.49%), and in 5 of 799 patients of group II (0.63%); no late reactions were observed in group III.

All but one late reaction occurred in patients in whom the exposure time was 48 hr. Thus, the proportions of late positive reactions were 1 of 592 patients with a 24-hr exposure time (0.17%), and 7 of 1074 patients with a 48-hr exposure time (0.65%). The difference was not statistically significant ($p = 0.27$). There were no positive

Table 3. Late patch test reactions to *p*-phenylenediamine (PPD)

Patient no.	Sex, age (years)	Occupation	Exposure to PPD*	Exposure time (hr)	Patch test concentration (%)	Patch test results					
						D1	D2	D3	D7	D14	D21
1 [†]	Male, 29	Mechanic	?	48	0.4	ND	—	—	—	—	+
2	Female, 44	Office clerk	?	24	0.5	—	—	—	—	+	+
3	Female, 37	Physician	Former patch test (negative)	48	0.4	ND	—	—	—	—	+
4	Male, 61	Retired	?	48	0.5	ND	—	—	—	+	ND
5 [‡]	Male, 57	Gardener	Hair dye (no skin reaction)	48	0.5	ND	—	—	—	+	++
6	Female, 24	Nurse	Hair dye (no skin reaction)	48	0.4	ND	—	—	—	+	+
7	Female, 47	Nurse	?	48	0.4	ND	—	—	—	+	+
8 [‡]	Male, 60	Parquet flooring fitter	Former patch test (negative)	48	0.4	ND	—	—	—	—	++

ND, no reading performed.

*All patients were exposed to dark clothes without having had any complaints.

Additional patch test readings were performed on D4–D6 ([†]) and on D4 ([‡]), and gave negative results.

Table 4. Patch test reactions in retested patients with late patch test reactions to *p*-phenylenediamine

Patient no. (see Table 3)	Patch test	Exposure time (hr)	Patch test concentration (%)	D1	D2	D3	D7	D14	D21
1	First test	48	0.4	ND	—	—	—	—	+
	Retest	48	0.4	ND	—	—	—	—	—
2	First test	24	0.5	—	—	—	—	+	+
	Retest	24	0.5	—	—	+	ND	ND	ND
4	First test	48	0.5	ND	—	—	—	+	ND
	Retest	48	0.5	ND	+	++	ND	ND	ND
5	First test	48	0.5	ND	—	—	—	+	++
	Retest	48	0.5	ND	+	++	ND	ND	ND
8	First test	48	0.4	ND	—	—	—	—	++
	Retest	48	0.4	ND	+	++	ND	ND	ND

ND, no reading performed.

patch test reactions at D7, and no doubtful reactions were observed at D7 and D14, respectively. At D21, only one doubtful reaction was observed. This patient was negative at all other readings. No retest was performed.

In 5 of the 8 patients with a late patch test reaction, retesting was performed (Table 4). In 1 patient (patient no. 1), retesting, which was performed after 13 months, gave negative results; 4 patients had a positive reaction at D2 and/or D3 (retesting in 1 patient 6 months later, and retesting in 3 patients 1 month later). Three patients belonged to group I and 1 patient to group II. As all of the 3 patients of group I who had a late reaction at the first patch test were retested, and all of them reacted positively at D2 and/or D3, it can be stated that, in group I, 3 of 607 patients tested with PPD 0.5% pet., representing 0.49%, had probably been actively sensitized by patch testing. In group II, only 2 of 5 patients with late reactions underwent retesting. One of these 2 patients had an early patch test reaction at retesting. This could mean, in the best case, that only 1 of 799 patients in this group had probably been actively sensitized (0.13%); in the worst case, it might have been 4 patients (0.50%).

Discussion

Patch test reactions occurring 7 days after patch test application or later are regarded as late reactions (11). Late reactions have been described for several allergens, for example corticosteroids, gold, neomycin, and PPD (11, 12). Late reactions, for example to gold salts, may appear after 10 days (13, 14), and late reactions to PPD can occur rarely even on D14 or later (8). Late reactions may develop as a result of the properties of the particular allergen ('late reactor') or because of an individual reaction pattern, but they may also reflect patch test sensitization. Traditionally, a negative patch test reaction followed by a flare-up after 10–20 days at the patch test site means that the sensitization was induced by the patch test procedure (11, 14). Recently, we showed in a prospective study that PPD 1% pet. elicited late reactions in 1.5% (21 of 1428) of patients tested. Of the 21 patients with a late reaction, 7 were retested, and 5 of these (71.4%, 95% CI 29.0–96.3%) had an early patch test reaction to PPD 1% pet. on this occasion. In the present study, late reactions were observed in 8 of a total of 1666 patients, that is 0.48%, which is significantly less than

1.5% ($p = 0.0047$). As late reactions in the present study exclusively occurred in patients tested with PPD 0.5% pet. and PPD 0.4% pet., respectively (group I and group II), but not in those patients tested with PPD 0.35% pet. (group III), it seems justified to calculate the proportion of late reactions related to these two subgroups only. This would mean that 8 of 1406 patients (0.57%) of groups I and II had a late reaction, which is still significantly less than the 1.5% of late reactions observed with PPD 1% pet. ($p = 0.0235$). In 20 of 21 patients with late reactions to PPD 1% pet. and 7 of 8 with late reactions to PPD 0.4% pet. or PPD 0.5% pet., respectively, the patch test occlusion time was 48 hr. Thus, elicitation of late reactions seems to depend on the patch test concentration and probably also on patch test duration (the difference between 24 and 48 hr of exposure was statistically significant only for PPD 1% pet.). A similar observation, although on a different time scale, has been made for elicitation of early patch test reactions to PPD. McFadden et al. (15) observed a positive reaction in 11 of 16 PPD-allergic individuals who were exposed to PPD 1% pet., and in 2 of 9 individuals who were exposed to PPD 0.01% pet. for 120 min. After reduction of the exposure time to 15 min, only 6 of 16 and 0 of 9 subjects were found to react to PPD 1% pet. and 0.01% pet., respectively. Hextall et al. (16) also showed that a positive patch test reaction to PPD is directly proportional to exposure time: application of PPD 1% pet. for 5, 15, 30 and 120 min, respectively, elicited positive reactions in 16%, 38%, 50% and 69% of the individuals. A similar direct relationship was found between the concentration of PPD and response: after 120 min, 22% of patients had responded to PPD 0.01% pet., and 69% to PPD 1% pet.

Because significantly fewer late reactions occurred after lowering of the patch test concentration to PPD 0.4% pet. and 0.5% pet. respectively, it may be concluded that active sensitization was also significantly reduced. However, patch test sensitization is proven if, on being repeated, the patch test reaction becomes early [up to D3 (D4)] positive (14). In the present study, 4 of the 5 patients (80%) with late reactions who were retested had a positive reaction within 3 days. This was not significantly different from the 71.4% of patients with late reactions who became early positive on retesting with PPD 1% pet. This means that the proportion of active sensitization among late reactions elicited with PPD 0.5% pet. and 0.4% pet., respectively, is in the range of the proportion of active sensitization among late reactions elicited with PPD 1% pet. Thus, lowering the patch test concentration of PPD to a range of 0.36–0.5% pet. really results in a reduction in the proportion of patients sensitized by patch testing, as the proportion of late reactions was significantly reduced. Induction

of sensitization (under patch test conditions) and elicitation of a patch test reaction depend on the dose per unit area (17). Thus, increasing the dose per unit area results in a higher proportion of sensitization to a certain allergen. Theoretically, this may occur even if a constant patch test concentration is applied by loading the Finn Chamber® with a higher amount of the patch test preparation. Avoiding overdosing of the Finn Chambers® is part of good clinical practice, and standard within the DKG and IVDK, but a certain variability in the amount of patch test preparation placed into the chamber may occur. However, the results of our study do not suggest that variability in loading the Finn Chambers® had an influence on the proportion of late reactions: 5.0% of the patients reacted on D3/D4 to the lowest concentration (PPD 0.35% pet.), which was significantly more than with the higher PPD concentrations (0.4% pet. and 0.5% pet., respectively). If this had been caused by 'over-loading' of the Finn Chambers®, one would expect a proportion of patients of group III to be actively sensitized, as active sensitization was observed in group II and the patch test concentrations of groups II and III were close together. However, this was not the case, as no late reactions were observed in group III.

Apart from patch test sensitization, three alternative mechanisms may be taken into consideration that theoretically could explain why a late patch test reaction is followed by an early positive reaction at retesting: (i) boosting; (ii) technical variation; and (iii) biological fluctuation.

1. Boosting. A pre-existing sensitization may be boosted by application of the first patch test, which then may result in accelerated reaction dynamics at retesting. This is very difficult to discriminate from active sensitization.
2. Technical variation. Recently, Bruze et al. (18) showed that the amount of the patch test preparation applied to the test chamber varied with the technicians, resulting in different doses per unit area. As elicitation reactions are dose-dependent (17), it is conceivable that, if a smaller amount of the patch test preparation is loaded onto the Finn Chambers® at the first patch testing than at the second, the elicitation reaction evolves earlier during the latter. However, it is very unlikely that, in our study, a consistently higher amount of the patch test preparation was loaded onto the Finn Chambers® at retesting. Moreover, Memon and Friedmann (19) showed, in nickel-allergic individuals, that there were no differences in the intensity scores of reactions for chambers loaded with 5 mg or more of a 5% nickel sulfate-containing ointment. Thus, as long as an adequate quantity

of the ointment containing the antigen is applied, reproducible results are obtained (17).

3. Biological fluctuation. In the present study, only patients in whom a late reaction had occurred were retested; thus, a late/early reaction pattern was investigated, which, if observed, is regarded as evidence for active sensitization (11). However, the possibility cannot be excluded, because of intra-individual fluctuation of the biological response, that opposite dynamics may also occur; thus, patients who show an early patch test reaction (at D3 and/or D4) to a certain allergen reveal a late reaction (early/late pattern) on repeating of the patch test under the same conditions (patch test preparation, test site, etc.). Analysing both reaction patterns may give additional evidence for active sensitization, namely whether the late/early reaction pattern is significantly more common than the early/late reaction pattern.

Lowering the patch test concentration may result in decreased sensitivity of diagnostic patch testing. In the patch test population of the IVDK, the frequency of sensitization to PPD when tested in the standard series ranged between 4% and 5% over time (20, 21). In our previous study with PPD 1% pet. a sensitization rate of 3.2% was observed. In comparison, 5.0% of the patients reacted on D3/D4 to the lowest concentration (PPD 0.35% pet.) applied in the present study. In contrast to their capacity to cause patch test sensitization, PPD 0.4% pet. and PPD 0.5% pet. elicited positive patch test reactions in only 1.8% of the patients on D3 (D4), which was significantly less than with PPD 0.35% pet. It has been shown that there is marked inter-individual variability in elicitation of a reaction to PPD on patch testing with regard to both the exposure time and the concentration required (15, 16). Therefore, the possibility cannot be excluded that the individuals in group III had low elicitation thresholds, so that nearly half of them reacted with a ++/+++ reaction to PPD 0.35% pet. In 1984, PPD base 1% pet. was replaced by PPD dihydrochloride 0.5% pet. in the baseline series. This led to fewer positive reactions. This was attributed to PPD dihydrochloride rather than to the reduced patch test

concentration (22). In a dose–response study, 15 PPD-sensitive individuals were tested with a serial dilution of PPD in concentrations of 0.0001–1% pet. (6). Patch tests were applied for 48 hr; 87% of the PPD-sensitive individuals reacted to PPD 1% pet. and PPD 0.5% pet., respectively, and PPD 0.1% pet. elicited positive reactions in 80% of the individuals tested. Malik et al. (23) also reported that concentrations of PPD of <1% detected contact allergy in a sizeable proportion of PPD-allergic patients. Moreover, in patients with a history of using temporary black henna tattoos, patch testing with PPD 1% pet. often results in unacceptably strong blistering reactions (24). Therefore, it was proposed to apply PPD 0.01% pet. in highly sensitized individuals, and this can elicit sufficiently positive reactions (24). Thus, at present, it can be concluded neither from the published literature nor from the present study that a significant or clinically relevant proportion of allergic reactions to PPD will be missed if the patch test concentration of PPD is lowered from 1% pet. to 0.35% pet.

Active sensitization is regarded as one of the most, if not the most serious, adverse reaction(s) to patch testing. Consequently, the risk of missing possibly clinically relevant contact allergies has to be judged against the risk of patch test sensitization (14). There is a consensus that PPD is an important allergen that should be tested in the baseline series; however, the most appropriate patch test concentration is still under discussion. The European Society of Contact Dermatitis and others recommended keeping PPD 1% pet. in the baseline series (25–27), whereas others have suggested reducing the patch test concentration of PPD to 0.3% pet. (28). Our investigation supports our previous findings, and indicates that even PPD 0.4% pet. and 0.5% pet. may cause active sensitization, especially if the exposure time is 48 hr. Reduction of the exposure time to 24 hr would be impractical for many clinics (26). From the present study, it may be concluded that patch testing with PPD 0.35% pet. is probably safe with regard to the risk of active sensitization. Therefore, the DKG would prefer the latter patch test concentration for screening purposes if this lower concentration will not miss a relevant proportion of patch test reactions; intra-individual patch testing of PPD 1% pet. with PPD 0.3–0.35% pet. is required to determine this.

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