

The risk of active sensitization to PPD

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Para-phenylenediamine (PPD) and para-aminoazobenzene are strong sensitizers. By the patch test procedure, the patient may be sensitized to these agents. Combined testing of para-compounds may increase the risk of active sensitization. We studied the % of positive patch test reactions and their relevance. In order to assess the risk of active sensitization, we compared the % of relevant reactions of both early (2/3 days) and late (7 days) reactions. We also compared the percentage of positive patch test reactions to PPD and their relevance if simultaneously tested with para-aminoazobenzene. We studied the patch test reactions to PPD in the routine series in 2058 patients. In a group of 678 patients we tested PPD and para-aminoazobenzene simultaneously. 4.3% and 3.1% of the patients reacted to PPD, respectively, with and without simultaneous testing with para-aminoazobenzene. We estimated the reactions as relevant in 21.1% and 39.7%, respectively, with and without simultaneous testing with para-aminoazobenzene. We considered none of the late reactions as relevant. We found a high proportion of relevant patch test reactions to PPD, but sensitization to PPD by the patch test procedure is a risk. We state that routine series should not contain PPD. The high number of irrelevant late positive reactions strongly suggests active sensitization. Moreover, PPD is not a ubiquitous allergen and can be tested on a non-routine basis if industrial exposure to para-compounds is suspected or if a specific localization (e.g., head or feet) prompts the testing of PPD. Testing PPD combined with para-aminoazobenzene does lead to a slight increase in positive reactions to PPD ($p < 0.25$) and to an increase in irrelevant reactions ($p < 0.10$).

Key words: PPD; para-aminoazobenzene; patch testing technique; active sensitization; clinical relevance. © Munksgaard, 2001.

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Para-phenylenediamine (PPD) is used in dyes for hair, fur, leather, printer's ink, fax machines, photographic products, X-ray film fluids and lithography. Para-aminoazobenzene is mainly used as a dye in the textile and clothing industry. These compounds are strong sensitizers. By patch testing, a subject may be sensitized to these agents. Late reactions may be an indication of active sensitization (1) and may be an argument for deleting a compound from standard series. A higher frequency of irrelevant late reactions compared to the rate of irrelevant reactions after 2–3 days (D) may also be an argument for active sensitization. Combined testing of para-compounds may increase the risk of active sensitization.

We studied the % of positive reactions and the relevance of positive early and late patch test reactions to PPD, with and without simultaneous patch testing with para-aminoazobenzene, in order to assess the risk of active sensitization to PPD.

Materials and Methods

We studied 2058 patients, aged 8 to 85 years, patch tested with PPD in the period September 1995 –

September 1999 at the Department of Dermatology of the University Hospital Nijmegen, The Netherlands, retrospectively (Group 1). PPD was tested as 4-phenylenediamine free base at 1.0% pet., the standard series PPD. The tests were performed using van der Bend patch test chambers, affixed with Fixomull Stretch tape. Tests were removed after 2 D and the results read according to ICDRG guidelines at D2 and D3. We advised the patients to come back later if a late reaction occurred.

We defined a positive patch test reaction as relevant if the patient had had skin contact with a para-compound and experienced worsening of the dermatitis after such contact. The localization of the dermatitis also had to correspond with the area of skin contact. We categorized the relevance of the positive patch test reactions as definite, probable or possible (2). Past relevance was also considered.

We compared the results to PPD in this group with the results to PPD in a group of 678 patients, 421 women (62%) and 257 men (38%), aged 14–79, tested with PPD and para-aminoazobenzene simultaneously between October 1992 and January 1994 (Group 2).

Table 1. Reactions to PPD evaluated according to the International Contact Dermatitis Research Group

9/1995–9/1999 (group 1)	D3		D3-D7		>D7	
	# patients	probable or definite relevance	# patients	probable or definite relevance	# patients	probable or definite relevance
+ reactions	37	15 (40.5%)	2	1 (50.0%)	3	0 (0.0%)
++ reactions	14	5 (35.7%)	1	1 (100.0%)	2	0 (0.0%)
+++ reactions	4	3 (75.0%)	0		0	

Differences in relevance were tested for significance using a χ^2 test.

Results

63 patients (3.1% of group 1), 45 women (71%) and 18 men (29%), reacted to PPD in the standard series. On D3, 37 reactions to para-phenylenediamine were read as +, 14 as ++ and 4 as +++. 3 reactions that were considered as doubtful on D3 became evident between D3 and D7, and 2 were read as + and 1 as ++ on D7. 5 patients showed late reactions (later than 7 D), 3 a + reaction and 2 a ++ reaction (Table 1).

We grouped the 63 positives into hand and foot dermatitis, dermatitis localized to the face and/or scalp, and a group with various localizations, such as the flexures, whole body, penis, external auditory canal and axillae (Table 2).

38 (60.3%) patients, 14 men and 24 women, had hand and/or foot dermatitis. In 17 of them (44.7% of 38) the positive reaction to PPD was considered to be probably or definitely relevant. 14 of them also reacted to patch tests with their own shoes. Here PPD used in dyes for leather could have been the responsible allergen. In 2 patients, both hairdressers, hair dyes seemed responsible. 1 patient had a definitely relevant reaction to the ink of a copying machine.

14 (22.2%) patients, 2 men and 12 women, had dermatitis on the face or scalp. In 8 of them (47.1%) the positive reaction to PPD was considered to be probably or definitely relevant, since there was also a positive reaction to their own hair dyes. In the group, consisting of 11 (17.5%) patients, 2 men and 9 women, with various localizations

of the dermatitis, we could not find any relevance for the positive reactions to PPD.

Probable or definite relevance in the group with hand and foot dermatitis was 44.7%, in the group with dermatitis on the face or scalp 47.1%, and in the 3rd group we could not find any relevance. The overall probable or definite relevance at D2 was 39.7% (Table 2).

In the group of 678 patients tested with PPD and p-aminoazobenzene simultaneously, 4.3% showed a positive reaction to PPD and 2.5% a positive reaction to p-aminoazobenzene.

At D2, there were 0 + reactions to p-aminoazobenzene, 3 ++ reactions and 3 +++ reactions. In this group, 11 patients returned to report a positive reaction later than 7 days, 2 with a + reaction, 8 with a ++ reaction and 1 with a +++ reaction. The % of self-reported, late reactions is 7.9% in Group 1 v 64.7% in Group 2. In the latter group, the overall probable or definite relevance was only 11.8%, because only 2 of the 17 patients had a clear history of allergic contact dermatitis from dark-colored textiles. The overall probable or definite relevance for PPD versus p-aminoazobenzene was 39.7% v 11.8%.

All of the 17 patients positive to p-aminoazobenzene also had a positive reaction to PPD. In Group 2, 12 patients were positive to PPD, but not to p-aminoazobenzene. In this group, the % positive to PPD was $([17+12]/678)$ 4.3%, with a relevance of 21.1% (Table 3).

Discussion

We found a high % of positive reactions with frequent relevance for early reactions to PPD, especially in the groups with dermatitis of the hands and feet or of the face and scalp. We found a significantly lower relevance at the 10% level in the group with late reactions to PPD (using a χ^2 test). A higher frequency of irrelevant late reactions compared to the rate of irrelevant reactions after 2–3 D is an indication of active sensitization.

The major prerequisites for a contact allergy to be clinically relevant are (1) exposure to the sensitizer and (2) presence of a dermatitis which is understandable and explainable with regard to ex-

Table 2. The 63 positives of group 1 divided into 3 groups based on the clinical appearance of the dermatitis

Localization	# patients	% patients	Probably or definitely relevant	
hands and feet	38	60.3	17	44.7%
face and scalp	14	22.2	8	47.1%
various	11	17.5	0	0%
total	63	100	25	39.7%

Table 3. Comparison of the results of the two patch test groups

Period of testing compound tested	Group 1 9/1995 – 9/1999	Group 2 10/1992 – 1/1994	
	PPD	PPD	para-aminoazo benzene
no. patients tested	2058	678	678
no. positive reactions	63	29	17
% positive reactions	3.1%	4.3%	2.5%
overall probable or definite relevance at D2	39.7%	21.1%	11.8%
self-reported late reactions	5 patients (7.9%)	2 patients (6.9%)	11 patients (64.7%)
probable or definite relevance of late reactions	0%	0%	0%

posure, and type, localization and course of the dermatitis (3).

There were no relevant patch test reactions to PPD in the 7 patients (groups 1 and 2) who self-reported a positive reaction later than 7 D. This strongly suggests that these patients were sensitized by the epicutaneous application of PPD during patch testing.

However, there is an inter-individual variability in eliciting a reaction to the PPD molecule on patch testing, with regard to both exposure time and concentration required (4). Subjects have been shown to react to lower concentrations of metabolic breakdown products of PPD than to the actual PPD molecule itself (5). This could also explain late reactions in individuals, not due to sensitization.

Arnold et al. (6) studied the effect of adding para-aminoazobenzene to the European standard series. It may increase the sensitivity of detecting contact allergy to dyes used in textile and clothing, but it also carries the risk of active sensitization.

Demands on a sensitizer in the standard series are (a) being common in the environment, (b) a contact allergy rate above 0.5–1.0% in routinely tested dermatitis patients, (c) reliable patch test results, (d) a high degree of clinical relevance and (e) minimal adverse effects (7).

Our opinion is that late positive patch test reactions to PPD may not be relevant in a large number of cases. Since it is a strong sensitizer, giving rise to active sensitization, it should be removed from the standard series.

Combined testing of para-compounds may increase the risk of active sensitization and combined sensitizations to different azo dyes, probably based both on true cross-sensitization and on simultaneous positive reactions, have frequently been described (8). However, our results do not show a significantly higher % of positive patch test reactions to PPD in the period of combined testing of the para-

compounds (4.3% v 3.1% when only PPD was tested).

We conclude that para-aminoazobenzene does not belong in a standard series and that the same can be stated for PPD. Patch test sensitization is considered the most serious adverse reaction of patch testing and therefore PPD should be tested only when indicated. The patient's history and clinical examination gives a clue to para-compounds as the responsible allergens, which then can be tested on an aimed basis.

References

1. Cronin E. *Contact dermatitis*: Edinburgh, London and New York: Churchill Livingstone, 1980.
2. Rietschel R M, Fowler J F. *Fisher's contact dermatitis*. 4th edition. Baltimore, MD: William & Wilkins, 1995: 14.
3. Bruze M. What is a relevant contact allergy? *Contact Dermatitis* 1990; 23: 224–225.
4. McFadden J P, Wakelin S H, Holloway D B, Basketter D A. The effect of patch duration on the elicitation of paraphenylenediamine contact allergy. *Contact Dermatitis* 1998; 39: 116–117.
5. Blohm S G, Rajka G. The allergenicity of paraphenylenediamine. *Acta Dermato-venereologica* 1970; 50: 51–54.
6. Arnold W P, van Joost T, van der Valk P G. Adding para-aminoazobenzene may increase the sensitivity of the European standard series in detecting contact allergy to dyes, but carries the risk of active sensitization. *Contact Dermatitis* 1995; 33: 444.
7. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White I R. Thoughts on sensitizers in a standard patch test series. *Contact Dermatitis* 1999; 41: 241–250.
8. Seidenari S, Mantovani L, Manzini B M, Pignatti M. Cross-sensitizations between azo dyes and para-amino compound. A study of 236 azo-dye-sensitive subjects. *Contact Dermatitis* 1997; 36: 91–96.

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