

Optimizing the patch-test concentration of *para*-tertiary-butylcatechol: results of a prospective study with a dilution series

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Para-tertiary-butylcatechol (PTBC), which has long been patch tested internationally at 1% and 0.5% concentrations, was recently shown to induce patch-test sensitization at the 1% patch-test concentration. In order to determine a safe patch-test concentration, we performed a prospective study with lowered patch-test concentrations. A dilution series of PTBC 0.25%, 0.1%, 0.01% and 0.001% (petrolatum, pet.) was tested on the upper back. Additionally, 0.25% PTBC was tested on the left upper arm to allow patients to carry out self-examination daily. Patch tests were read on D1–3, D7, D14 and D21 after patch-test application. Patients who were not able to return for all scheduled readings were telephoned and asked to report any reaction at the patch-test sites. 65 out of the 101 patients included completed the study. A positive patch-test reaction was observed in 4 patients during D1–D3, indicating previous sensitization. 1 patient had a doubtful reaction at D3 reading. Negative patch-test results were noted in 60 patients. None of the patients developed a positive patch-test reaction during the late readings (D7–D21). Thus, patch-test sensitization was not observed in any case. *Para*-tertiary-butylcatechol 0.25% pet. is recommended for patch testing internationally.

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Para-tertiary-butylcatechol (PTBC) is a potent allergen. As early as 1958, Matz and Blank (1), who investigated a patient with contact allergy to Thermofax copy paper, observed a positive reaction to 0.01%, 0.1% and 1% PTBC. Freeman (2) emphasized that exposure to polyester resins and oils containing PTBC at a concentration of only 0.005% could cause allergic contact dermatitis. Estlander et al. (3) showed in 2 occupationally sensitized patients that even 0.001% and 0.0005% concentrations of PTBC could elicit a positive patch-test reaction. *Para*-tertiary-butylcatechol has been patch tested internationally at 1% and 0.5% concentrations for a long time. Recently, the 1% patch-test concentration was shown to induce patch-test sensitization in a retrospective analysis (3) and in a prospective study (4). In order to determine a safe patch-test concentration, we performed a prospective study with lowered patch-test concentrations.

Patients and Methods

101 patients (82 males and 19 females) in whom patch testing of PTBC was indicated for investigation of their contact dermatitis (known or possible exposure to PTBC) were included in the study. A dilution series of PTBC 0.25%, 0.1%, 0.01% and 0.001% (petrolatum, pet.) was tested. The patch-test substances were supplied by Hermal (Reinbek, Germany). The dilution series was applied to the left side of the upper back for 24 hrs (29 patients) and 48 hrs (36 patients) respectively; additionally, 0.25% PTBC was tested on the volar side of the left upper arm to allow patients to carry out daily self-examination. Patch tests were read on D1–3, D7, D14 and D21 after patch-test application. Patients who were not able to return for all scheduled late readings were instructed to carry out self-examination and to return to the clinic if a test reaction

occurred. Additionally, they were telephoned on D7, D14 and D21 and asked about a reaction at the patch-test sites.

In addition, in 6 PTBC-allergic patients who had had a positive patch-test reaction to PTBC 1% 1.5–5 years ago, rechallenge patch testing was performed to find out if the sensitization could also be detected with the lower patch-test concentrations. Application times were identical in both patch tests.

The patch-test reactions were scored according to the criteria of the German Contact Dermatitis Research Group (5) and the ICDRG (6).

If depigmentation at the patch-test sites occurred, it was additionally recorded.

Results

Altogether, 101 patients (82 males and 19 females) were enrolled in the study. Data of 36 patients were discarded from evaluation because of protocol violation. Out of 65 patients whose data were evaluable, 41 returned for all late readings, and 24 patients who were not able to return for all scheduled late readings were asked about a reaction at the patch-test sites by telephone. 24 hrs allergen application was performed in 29 patients and 48 hrs allergen application in 36. No different results were observed in both groups, and none of the patients showed an irritant patch-test reaction. During D1–D3, a positive patch-test reaction was observed in 4 patients, indicating previous sensitization. The patch-test results are summarized in Table 1. Negative patch-test results were noted in 60 patients. 1 patient had a doubtful reaction at D3 reading, which was no longer verifiable on D4. No patient developed a positive patch-test reaction during the late readings (D7–D21).

The patch-test results of the 6 PTBC-allergic patients in whom the rechallenge testings were performed are summarized in Table 2. In patient nos. 1–3, who previously had had a + reaction to PTBC 1%, patch testing with the lower patch-test concentrations gave negative results. Patient no. 4 showed a positive patch-test reaction to PTBC 0.25% and 0.1%; patch testing with PTBC 1% 22 months ago had revealed a ++ reaction. Patient nos. 5 and 6, having previously shown a + and ++ reaction to PTBC 1%, respectively, had a ?+ reaction only to PTBC 0.25%.

None of the 65 patients developed depigmentation at the patch-test sites.

Discussion

Para-tertiary-butylcatechol is used as an antioxidant in mineral oils, as a stabilizer for styrene,

butadiene, isoprene, chloroprene and vinyl toluene, and as a polymerization inhibitor for polyester resin and polyvinylchloride (3,7). *Para*-tertiary-butylcatechol is utilized in the rubber, paint, petroleum and plastics industries, and reports on contact dermatitis in patients who were occupationally exposed to PTBC have been published (3, 8). Contact dermatitis has also been reported in patients who were exposed to PTBC used in Thermofax copy paper, phototypesetting paper and in artificial limbs (1, 2, 9, 10). Moreover, it was shown by Zimerson et al. (11) that there is a significant over-representation of simultaneous contact allergies to *para*-tertiary-butylphenol-formaldehyde resin (PTBP-F-R) and PTBC, that PTBC can be present in at least some brands of PTBP-F-R, and that, therefore, contact sensitivity to PTBP-F-R may be an indicator of a sensitization to PTBC (12). *Para*-tertiary-butylcatechol is an important allergen in patients exposed to plastics. Kanerva et al. (13) reported on patch tests performed during a 6-year period with 50–53 plastic and glue allergens in patients occupationally exposed to such materials. *Para*-tertiary-butylcatechol was positive in 8 out of 308 patients (2.6%) and held 3rd place in the rank order of the 10 most common allergens. Thus, PTBC needs to be patch tested further and a safe patch-test preparation should be available.

Although infrequent, patch-test sensitization (also termed active sensitization) is considered one of the most serious adverse reactions of patch testing (14). Patch-test sensitization means that the sensitization is induced iatrogenically because of the patch-test procedure; it is traditionally defined as a negative patch-test reaction followed by a flare-up at least 10 days after patch-test application; when repeated, the test becomes positive after as few as 2–4 days (14, 15). A patient sensitized because of the patch-test procedure generally needs to be advised to avoid the allergen concerned, though the rate at which patch-test sensitizations become clinically relevant is not known (14). Patch-test sensitization has been reported for several chemicals, e.g. acrylates (16), *para*-phenylenediamine (17) and plant allergens, e.g. *Compositae* mix (18, 19). Patch-test sensitization because of PTBC was reported for the first time by Yu et al. (20) in 1990. While investigating contact allergy to a limb prosthesis, they applied PTBC 0.1%, 0.5% and 1.0% to the flexural side of the patient's forearm for 48 hrs. 10 weeks later, the patient developed erythematous plaques at the test sites. On rechallenge with the same concentrations of PTBC 3 months later, the patient showed a vesicular patch-test reaction at the 48 hr reading. By now, patch-test sensitization because

Table 1. Results of patch testing with the dilution series in 4 patients sensitized to *para*-tertiary-butylcatechol

Patient no.	Age (year)	Sex	Test concentrations (%)	Test site	Results		
					D1	D2	D3
1	38	M	0.25	Upper back	ND	?+	+
			0.1	Upper back	ND	–	–
			0.01	Upper back	ND	–	–
			0.001	Upper back	ND	–	–
2	38	M	0.25	Left arm	ND	+	+
			0.25	Upper back	ND	+	++
			0.1	Upper back	ND	–	+
			0.01	Upper back	ND	–	–
3	49	F	0.001	Upper back	ND	–	–
			0.25	Left arm	ND	+	++
			0.25	Upper back	+	++	++
			0.1	Upper back	+	++	++
4	50	F	0.01	Upper back	–	–	+
			0.001	Upper back	–	–	–
			0.25	Left arm	–	+	+
			0.25	Upper back	–	–	+
			0.1	Upper back	–	–	+
			0.01	Upper back	–	–	–
			0.001	Upper back	–	–	–
			0.25	Left arm	–	–	+

ND = not done. Patch-test score according to the recommendations of the ICDRG (6).

of PTBC has been confirmed in 2 studies. Estlander et al. (3), in a retrospective analysis of their patch-test data collected between 1974 and 1995 at the Finnish Institute of Occupational Health, found 9 patients who were sensitized to PTBC, 5 of them considered to have been sensitized because of patch testing. To obtain more precise data on the patch-test sensitization rate of PTBC on routine patch testing, we recently performed a prospective study and found 4 of the 40 evaluable patients having been sensitized because of patch

testing with PTBC at concentrations of 1.0–0.1% (4). In 2 of these patients, it could not be excluded that 0.25% PTBC or even lower concentrations had induced patch-test sensitization. We concluded that the optimal patch-test concentration might be in the range of 0.01–0.25% PTBC. In this study, we therefore investigated a dilution series with concentrations of 0.25–0.001% PTBC to determine the safe patch-test concentration. None of the 65 patients developed a positive patch-test reaction only during the later readings.

Table 2. Rechallenge patch testing with the dilution series of *para*-tertiary-butylcatechol 0.25–0.001% in patients with positive patch tests to *para*-tertiary-butylcatechol (PTBC) 1%

Patient no.	Age (year)	Sex	PTBC (1%)		PTBC dilution series (0.25%, 0.1%, 0.01%, 0.001%)			
			Date (month/year)	Results (D3)	Date (month/year)	Results		
						D1	D2	D3
1	64	M	4/96	+	3/01	ND	–	–
2	59	M	3/98	+	3/01	ND	–	–
3	50	M	6/99	+	3/01	ND	–	–
4	39	M	3/99	++	1/01	ND	0.25% + 0.10% + 0.01% – 0.001% –	0.25% + 0.10% + 0.01% – 0.001% –
5	27	M	4/00	+	11/01	ND	–	0.25% ?+ 0.10% – 0.01% – 0.001% –
6	44	M	2/97	++	2/01	ND	–	0.25% ?+ 0.10% – 0.01% – 0.001% –

ND = not done. Patch-test score according to the recommendations of the ICDRG (6).

Thus, patch-test sensitization was not observed in any case. Internationally, patch tests are usually applied for 48 hrs, but a shorter application time may be advantageous, at least for some substances, because less false-positive irritant reactions are provoked and a higher reaction index is obtained (21, 22). As PTBC is a skin irritant (3), a 1-day application was performed in approximately 1/2 of the patients. No differences between the 1-day and 2-day patch-test groups were observed; in particular, no irritant reactions were seen in either group. Therefore, application of PTBC 0.25% (pet.) may be considered sufficiently safe for patch testing.

As a result of reducing the patch-test concentration, it should be taken into account that some cases of PTBC allergy in the future may be missed or detected later: 3 patients who had had a + positive reaction to PTBC 1% showed a negative patch-test result during rechallenge patch testing with 0.25% PTBC; in 2 patients who had had a ++ reaction to PTBC 1%, only a + reaction and a ?+ reaction to PTBC 0.25% respectively were observed. Thus, in some cases, weak sensitizations may not be detected when applying the lowered concentration. On the other hand, patch testing is often performed several times by different investigators. If a patch test becomes positive because the patient has been patch-test sensitized in the past, it may be difficult to determine the relevance of such a result, if exposure to the allergen is possible but neither definitely known nor ruled out. Concerning PTBC, in the future, one may expect less patch-test reactions of unexplained relevance, because positive patch-test reactions originating from patch-test sensitization are minimized by applying the 0.25% concentration. Generally, patch-test sensitization is considered to be an extremely infrequent adverse event of patch testing (14), but in the case of PTBC patch-test sensitization at 1% and 0.5% concentration, was presumably induced in a substantial number of patients. In accordance with Estlander et al. (3), we recommend patch testing with PTBC 0.25% pet. internationally.

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