

Patch tests with thiurams at 0.25% pet. and 1% pet. are of equal diagnostic value

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Thiuram mix is tested in the standard series at a test concentration of 1% pet. The single thiurams (DPTD, TMTD, TMTM, TETD), however, are usually tested at 0.25% pet. in Germany. In other countries, the individual components of thiuram mix are tested at 1% pet. The German Contact Dermatitis Research Group (DKG) compared both patch test concentrations in 530 patients in order to find out if (i) a significant number of positive patch tests are missed by testing at the lower concentration, (ii) problems with irritant test reactions occur by increasing the test concentration to 1%, and (iii) the sensitivity of the thiuram mix rises when the breakdown test is done with the higher concentration. Slightly more positive reactions were seen with the higher concentration, but this increase did not reach statistical significance. The reaction index, as a measure for the relation of positive to irritant and/or questionable reactions, remained unchanged for the individual thiurams. The sensitivity of the mix also did not change when the breakdown test was performed with 1% pet. instead of 0.25% pet. Thus, we conclude that both concentrations are of equal diagnostic value in patch testing.

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Although their use in protective gloves may possibly have declined during recent years, thiurams still are one of the most important group of rubber chemical allergens, especially in medical gloves (1–4). Thiuram mix constantly yielded about 2.5% positive reactions when tested in the standard series in Germany in recent years (5, 6). Gibbon et al. reported decreasing frequencies of sensitiza-

tion to thiurams in health care workers in the UK, from 27% in 1994 to ca. 10% in 1998 (1). In nurses, the respective percentages were 7.3% in Germany from 1992 to 1995 (4) and 6.7% in Lodz, Poland, from 1995 to 1999 (2). Although the mix composition changes with time, and new thiuram disulphides are spontaneously formed in the test preparation (7), thiuram mix as tested in the standard series indicates a contact allergy to one or more of its constituents with a sensitivity of 0.84 (95% confidence interval: 0.78–0.89), which is better than other rubber mixes, e.g. mercapto mix (8, 9). In Germany, thiuram mix consisting of tetramethylthiuram monosulphide (TMTM), tetramethylthiuram disulphide (TMTD), tetraethylthiuram disulphide (TETD), and dipentamethy-

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lene disulphide (DPTD) is usually tested at 1% in petrolatum (pet.) (<http://www.ivdk.gwdg.de/dkg/dkgblo.html>). The individual thiurams, however, are tested at 0.25% pet. In other countries, a concentration of 1% pet. is used for patch testing the individual components of the thiuram mix (10). The German Contact Dermatitis Research Group (DKG) undertook a study comparing patch test preparations of thiurams at 0.25% pet. and 1% pet. to find out if (i) a significant number of positive patch tests are missed by using the lower concentration, (ii) problems with irritant test reactions occur by increasing the test concentration to 1%, and (iii) the sensitivity of the thiuram mix rises when the breakdown test is done with thiurams at 1% pet. instead of 0.25% pet.

Materials and Methods

In all, 8 departments of dermatology, members of the DKG and of the Information Network of Departments of Dermatology (IVDK) (<http://www.ivdk.gwdg.de>, 11), took part in the study. During the period from November 1999 to December 2000, 530 patients with suspected rubber allergy were patch tested with thiuram mix 1% pet. and the thiurams contained in the mix at 0.25% pet. and 1% pet. whenever the rubber series was applied. Allergen preparations were supplied by Hermal (Trolab, Reinbek, Germany). Patch tests were performed in accordance with internationally accepted guidelines (12). Test reactions were documented following the recommendations of the International Contact Dermatitis Research Group (ICDRG) with slight amendments made by the DKG (13). Patch test exposure time was 24 h in 2 centres (122 patients), and 48 h in 6 centres (408 patients). Test reactions were recorded in the participating centres and transferred to the IVDK headquarters within the IVDK routine procedure (14). For this study, test reactions at day 3 (D3) were evaluated.

Data were analysed using the statistical software SAS 8.1 for Windows (SAS Institute, Cary, NC, USA). A preliminary data analysis revealed no substantial differences between centres with 24 h and 48 h patch test exposure, so we decided to present the complete data as a whole in this paper. Sensitivity and specificity of the mix patch test for detecting a contact allergy to one or more of its components were calculated from the corresponding 2×2 tables and supplemented by the exact 95% confidence intervals (CI) computed using the binomial distribution. In comparing reaction frequencies between different concentrations of the same allergen in the same group of patients, the exact McNemar test was used. The resulting *p*-

values reported throughout this paper were two-sided, those of <0.05 being regarded significant. Reaction indices were calculated according to the method suggested by Brasch & Henseler (15).

Results

In the study sample, 36 patients (6.8%) had a positive reaction to thiuram mix. 33 patients (6.2%) reacted to at least one thiuram at 0.25% pet. and 36 patients (6.8%) to one or more thiurams at 1% pet. This difference was not statistically significant ($p = 0.18$). Clinical relevance was confirmed in 22 out of the 33 patients with positive reaction(s) (67%) to thiuram(s) at lower concentration(s), and in 23 out of the 36 patients (64%) reacting to thiuram(s) at 1% pet. In 13 patients, the patch test with the higher concentration of at least 1 thiuram was positive at D3, while the lower concentration of the same thiuram led to an erythematous, slightly irritant or negative reaction. The opposite occurred in 3 patients. Both phenomena were seen at the same time in one patient. Test reactions to thiuram mix and to the individual thiurams at 2 concentrations are shown in Table 1. This presentation is reaction-orientated; the count of patients as mentioned above cannot be read from this Table, because several patients had reactions to more than 1 thiuram. With DPTD and TMTD, the increase in erythematous, doubtful (questionable) and/or slightly irritant reactions outweighed the gain in positive reactions, thus leading to a slightly lower reaction index. The opposite occurred with TMTM and TETD.

Table 2 shows a comparison of patch test reactions to the two tested concentrations of each thiuram. With the exception of TMTD, with all thiurams, slightly, albeit not significantly, more positive reactions were observed with the higher test concentration. However, it was not a simple general gain in positive reactions: in some patients, the test with 0.25% DPTD, TMTD, or TETD became positive while the test with the same thiuram at 1% remained negative or doubtful. The breakdown tests with thiurams at 0.25% pet. and 1% pet. gave the following results (see Table 3). With 0.25% pet., the sensitivity of the mix was $28/33 = 0.85$ (95% CI: 0.68–0.95), and its specificity 0.99. In this setting, the prevalence of the disease (expressed as positive reactions to 1 or more single thiurams) was 6.2%, and the prevalence of the positive mix test was 6.8%. With thiurams tested at 1% pet., the sensitivity of the mix was $31/36 = 0.86$ (95% CI: 0.71–0.95), and its specificity 0.99 (disease prevalence 6.8%, prevalence of the positive test 6.8%).

Table 1. Patch test reactions at D3

Allergen	Concentration	Reactions				% Positive reactions	Reaction index
		Neg.	?/irr.	+	+ +/+ + +		
DPTD	0.25% pet.	518	3	7	2	1.7%	0.5
	1% pet.	514	5	8	3	2.1%	0.4
TMTD	0.25% pet.	510	4	11	5	3.0%	0.6
	1% pet.	509	5	12	4	3.0%	0.5
TMTM	0.25% pet.	503	9	11	7	3.4%	0.3
	1% pet.	500	9	10	11	4.0%	0.4
TETD	0.25% pet.	500	5	16	9	4.7%	0.7
	1% pet.	499	2	17	12	5.5%	0.9
Thiuram mix	1% pet.	486	8	18	18	6.8%	0.6

Table 2. Test reactions to individual thiurams at 0.25% pet. vs 1% pet

		1% pet.			McNemar test
		Positive	Neg.,?, irr.	Total	
DPTD 0.25% pet.	Positive	7	2	9	$p = 0.41$
	Neg.,?, irr.	4	517	521	
	Total	11	519	530	
TMTD 0.25% pet	Positive	14	2	16	$p = 1.0$
	Neg.,?, irr.	2	512	514	
	Total	16	514	530	
TMTM 0.25% pet.	Positive	18	0	18	$p = 0.08$
	Neg.,?, irr.	3	509	512	
	Total	21	509	530	
TETD 0.25% pet.	Positive	24	1	25	$p = 0.10$
	Neg.,?, irr.	5	500	505	
	Total	29	501	530	

Discussion

The comparison of patch test results with thiurams at 0.25% pet. and 1% pet. showed that only a slight, insignificant increase in positive reactions is observed with the higher test concentration. The share of clinically relevant reactions was about the same with both test concentrations (0.25% pet. 67%; 1% pet. 64%). The assessment of the clinical relevance of a positive patch test reaction depends to a great extent on the investigator's knowledge of the allergen and curiosity, and on the patient's ability to report their individual exposure. This is why this item usually has a certain variability in multicentre studies (16, 17). However, regardless of whether this share reflects reality, there is no convincing evidence of an undue increase in irrelevant positive reactions with the higher test concentration. On the other hand, clearly no excessive numbers of relevant positive patch tests are missed by testing at the lower concentration.

While in 14 tests (13 patients) without positive reaction to a thiuram at 0.25% pet., a positive reac-

tion with the higher concentration was seen (see Table 2), the opposite occurred in 5 tests (3 patients). These differences can easily be explained by non-reproducibility of the patch test (18), and are no proof of diagnostic superiority for the higher test concentration. On the other hand, as can be seen from the fact that no consistent decrease in the reaction index was observed when the test concentration was increased, patch tests with

Table 3. Breakdown tests of the thiuram mix

Thiuram mix 1% pet.	Single thiurams 0.25% pet.		
	Positive	Neg.,?, irr.	Total
Positive	28	8	36
Neg.,?, irr.	5	489	494
Total	33	497	530
Thiuram mix 1% pet.	Single thiurams 1% pet.		
	Positive	Neg.,?, irr.	Total
Positive	31	5	36
Neg.,?, irr.	5	489	494
Total	36	494	530

thiurams at 1% pet. do not generally have the disadvantage of more questionable or irritant reactions. The reaction index for both concentrations was positive, i.e. within an acceptable range known from other standard allergens (19). The sensitivity of the thiuram mix in this study was the same as calculated from a study in 1990–1993 (8). Virtually no difference was observed when comparing sensitivity and specificity of the mix calculated on the basis of 0.25% pet. or 1% pet. patch tests.

One has to keep in mind that all results presented here are based on a relatively small effective sample size. Although we included 530 patients in the study, only those with a non-negative reaction, i.e. about 10% of the recruited sample, are informative with respect to the study objective. It therefore cannot be excluded that the slight differences between the patch test results obtained with individual thiurams tested at 0.25% pet. and 1% pet. would become statistically significant with a larger number of patients being tested. However, as the differences are rather small, they do not seem to be important for the diagnostic quality of thiuram patch tests. Therefore, we do not plan to extend the study.

As a secondary result of this study, the good diagnostic properties of the thiuram mix, i.e. its good reaction index and its high sensitivity and specificity in detecting contact allergies to individual thiurams, were confirmed. Thus, thiuram mix in its present form can be recommended as a screening test substance in the standard series.

Conclusions

Patch testing with individual thiurams at 0.25% pet. and 1% pet. revealed no superiority of either concentration concerning (i) percentage of positive reactions, (ii) reaction index, or (iii) sensitivity of the thiuram mix on breakdown testing. Thus, we conclude that both concentrations are of equal diagnostic value in patch testing.

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