

Patterns of simultaneous patch test reactions to thiurams and dithiocarbamates in 164 patients

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Summary

Background. Thiurams and dithiocarbamates are structurally related sensitizing rubber accelerators.

Objectives. To study patterns of simultaneous patch test reactions to thiurams and dithiocarbamates at the Finnish Institute of Occupational Health in 1991–2015.

Methods. We searched the patch test files for patients with allergic reactions to thiuram mix, its four components, and three dithiocarbamates, and analysed patterns of simultaneous reactions to these test substances.

Results. We found 155 patients who reacted positively to at least one thiuram or dithiocarbamate in the rubber chemical series. Thirty-four (22%) of these patients reacted positively to some dithiocarbamate derivatives. Twenty-one reacted positively to zinc dimethyldithiocarbamate, 20 to zinc diethyldithiocarbamate, and 1 to zinc dibutyldithiocarbamate. All dithiocarbamate-allergic patients reacted positively to some thiurams, and their thiuram reactions were often strong or extreme positive. Nine thiuram mix reactions turned out to be false-positive reactions, without reactions to the constituents, and 24 patients showed false-negative reactions to thiuram mix during the same time period.

Conclusions. Dithiocarbamate contact allergy was always connected to thiuram allergy. Screening dithiocarbamate allergy with carba mix thus appears to be unnecessary, but ways to improve the present thiuram mix should be investigated. Meanwhile, individual thiurams are best for diagnosing contact allergy to these accelerators.

Key words: 1,3-diphenylguanidine; contact allergy; screening; thiuram mix; zinc dibutyldithiocarbamate; zinc diethyldithiocarbamate; zinc dimethyldithiocarbamate.

Thiurams and dithiocarbamates are chemically related accelerators used in the vulcanization of rubber. Gloves constitute the main source of contact allergy to rubber chemicals (1). In the 1990s, the use of dithiocarbamates instead of thiurams in the manufacture of rubber gloves was recommended (2). Today, dithiocarbamates are the

predominant accelerators in these products (3–6). Some decline in the frequency of allergic reactions to thiurams has been seen in Denmark and the United Kingdom (2, 7), but no change was seen in a large Information Network of Departments of Dermatology (IVDK) study (8), in which the patterns of reactions to various rubber chemicals also remained unchanged.

Two recent European studies (9, 10) found an increase in the prevalence of allergic reactions to carba mix, and the authors proposed the reintroduction of this rubber chemical mix to the European baseline series. As a response, we want to report the results of 25 years of testing with the individual components of thiuram mix and carba mix at the Finnish Institute of Occupational Health (FIOH). In this retrospective analysis, we focused

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on patterns of concomitant allergic reactions to thiurams and dithiocarbamates.

Patients and Methods

We performed the patch tests with Finn Chambers® (Smart Practice, Phoenix, AZ, USA), in accordance with the recommendations of the ICDRG. We read the tests two or three times: on D (D) 2, D3 and D4, on D2, D3, and D6, or on D2 and D5, depending on the day of application (Monday, Tuesday, or Wednesday). We also asked patients to tell us whether they had noticed new reactions after the final reading. All patients patch tested at the FIOH have a suspected occupational skin disease. They come from all parts of Finland. Many of them have been patch tested in local hospitals prior to investigations at the FIOH.

Thiuram mix (1% pet.; Trolab Almirall Hermal, Reinbek, Germany) was tested in the baseline series. The components of thiuram mix, tetramethylthiuram monosulfide (TMTM) (CAS no. 97-74-5), tetramethylthiuram disulfide (TMTD) (CAS no. 137-26-8), tetraethylthiuram disulfide (TETD) (CAS no. 97-77-8) and dipentamethylenethiuram disulfide (PTD) (CAS no. 94-37-1) were purchased from Chemotechnique (Vellinge, Sweden), and tested 1% pet. in the rubber chemical series. Zinc dibutylthiocarbamate (ZDBC) (CAS no. 136-23-2), zinc diethylthiocarbamate (ZDEC) (CAS no. 14324-55-1) and zinc dimethylthiocarbamate (ZDMC) (CAS no. 137-30-4) were also purchased from Chemotechnique, and also tested 1% pet. Between November 2007 and December 2011, ZDEC and ZDBC were tested in the baseline series instead of the rubber chemical series. ZDMC, however, was tested in the rubber chemical series throughout the study period.

We searched the files for all patients with allergic reactions to thiuram mix, TETD, TMTM, TMTD, PTD, ZDEC, ZDMC or ZDBC during a 25-year period from 1991 to 2015. We only included patients who had been tested with the rubber chemical series; that is, we excluded patients who had reacted positively to thiuram mix in the baseline series, but had not been tested with the rubber chemical series.

1,3-Diphenylguanidine (1,3-DPG) (CAS no. 102-06-7) has been tested in the rubber chemical series at two concentrations – 1% pet. (Chemotechnique) and 0.33% pet. (diluted at the FIOH from the commercial test preparation) – since March 2014.

Results

During the study period, 5194 patients were patch tested at the FIOH, and 1478 of these were patch tested with the rubber chemical series. Of these, 164 patients reacted

positively to thiuram mix or some individual thiuram or dithiocarbamate, and were included in the study group.

Between November 2007 and December 2011, when ZDEC and ZDBC were included in the baseline series, 527 patients were tested with the baseline series and 144 patients with the rubber chemical series. Three (0.6%) patients had allergic reactions to ZDEC, and all of these reacted positively to thiuram mix and TETD. During this time period, we observed no reactions to ZDBC.

The study group comprised 155 patients who reacted positively to at least one individual thiuram or dithiocarbamate, and 9 patients who reacted positively to thiuram mix but did not show allergic reactions to any of its components. The latter reactions were considered to be false-positive reactions to thiuram mix (7.3% of 123 thiuram mix reactions).

One hundred and twenty-three patients in the study group reacted positively to thiuram mix. However, the total number of thiuram mix-positive cases in the study group was 140, as 17 of them were not tested with thiuram mix at the FIOH, because of a previous allergic reaction to thiuram mix in a local hospital. During the study period, 15 patients with allergic reactions to thiuram mix were not tested with the rubber chemical series at the FIOH, because their thiuram allergy had only past relevance. These patients were not included in the study group.

Eleven patients had negative results with thiuram mix, but showed allergic reactions to some components of the mix. Another 11 patients had doubtful reactions to thiuram mix, and 2 patients had irritant reactions to thiuram mix, but reacted positively to at least one component. Thus, the total number of these false-negative reactions was 24 (17% when related to the total number of thiuram mix-positive cases, $n = 140$). One hundred and fifteen patients reacted positively to TMTM, 81 reacted positively to TETD, 66 reacted positively to TMTD, and 36 reacted positively to PTD. A total of 57 (86%) of the TMTD-allergic patients reacted positively to TMTM.

The study group included 34 patients (21%) with an allergic reaction to at least one dithiocarbamate. Twenty-one patients reacted positively to ZDMC, 20 reacted positively to ZDEC, and 1 reacted positively to ZDBC. The patch test reactions of these patients are shown in Table 1. It is noteworthy that all patients with ZDEC allergy reacted positively to the corresponding thiuram disulfide, namely TETD, and that all ZDMC-allergic patients reacted positively to one of the corresponding thiuram sulfides, namely TMTM or TMTD. Our rubber series did not include thiuram sulfides corresponding to ZDBC, tetrabutylthiuram monosulfide (TBTM), or tetrabutylthiuram disulfide (TBTD).

Table 1. Patch test reactions to thiuram mix, its four components and three dithiocarbamates in patients reacting to a dithiocarbamate

No.	Thiuram mix	TETD	TMTM	PTD	TMTD	ZDMC	ZDEC	ZDBC
1	++	+++	+++	++	+++	+++	–	–
2	++	–	?+	–	+	+	–	–
3	++	++	++	–	++	+	–	–
4	++	–	++	–	++	+	–	–
5	NT*	++	+++	++	++	++	?+	–
6	+	NT	NT	NT	++	+	–	–
7	+	–	++	–	+	+	–	–
8	NT*	–	+++	–	+++	+++	–	–
9	++	–	+++	–	+++	+	–	–
10	+	–	+++	–	++	+	–	–
11	++	–	+	–	–	++	–	–
12	+	+	+	+	+	+	–	–
13	+++	+++	+++	+	+++	++	–	–
14	+	++	–	++	++	++	?+	–
15	+++	+++	+++	+++	+++	++	+++	+++
16	+++	+++	+++	+++	+++	+	++	–
17	++	++	+++	++	++	++	++	–
18	++	+	+	+	+	+	+	–
19	+++	+++	+++	+++	NT*	+++	++	–
20	NT*	+++	++	++	++	++	++	–
21	++	+++	+++	+++	++	++	++	–
22	+++	+++	+++	–	?+	–	++	–
23	++	++	+	+	+	–	+	–
24	++	+	++	–	–	–	+	–
25	+	++	++	+	+	–	+	–
26	+++	++	++	–	+	–	+	–
27	++	++	?+	–	+	–	++	–
28	++	+++	?+	–	–	–	++	–
29	NT*	+++	+++	?+	+++	–	+++	–
30	++	+++	–	–	–	–	+	–
31	+++	++	++	–	+	–	++	–
32	+++	+++	+	–	++	–	++	–
33	–	++	–	–	–	–	++	–
34	+++	+++	++	++	+	–	++	–

NT*, not tested because of an allergic reaction in a previous test at a local hospital; NT, not tested, previous test result unknown; PTD, dipentamethylenethiuram disulfide; TETD, tetraethylthiuram disulfide; TMTD, tetramethylthiuram disulfide; TMTM, tetramethylthiuram monosulfide; ZDBC, zinc dibutylthiocarbamate; ZDEC, zinc diethylthiocarbamate; ZDMC, zinc dimethylthiocarbamate.

The strength of the thiuram mix reactions could be evaluated in 30 dithiocarbamate-allergic patients: 9 (30%) had +++ reactions, 14 (47%) had ++ reactions, 6 (20%) had + reactions, and 1 (3%) had negative results. The corresponding figures for 117 evaluable dithiocarbamate-negative patients were: 11 (9%) +++ reactions; 61 (52%) ++ reactions; 22 (19%) + reactions; and 23 (20%) negative, irritant or doubtful reactions.

In the present study population, most patients with contact allergy to ZDEC and ZDMC had strong or extreme positive reactions to the corresponding thiurams. Of the 20 ZDEC-allergic patients, 11 (55%) had +++ reactions and 7 (35%) had ++ reactions to TETD, the corresponding thiuram disulfide. The corresponding figures were 5 (3%) and 40 (28%) for the 144 patients who did not have

allergic reactions to ZDEC. Thus, 90% of ZDEC-allergic patients had either strong or extreme positive reactions to the corresponding thiuram disulfide, whereas only 31% of ZDEC-negative patients had equally strong reactions. Similarly, of the 20 evaluable ZDMC-allergic patients, 11 (55%) had +++ reactions and 4 (20%) had ++ reactions to TMTM, whereas, of the 143 ZDMC-negative patients, only 23 (16%) had +++ reactions and 41 (29%) had ++ reactions. Thus, 75% of ZDMC-allergic patients had strong or extremely strong positive reactions to TMTM, whereas only 45% of ZDMC-negative patients had equally strong reactions.

1,3-DPG was tested in two concentrations (March 2014 to May 2016) in 76 patients: 1% pet. yielded 10 irritant reactions and 0.33% pet. yielded no reactions.

Discussion

Thiuram disulfides and dithiocarbamates constitute a redox pair, which means that, during oxidation of a dithiocarbamate, the corresponding thiuram disulfide is formed. Reduction of the thiuram disulfide restores the dithiocarbamate (11). Bergendorff et al. analysed accelerator compounds during vulcanization, and found that thiuram disulfides rarely appeared in the final rubber, even if they were added during the process. Instead, thiurams were often converted to dithiocarbamates. They may also combine with mercaptobenzothiazoles, if these chemicals are used in the process (12).

An early Danish study showed that allergic reactions to ZDEC were strongly associated with the strength of the patch test reaction to thiuram mix (13). In the IVDK study, the findings were similar: sensitization to dithiocarbamates was almost always combined with thiuram sensitization, and dithiocarbamate reactions were more common in patients with ++/+++ reactions to thiurams than in patients with weak positive (+) reactions. Approximately one-quarter of thiuram-positive patients reacted to dithiocarbamates, and almost all ZDEC-positive patients reacted to the corresponding thiuram, namely TETD (8). Our results confirmed these findings: dithiocarbamate allergy is associated with strong thiuram allergy. We found no patients with independent dithiocarbamate contact allergy. Our small screening study on 527 consecutive patients also confirmed earlier findings that contact allergy to ZDEC and ZDBC is still quite rare (14).

At the FIOH, we have a tradition of testing rubber chemical series in patients with the slightest suspicion of contact allergy, and we always test the components of rubber mixes as a requirement for the diagnosis of rubber chemical contact allergy. This is why as many as 92% of our patients with thiuram allergy were tested with the components of thiuram mix. Our patients have often (probably a great majority; no exact data available) been patch tested in local hospitals prior to our investigation, so our diagnoses of contact allergy are usually based on the final result of not only a single patch test session, but of several sessions. That is why our results are not directly comparable with other data, and we preferred to not calculate specificity or sensitivity estimates.

In the present study population, even after repetitive testing, thiuram mix still showed a surprisingly high discordance with the breakdown testing of its components: 9 (7.3%) false-positive and 24 false-negative reactions. In an early IVDK study on 222 thiuram mix-positive patients, the number of false-positive results was even higher (60/222; 27%) (15). In Germany, individual thiurams are tested at a concentration of 0.25%, whereas at the FIOH we use a concentration of 1%. This probably

explains why we see fewer false-positive test results with thiuram mix. Our approach of considering a positive reaction to a mix in combination with negative results with all of its ingredients as a 'false-positive' reaction is rather simplistic, because, in individual cases, the reactions to the components might be false-negative reactions. Unfortunately, the relevance of positive patch test reactions to rubber additives is difficult to evaluate (e.g. with use or challenge tests).

Taken together, allergic reactions to thiurams and dithiocarbamates represent the same phenomenon. It does not seem to matter whether thiurams or dithiocarbamates are used in the production of rubber items: in both cases, a sensitized patient usually shows allergic reactions to thiuram(s), and, if the contact allergy is of high grade, also to the corresponding dithiocarbamate(s). The real hapten of a thiuram/dithiocarbamate pair is unknown, but a Swedish study implied that it might contain half a molecule of the thiuram, that is, a thiocarbamate structure (16). Recently, a Swedish study on 18 thiuram-allergic patients showed that thiuram monosulfides are better markers of thiuram sensitivity than the corresponding disulfides or dithiocarbamates (11).

There is little evidence that patients are exposed to thiurams. First, thiurams are nowadays rarely added, and, even if they are added during the manufacturing process, they rarely appear in the final products (3–6, 12). It is possible that the exposure has not changed much during the past 30 years. Allergic reactions to dithiocarbamates have always been rare as compared with thiuram reactions. The fact that not much has changed in the frequency and patterns of thiuram/dithiocarbamate allergy since the 1990s would be perfectly in line with the notion that contact allergies to thiurams and dithiocarbamates represent the same phenomenon.

Allergic reactions to ZDBC were rare in the present study. This is in accordance with a previous IVDK study (14). However, ZDBC is quite commonly present in rubber gloves (3, 4, 6). The rarity of allergic reactions is possibly attributable to its relatively weak sensitizing capacity: ZDBC was a much weaker sensitizer in a modified local lymph node assay than, for example, ZDEC or ZDMC (17). It must also be taken into account that the corresponding thiurams, namely TBTM and TBTD, have not been widely tested.

Carba mix 3% pet. (1% 1,3-DPG, 1% ZDEC, and 1% ZDBC) was introduced for the screening of rubber chemical allergy in 1971 (18), but in 1988 its removal from the baseline series was recommended, owing to many irritant reactions and the need to check a positive test result by testing the individual components separately (19). Some years later, Geier and Gefeller analysed the data for 20

patients with allergic reactions to carba mix, and found that 60% of these had false-positive reactions; that is, the patients did not react positively to any of the three components (15). This is not surprising, as 1% 1,3-DPG (CAS 102-06-7) is an irritant test substance that causes mostly false-positive reactions (14). Some centres have continued to test carba mix in the baseline series, and have reported increasing frequencies of positive reactions in patch tested patients (9, 10). This might be a sign that the frequency of contact allergy to 1,3-DPG is increasing, and has caused an epidemic of contact allergy in Sweden and Belgium, owing to its use in sterile synthetic rubber gloves (20, 21).

Carba mix is an unreliable screening test substance, and, in our opinion, should now be abandoned. An allergic reaction to this mix must always be confirmed by retesting the patient with the individual components, to rule out a false-positive reaction.

We want to take a strong stand against the reintroduction of carba mix by showing that the screening of

dithiocarbamates is not necessary, because independent dithiocarbamate allergy is practically non-existent. 1,3-DPG contact allergy is best screened for as such. The present 1% concentration is clearly irritant, but a lower concentration of 0.33% (pet.) could be added to the rubber series. According to our 2 years of experience, 0.33% is not irritant.

As the few independent reactions to dithiocarbamates are mostly attributable to false-negative reactions to thiuram mix or its components, efforts could focus on improving the present thiuram mix. One possibility worth studying might be a mix of different thiuram monosulfides, which were better markers of thiuram/dithiocarbamate allergy than the corresponding thiuram disulfides or dithiocarbamates in a small Swedish study (11). This result should, of course, first be confirmed in a larger study population. At present, the best way of diagnosing contact allergy to thiurams and dithiocarbamates is to use individual thiurams, preferably at a concentration of 1%.

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