

Cross-reactivity between thiurams

ANNE LERBÆK¹, TORKIL MENNÉ² AND BODIL KNUDSEN²

¹National Allergy Research Centre, and ²Department of Dermatology, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark

Retesting with an allergen at a site with previous allergic contact dermatitis has been shown to enhance reactivity. It has been suggested that retesting with a cross-reactive allergen will also induce hyperreactivity. Concurrent sensitization to more than 1 thiuram is common, but whether this is due to concomitant primary sensitization or cross-reactivity is uncertain. The aim of this study was to investigate the use of retesting to distinguish between concomitant sensitization and cross-reactivity in the rubber chemicals tetraethylthiuram disulphide (TETD) and tetramethylthiuram disulphide (TMTD). There was a non-significant trend towards enhanced reactivity for both TETD and TMTD when testing in an area with previous allergic contact dermatitis due to TETD. Cross-reactivity between the 2 chemicals is likely, but a definite conclusion from this pilot study is not possible.

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Thiurams are chemicals used as accelerators in the production of both natural rubber latex and synthetic rubber. They are well-known human skin sensitizers, and use of rubber gloves is the commonest cause of sensitization. Thiuram mix is part of the European Standard Series and contains the following 4 compounds (each 0.25% in pet.): tetraethylthiuram disulphide (TETD), tetramethylthiuram disulphide (TMTD), tetramethylthiuram monosulphide (TMTM) and dipentamethylenethiuram disulphide (PTD) (1). Sensitization rates vary considerably over time and depend on the test population. In Europe, reported sensitization rates range from a few per cent to more than 25% (2–5). The frequency of positive patch tests to thiurams seems to be declining in Denmark (B. Knudsen, A. Lerbæk and T. Menné, submitted for publication). This may be due to improved production skills and manufacture of rubber gloves with a lesser content of thiurams or the use of alternative rubber chemicals.

Sensitization to more than 1 thiuram is frequent but not uniform, and whether this is due to concomitant sensitization or cross-reactivity is uncertain. Consequently, there is no consensus concerning how to advise patients with a contact allergy to rubber chemicals. Should contact with all thiurams be avoided or only those where the patient has a positive patch test reaction?

Labelling of rubber products is not obligatory, but manufacturers are, upon request, obliged to disclose information on rubber allergens in medical gloves for single use (6). Concomitant sensitization might occur since rubber gloves frequently contain more than 1 accelerator and cross-reactivity is theoretically plausible since the chemicals are structurally related.

Cross-reactivity among contact allergens with structural similarities is well-known. A definite distinction between cross-reactivity and simultaneous sensitization can only be made in animal experiments where the exposure factor can be strictly controlled. Knowledge in humans is based on statistical analysis of patch test data and theoretical speculations. However, there is no standardized way of differentiating with certainty between cross-reactivity and concomitant sensitization in man, since it is often difficult to obtain accurate information on previous exposure.

In a guinea-pig model, Rustemeyer et al. (7) showed that retesting with a cross-reactive allergen at a former allergic contact dermatitis reaction site caused hyperreactivity as opposed to retesting with a non-cross-reacting contact allergen. The authors suggested that a similar model could be used in man. Hindsén and Bruze (8) performed retesting with nickel at sites with former allergic contact dermatitis from nickel and

cobalt and at sites with former irritant contact dermatitis from SLS. They found increased reactivity at the site with former contact dermatitis from nickel but not at the sites with former contact dermatitis from cobalt or SLS. The method used by Hindsén and Bruze (8), for the elicitation of allergic contact dermatitis and subsequent retesting, served as a model for the present study. The aim of this study was to (1) evaluate the possible use of retesting as a way to differentiate between cross-reactivity and concomitant sensitization and (2) investigate possible cross-reactivity between TETD and TMTD.

Materials and Methods

Patients

5 participants, 4 females and 1 male, who on a prior occasion had at least a 1+ reaction to TETD and TMTD (both 0.25% pet.) were included. The local Ethics Committee approved the study, and all patients gave their informed consent. The mean age of the patients was 48.2 years (range 33–69 years). None of the included patients had ongoing eczema.

Patch testing

Participants were patch tested with TMTD 1% (pet.) (Hermal, Reinbeck, Germany) and a serial dilution of TETD (Hermal, Reinbeck, Germany) in the following concentrations: 1%, 0.5%, 0.1%, 0.01%, 0.001% and 0.0001% (pet.) on the lower left part of the back (Fig. 1a). 8 mm Finn Chambers[®] (Epitest, Tuusula, Finland) on Scanpor[®] tape (Alpharma AS, Norgesplaster Facility, Norway) was used for patch testing. Test material was removed after 2 days, and reactions were recorded after 2 and 3/4 days. Reactions were scored according to ICDRG guidelines (1). In addition, reactions were recorded by measuring the diameter (mm) of infiltration.

Induction of experimental allergic contact dermatitis

2.5 ml of the TETD dilution in the lowest concentration resulting in a 1+ reaction was evenly distributed in a thin layer on a non-adherent wound dressing, measuring 8 × 12 cm and made of cotton with an outer shell of polyester (Solvaline[®] N, Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, Germany). The dressing was fixed with adhesive tape (Mefix[®], Mölnlycke Health Care AB, Göteborg, Sweden) on the upper back above the scapula, on the left side if right-handed and vice

versa. The distance between the spine and the dressing was measured. After 2 days, the dressing was removed. On day 3, the area was inspected and the presence of at least a homogenous infiltrated erythema was assured (Fig. 1b). The area was then left to heal.

Retesting

After 1–2 months, when the area with allergic contact dermatitis was macroscopically healed, serial dilutions of TETD and TMTD were applied to the area with previous allergic contact dermatitis and to an area with unaffected skin on the opposite side of the upper back (Fig. 1c). The following concentrations were used: 1%, 0.5%, 0.1%, 0.01%, 0.001% and 0.0001% (pet.). Patch testing followed the procedure described above.

Results

For each dilution series, the total sum of recorded diameters in millimetres was calculated (x_1, y_1, x_2, y_2) (Fig. 1d). For each chemical, the values obtained from unaffected skin (x_2, y_2) were subtracted from the values obtained from the area with previous allergic contact dermatitis (x_1, y_1). The resulting differences (Δx and Δy) are presented in Table 1. Patients 1–4 had an enhanced response when retesting with TETD, and Patients 1, 2, 3 and 5 had an enhanced response when retesting with TMTD. However, the increased responses were not statistically significant using Wilcoxon rank sum test.

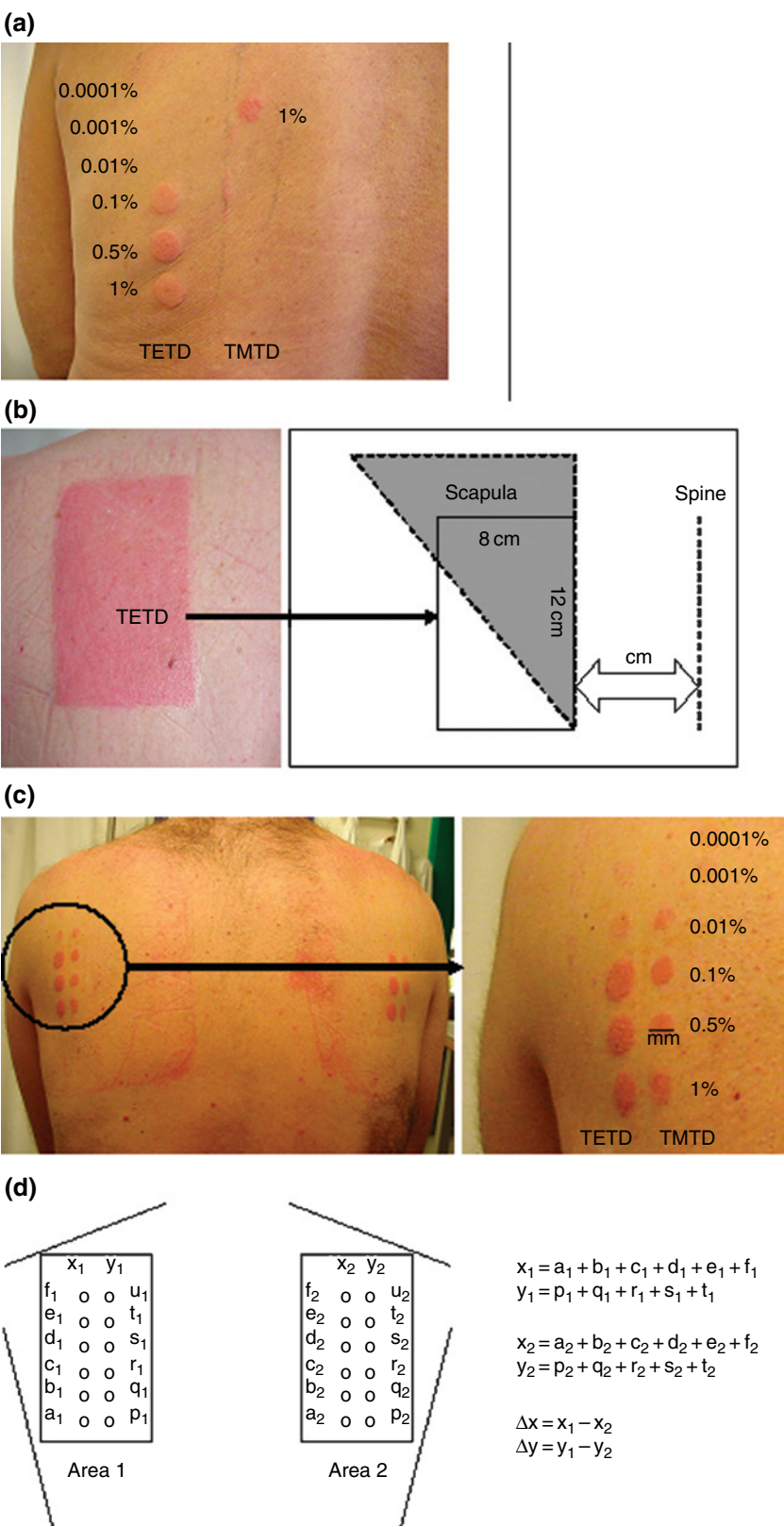
Discussion

The aim of this study was 2-sided. Firstly, we wanted to evaluate whether it is possible to assess cross-reactivity between 2 allergens using retesting in an area with former allergic contact dermatitis induced by 1 of the allergens. Secondly, we used the method to investigate possible cross-reactivity between TETD and TMTD.

The number of patients in this pilot study was limited. It was difficult to recruit patients with at least 1+ positive patch test to both TETD and TMTD, not suffering from any excluding disease, e.g. ongoing eczema, and willing to participate in an experimental study requiring up to 10 visits. The statistic possibilities were thus very limited.

Reactions were scored according to ICDRG guidelines and in addition, the diameters of reactions were measured. However, the study did not include any validation of this way of quantifying the patch test response. A duplicate testing of

Fig. 1. (a) Patch testing with tetramethylthiuram disulphide (TMTD) 1% (pet.) and tetraethylthiuram disulphide (TETD) dilution series (pet.) on the lower back. (b) Induction of experimental allergic contact dermatitis on the upper back. (c) Serial dilutions of TMTD and TETD (both pet.) on the area with previous allergic contact dermatitis and on unaffected skin on the opposite side. Diameters of positive reactions are recorded in millimetres. (d) Method of calculation. Area 1: previous allergic dermatitis; area 2: previous unaffected skin. x_1 og x_2 : TETD dilution series; y_1 og y_2 : TMTD dilution series.



patients would be preferable but was considered to be unacceptable for the patients.

Ideally, reading of the retest patch test reactions should be blinded. Assuming that the observer has certain expectations, this could influence

the scoring of reactions in both directions. Due to the relatively complicated experimental set-up, blinding was not part of the design. Blinding is, however, preferable in future research studies.

Table 1. Difference in diameter (mm) of positive patch test reactions on skin with previous allergic contact dermatitis due to tetraethylthiuram disulphide (TETD) and unaffected skin

Patient no.	Δx	Δy
1	15	20
2	14	1
3	7	11
4	1	-2
5	-9	8

Δx = difference in diameter of positive patch test reactions to TETD; Δy = difference in diameter of positive patch test reactions to tetramethylthiuram disulphide.

With this model, an increase in reactivity was expected on previous eczematous skin compared to previous normal skin, when testing with TETD. This was found in Patients 1–4, but not in Patient 5. There was no obvious explanation for the result in Patient 5. If TETD and TMTD were fully cross-reactive, an increased response on eczematous skin would also have been expected for TMTD, compared with the reactions on previous normal skin. Increase in reactivity was observed for Patients 1, 2, 3 and 5. A Wilcoxon test on the smallest number possible (5) was not significant for enhanced responses for either TETD or TMTD. It was not possible to make any statistical calculations between the increased responses for TETD compared with TMTD. From this experiment, it is not possible to conclude with certainty whether the TETD and TMTD reactivity was due to cross-reactivity or concomitant reactivity, although there seems to be a trend towards an increase in response for both compounds, indicating cross-reactivity.

An additional explanation for the insignificant result may be that some patients exhibited concomitant sensitization and some patients exhibited cross-reactivity, as cross-reactivity between the 2 chemicals may not be obligatory. Even a careful history taking on exposure or inclusion restricted to patients with a short history of allergic contact dermatitis would not enable us to differentiate with certainty between these 2 groups of patients, since exposure to multiple thiurams at the same time is frequent.

Retesting in an area with previous contact dermatitis to a different, non-cross-reacting allergen

or an irritant could have been included as control. However, Hindsén and Bruze (8) has shown that retesting with nickel at sites with previous contact dermatitis due to cobalt or SLS did not result in increased reactivity.

In conclusion, data supported the findings of Hindsén and Bruze (8) and Rustemeyer et al. (7). The data did not allow us to conclude on possible cross-reactivity or concomitant reactivity for the 2 thiuram compounds investigated. The set up may be useful in selected cases of work-related allergic contact dermatitis, when accurate knowledge on cross-reactivity versus concomitant sensitization is valuable. However, more experience with the method is necessary.

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Address:

Anne Lerbæk, MD

National Allergy Research Centre

Gentofte Hospital

Ledreborg Allé 40, 1

2820 Gentofte, Denmark

e-mail: anleso01@gentoftehosp.kbhamt.dk