

The preservative 2-(thiocyanomethylthio)benzothiazole: A potential allergen in leather products

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Abstract

Background: Allergic contact dermatitis caused by leather is common, and several responsible allergens, such as tanning agents, glues, mercaptobenzothiazole derivatives, and dyes, but also antimicrobials and antifungals, are involved.

Material and methods: Three female patients were referred to the Departments of Dermatology in a Belgian university hospital following skin reactions caused by leather products (shoes, belt, and car seats). They were patch tested with the European baseline series and samples of suspected leather products, and additionally with 2-(thiocyanomethylthio)benzothiazole (TCMTB), an antifungal agent previously reported to be a contact allergen in footwear. Chromatographic analyses of samples of all the leather materials tested were performed at the Department of Occupational and Environmental Dermatology in Malmö, Sweden.

Results: The patients reacting to the leather samples were shown to be sensitized to TCMTB, the presence of which could be confirmed by chemical analyses of samples obtained from the patients.

Conclusion: Patch tests with TCMTB should be considered in patients with contact dermatitis caused by leather items.

KEYWORDS

2-(thiocyanomethylthio)benzothiazole, allergic contact dermatitis, antifungal, antimicrobial, CAS no. 21564-17-0, chemical analysis, cross-reactions, footwear, leather, preservative

1 | INTRODUCTION

Allergic contact dermatitis (ACD) caused by leather materials is frequent, and is caused by several responsible allergens, such as chromium (tanning), cobalt salts (dyeing), *p*-tert-butylphenol-formaldehyde resin (glues), mercaptobenzothiazole derivatives, and dimethyl fumarate, octylisothiazolinone, and 2-(thiocyanomethylthio)benzothiazole (TCMTB) (antimicrobials and antifungals),¹ the last of which was involved in the three cases described here. TCMTB (CAS no. 21564-17-0) is also known as Tolcide 2230 (Santa Cruz Biotechnology, Dallas, Texas).

2 | PATIENTS AND METHODS

2.1 | Patients

Case 1: A 15-year-old girl, with no history of personal or familial atopy, presented with eczematous dermatitis located at three different body sites, namely, on the backs of the feet, 2 days after she had started wearing a new pair of shoes, on the abdomen underneath her leather belt, and on the backs of both thighs; the last of these had started shortly following the first contact with the leather seat of her father's new car (Figure 1).

Case 2: A 34-year-old woman, suffering from atopic dermatitis, presented with an erythematous and squamous eruption limited to the

FIGURE 1 Allergic contact dermatitis in case 1 on the backs of the feet, caused by shoes (A), and on the thighs, caused by a leather car seat (B)



upper and back sides of both thighs (Figure 2), which had appeared following repeated contact with the leather seats of her new car.

Case 3: A 51-year-old woman, a schoolteacher, without any history of atopic dermatitis, had suffered for >3 years from dermatitis on the backs of her feet, sometimes spreading towards the legs. This appeared a few days following contact with some leather shoes, but never after contact with shoes made from canvas, other fabric, or rubber.

2.2 | Patch testing

The three patients were evaluated at the Department of Dermatology at the Cliniques universitaires Saint-Luc in Brussels, Belgium, and patch tested with the European baseline series (Chemotechnique Diagnostics,

Vellinge, Sweden and/or Allergeaze, SmartPractice, Phoenix, Arizona). Additional series were also tested, that is, a rubber, a plastic and a glues series (patients 1-3), and a dye and (meth)acrylate series (patient 2); all allergens were from Chemotechnique Diagnostics and/or Allergeaze. The patients' own materials (tested "as is," humidified with physiological saline and fixed on acrylic tape) were also tested: in case 1, a sample of the leather belt, the leather interior part of a shoe and a sample of the leather car seat provided by the car company were tested; the last of these was also tested in case 2; in case 3, pieces of different parts of the interior leather of shoes (sole and counter) were tested.

The preservative TCMTB (obtained at 90% purity from Toronto Research Chemicals, North York, Ontario, Canada), prepared in 0.1% pet. by the Department of Occupational and Environmental Dermatology in Malmö, was tested on a second occasion, after its identification by chemical analyses. From January 2018 to January 2019, 12 other dermatitis patients were patch tested with the same test substance, TCMTB 0.1% pet., and these may be regarded as control subjects. Patch tests were applied on the upper back, and occluded for 2 days with IQ Ultra test chambers from Chemotechnique Diagnostics; they were fixed with Fixomull stretch (BSN Medical, Hamburg, Germany). Readings were performed on day (D) 2 and D4, according to European Society of Contact Dermatitis criteria.²

2.3 | Chemical investigations

Chemical investigations of the patients' leather items were carried out at the Department of Occupational and Environmental Dermatology in Malmö. Acetone extracts of the belt from case 1, the piece of car seat leather provided by the car company from case 2, and a shoe from case 3 were analysed with gas chromatography-mass spectrometry (GC-MS).³ For these analyses ~10 g of each material was extracted in acetone in an ultrasonic bath for 5 minutes. The extracts were then evaporated to a volume of 0.5 mL with a rotary evaporator before being analysed with GC-MS. The National Institute of Standards and Technology (Gaithersburg, Maryland) library of mass spectra was used for identification of substances.

Quantitative analyses of TCMTB were performed with a high-performance liquid chromatography (HPLC) method suitable for



FIGURE 2 Allergic contact dermatitis in case 2 on the posterior sides of the thighs, caused by leather car seats

TABLE 1 Demographic data, test series and allergens tested, and patch test results for the three patients examined

Patients	Age (y)	Sex	2-(Thiocyanomethylthio)benzothiazole 0.1% D2/D4	Pieces of leather products D2/D4	Baseline series D2/D4	Additional series D2/D4
1	15	F	++/+++	Belt ++/++	–	P&G: –
				Shoes ++/+		Rubber: –
2	33	F	+ / ++	Car seat –/+	–	P&G: –
						Rubber: –
						MA: –
						Dye: –
3	51	F	–/?+	Four different shoes +/++	PTBP-FR +/+	P&G: –
						Rubber: –

Abbreviations: F, female; MA, (meth)acrylate series; P&G, plastic and glues series; PTBP-FR, *p*-tert-butylphenol-formaldehyde resin.

**FIGURE 3** Positive patch test reaction to 2-(thiocyanomethylthio)benzothiazole 0.1% (++++) in case 1 (day 4 reading)

identifying allergens in rubber items,⁴ as 2-mercaptobenzothiazole (MBT) and other chemically related benzothiazole derivatives are easily analysed in this system.

3 | RESULTS

Patient characteristics and patch test results are shown in Table 1. All three patients reacted positively to TCMTB 0.1% pet.; one patient had an extreme positive reaction (+++) (Figure 3), one patient had a strong positive reaction (++) , and one patient had a doubtful reaction

(?+). All three reacted positively to the individual leather samples tested (seat car, pieces of belt, and/or shoes). Among the 12 control subjects tested with TCMTB 0.1% pet., none reacted positively.

According to GC-MS analyses TCMTB was present in the car seat leather, and in the leather belt, the latter also containing octylisothiazolinone. Possible traces of TCMTB were also observed in the extract of the shoe from case 3. HPLC analysis did not show any known contact allergens apart from TCMTB. The retention time of TCMTB was 12 minutes, and it showed an ultraviolet spectrum that is characteristic for sulfur-bound mercaptobenzothiazoles. By comparison of the areas in the chromatograms, we determined the concentrations of TCMTB to be 0.017 mg/g in the belt from case 1, 0.250 mg/g in the leather sample of the car seat from case 2, and 0.005 mg/g in the shoe from case 3. In no other samples could TCMTB be detected under the conditions used, with an estimated detection limit of 0.001 mg/g. The results of the HPLC analyses are summarized in Table 2.

4 | DISCUSSION

Three patients suffering from ACD caused by leather goods are reported. Besides many other allergens responsible for ACD caused by leather,^{1,5} antimicrobials and antifungals are also potential culprits. In the past, dimethyl fumarate was responsible for an epidemic of ACD, owing to its presence in small sachets that are used during the storage and transport of leather goods, such as shoes⁶ and sofas⁷ imported from China, in particular. More recently, Vandevenne et al⁸ described methylisothiazolinone, present in leather care products for sofas, as the

TABLE 2 Results of chromatographic analysis of the leather products involved

Patients	Leather products analysed with CG-MS	Presence of 2-(thiocyanomethylthio)benzothiazole
1	Belt	0.017 mg/g
2	Car seat	0.250 mg/g
3	Shoes	0.005 mg/g

GC-MS, gas chromatography-mass spectrometry.

responsible allergen in a case of severe ACD mainly located on the posterior sides of the thighs. Moreover, other isothiazolinone derivatives, such as octylisothiazolinone, have also been implicated as responsible allergens in leather goods, that is, sofas, belts, and shoes.⁹⁻¹¹ The GC-MS analysis of the belt from case 1 showed the probable presence of octylisothiazolinone, but the patient did not react positively to it. Testing with leather items sometimes gives positive results, but no sensitizing culprits can be identified, either when testing is performed with the European baseline series or when it is performed with additional series. Hence, chemical analyses of the leather products may be useful to identify the responsible allergens, for example, TCMTB in the cases described here, as it was detected in three of the leather articles that had caused ACD.

TCMTB is a fungicidal biocide used during the leather-tanning process, because it inactivates the growth of fungi encountered in tanneries, that is, *Aspergillus flavus*, *Aspergillus niger*, *Peecilocyces variotii*, *Trichoderma viridi*, and *Penicillium* spp. It has been used in leather since the emergence of legislation placing restrictions on the use of phenols (including pentachlorophenol).¹² In a Belgian study carried out in the Department of Dermatology at the KU Leuven university hospital in Leuven between 1990 and 2001, TCMTB was considered to be the second most frequent allergen in leather footwear¹: during this period, 781 patients suffering from foot dermatitis were tested with TCMTB, of whom 37 had positive reactions to it, 27 of these being cross-reactions with mercapto-mix and/or mercaptobenzothiazole. However, because of the subsequent lack of this test chemical, no data on its frequency are available for the period 2002 to 2015. Since 2016, 12 patients have been tested with TCMTB obtained from the Malmö department, and two positive cases were observed.

In 2007, Domingo et al.¹³ reported a case of ACD on the hands and wrists of an employee manipulating wood packaging that had previously been treated with a varnish containing a 30% concentration of TCMTB as the active wood preservative, that is, Mirecide-TC/45-Glicolo (Lamirsao, Terrassa, Spain). Patch tests performed with serial dilutions (1:100, 1:200, and 1:400) of TCMTB in pet. gave positive results; the authors recommended a patch test concentration of 1% in pet.¹³ Because MBT is a metabolite produced by degradation of TCMTB, cross-reactions with MBT may be observed.¹ However, our analyses could not detect MBT in the leather samples. The dermatitis in the three patients sensitized to TCMTB eventually resolved after cessation of contact with the causal leather objects.

In conclusion, we present three patients suffering from ACD caused by leather goods who had positive patch test reactions to the antifungal agent TCMTB. Chemical investigations showed the presence of TCMTB in the leather samples obtained from them. Patch testing with TCMTB should thus be considered in patients suspected of having leather dermatitis, particularly as the chemically related MBT or mercapto mix do not always cross-react. Therefore, its inclusion in the shoe series is suggested.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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