

CONTACT POINTS

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Primary sensitization to cinnamyl chloride in an operator of a pharmaceutical company

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It is known that if an irritant chemical is also a contact allergen, a single skin exposure may induce primary sensitization (1). Several examples have been reported in the literature, and the sensitizing exposure may be accidental, such as to the tear gas chemicals—omega-chloroacetophenone and ortho-chlorobenzylidene malonitrile—, occupational, as with many chemicals including epoxy resins and acrylates, and via patch testing, for example with the mixture of methylchloroiso-thiazolinone and methylisothiazolinone (2–4). Moreover, even non-primary irritants such as *p*-phenylenediamine in temporary tattoos, which may contain very high concentrations (up to 15–20%) of this allergen (5), are perhaps nowadays the most frequent causes of primary sensitization after one single exposure, often in children, with potential cross-sensitization to azo dyes used in textiles such as Disperse Orange 3 (6).

Contact with chemicals causing skin burns, followed by primary sen-

sitization, particularly occur in chemical and pharmaceutical laboratories and industries where workers may be accidentally exposed to allergenic, very chemically reactive intermediates (7).

Regarding the mechanisms of primary sensitization, it has been hypothesized that primary sensitization and subsequent flare-up of dermatitis or patch test sites, without further contact with allergen, result either from allergen or from T-cell retention at the contact site. This has been confirmed by experimental studies in humans (8).

Case Report

A 31-year-old operator in a pharmaceutical company presented to us because of severe dermatitis. 2 weeks previously, he had splashed a liquid, used in the synthesis of a pharmaceutical active compound and consisting of cinnamyl chloride (formed by interaction of cinnamyl alcohol, hydrochloric acid, and sodium carbonate), on his left cheek, left and right hands, and trousers. To prevent a chemical burn, the product was immediately washed off with water and soap and neutralized with Diphoterine® (Prevor, Valmondois, France) spray (an active eye and skin

decontamination solution), so he only developed a slight redness at the contact sites.

However, 10 days later, he developed acute itching lesions, i.e. redness and swelling at exactly the same locations but spreading to the arms and, 1 day later, also to his scrotum, the thighs, and upper legs. His general practitioner gave him an intramuscular injection with a corticosteroid and prescribed him a local treatment with betamethasone dipropionate cream twice daily, as well as systemic antihistamines. Thereupon, the lesions on the cheek, hands, and arms almost cleared completely, but the dermatitis localized on the legs extended, which, when he consulted us 4 days later, presented as sharply demarcated erythematous infiltrated plaques at the anterior side of both upper and lower legs, accompanied by erythema-multiform-like lesions on the thighs (Fig. 1). We prescribed again oral therapy with corticosteroids, i.e. methylprednisolone (starting dose of 32 mg a day, which was decreased with 8 mg every 4 days) and ranitidine as a stomach protective agent as well as antihistamines. Local treatment was initiated with mometasone-furoate lipophilic cream once a day and application of a moisturizing cream. 1 month later, only a slight residual pigmentation



Fig. 1. Primary sensitization 2 weeks after accidental exposure to cinnamyl chloride.

was noted and all treatment could be stopped.

The patient was otherwise in good health and did not take any other medication. There was no history of contact allergy; the personal atopic history was positive for hay fever.

Patch testing was performed with the European standard series, components of the materials he had brought with, namely his soap and shower gel (semi-open tests), Diphoterine® spray (as is), cinnamyl chloride 0.5% ethanol, and cinnamyl alcohol 0.5% and 2% pet. He showed a 1+ reaction (D3) to *Myroxylon pereirae* (balsam of Peru), a 1+ (D2) and 2+ (D3) reactions to cinnamyl alcohol 0.5% pet., a 2+ reaction (D2 and D3) to cinnamyl alcohol 2% pet., and a 3+ reaction (D2 and D3) to cinnamyl chloride 0.5% ethanol, the latter presenting as a combined contact allergic (papules and infiltration spreading outside the patch test area) and irritant reaction (sharply demarcated vesiculobullous reaction under the chamber).

Discussion

According to the safety data sheet obtained from the pharmaceutical company involved, cinnamyl chloride (synonym 3-chloro-1-propenyl benzene) (Fig. 2) is a light-yellow to brownish liquid with a pH of 4 (at 0.2 g/l), known to be irritant to the eyes, skin, and airways, however, not as a potential sensitizer. Cinnamyl chloride may, upon skin contact, again be hydrolyzed and form cinnamyl alcohol and hydrochloric acid, the latter being responsible for the partly irritant aspect of the patch test reaction.

Whereas cinnamyl chloride is a reactive electrophilic hapten reacting covalently to skin proteins to form the complete allergen, cinnamyl alcohol is not a protein-reactive molecule but is a so-called 'prohapten' that requires oxidative metabolic activation to the protein-reactive cinnamic aldehyde to become sensitizing, being a more potent skin sensitizer than cinnamyl alcohol as determined by *in vivo* and *in vitro* tests. Such activation could presum-

ably be performed by cutaneous oxidoreductase enzymes such as alcohol dehydrogenase or cytochrome P450 2E1, which are known to be present, predominantly in the epidermis of human skin (9).

Cinnamyl alcohol, a widely used fragrance and flavouring agent, occurs in many natural products among which *M. pereirae* (balsam of Peru) (10), also provoked a positive patch-test reaction in this case.

Conclusion

Thus, this patient suffered from an occupationally induced primary sensitization to cinnamyl chloride following accidental exposure and a (weak) chemical burn 2 weeks previously causing skin damage and, hence, enhanced skin penetration of the allergen, with cross-reaction to cinnamyl alcohol and balsam of Peru containing the latter.

To our best knowledge, this is the first described case of primary sensitization to cinnamyl chloride.

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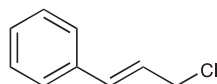


Fig. 2. Chemical structure of cinnamyl chloride.