

The rôle of coumarin in patch testing

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Coumarin (2-oxo-1,2-benzopyran; 1,2-benzopyrone; cis-o-coumaric acid lactone; coumarinic anhydride; tonka bean camphor; CAS-91-64-5; Fig. 1) is a naturally occurring substance with a sweet, herbaceous, warm, somewhat spicy odor. It is used in many cosmetic products as a fragrance or as a masking agent and as a flavouring agent in food and tobacco (1, 2).

Patients and Methods

We reviewed the case notes of patients with positive reactions to coumarin and examined which other fragrance markers (fragrance mix, balsam of Peru and colophony) in the European standard series were positive in these patients, and whether a positive reaction to coumarin had additional value in establishing contact allergies in these patients. Coumarin has been part of our additional standard series for many years and is also a component of our series of fragrances and balsam of Peru-related chemicals and products. The fragrance and balsam of Peru series are added to investigate further possible cases of fragrance and flavouring allergy. Coumarin was usually tested at 5% in pet., although 8% was used as well for a short period. We retrospectively studied the case notes of patients, tested in our department from 1978 until the end of 1997, who had positive patch test reactions to coumarin.

Results

About 14,000 patients were patch tested in our department. Of these, 58 patients had positive ($\geq +$) reactions to coumarin (Table 1). 38 of these 58 patients also had positive reactions to other fragrance markers, leaving 20 patients with positive reactions to coumarin alone. The presentations of these 58 patients included hand and foot eczema, eczema on all other parts of the body, urticaria, and prurigo. The clinical relevance of the positive reactions to coumarin in the 20 patients with positive reactions to coumarin alone, who showed a variety of clinical patterns, was difficult to establish. Nevertheless, positive reactions to coumarin were considered to be an indicator of fragrance allergy. All 58 patients were warned about the use of fragranced toiletries and cosmetics.

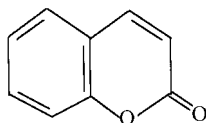


Fig. 1. Structure of coumarin.

Discussion

Nowadays, mainly synthetic coumarins are in use (1, 2). Hepatotoxic effects have been described in rats and dogs, but its effects in humans are not clear. The use of coumarin in food has long been forbidden in the USA, Japan and many European countries (1, 2). In a study in The Netherlands, coumarin was found in 80% of the 112 cosmetic products examined, with levels varying from 6–9500 mg/kg; the highest levels were found in perfumes and aftershaves (3). Synthetic coumarin was also found in cosmetic products claiming to contain only natural ingredients (4).

The sensitizing capacity of derivatives of coumarin was investigated by Hausen et al. (5–7) who found that coumarin itself was not capable of sensitizing guinea pigs. Photomaximization tests showed that topically applied coumarin was not a primary photosensitizer (8). Are patients, therefore, primarily sensitized by a coumarin derivative and do they react because of cross-sensitivity to coumarin (8–10)? Studies in patients suspected of fragrance allergy all show a low % of reactions to coumarin, varying from 0% to 1.2%: these patients were all considered to be fragrance-allergic (11–14). Coumarin 5% pet. has been shown to be a safe concentration, though 8% pet. has also been used without problems (14). The clinical pattern of coumarin contact allergy is comparable to the pattern of fragrance or cosmetic allergy, most commonly axillary, facial, including the eyelids, neck, hands, wrists and behind the ears (13–15).

Coumarin was the only positive marker of fragrance allergy in 20 of our 58 patients. These reactions would have been missed if coumarin had not been part of our additional standard, fragrance, and balsam of Peru series. Although the clinical relevance in our patients was not always clear-cut, positive reactions to coumarin can give additional value.

Table 1. Patients with positive reactions to coumarin, patch tested between 1978 and 1997, and their reactions to the fragrance mix, balsam of Peru and colophony, in relation to the strength of the reactions to coumarin

	Coumarin ++/+++ (n)	Coumarin + (n)	Total (n)
n=38			
fragrance mix (FM)	3	7	10
balsam of Peru (BP)	9	7	16
colophony	2	1	3
FM+BP	3	6	9

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Occupational contact sensitization to corticosteroids

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Contact sensitization to topical glucocorticosteroids usually occurs during topical treatment of skin diseases (1–3).

Case Report

A 58-year-old woman had worked as a pharmacist for over 30 years. Her work had included handling and manufacturing of *ex tempore* corticosteroid creams and ointments for over 10 years, which had been done with bare hands. She had no previous history of skin disease and denied any medical use of topical corticosteroids prior to her present problem. During a winter skiing vacation, she suffered from mild sunburn on the face. As treatment, she applied betamethasone-17-valerate and hydrocortisone creams. Use of the latter cream caused worsening and spreading of her skin lesion. She presented to dermatologic outpatients, where topical corticosteroid use was discontinued.

She was patch tested with a standard series and was found to react to balsam of Peru and fragrance mix. Additionally, she reacted to a 1:10 mixture of Pivalone® nasal spray and ethanol (eth.), suggesting hydrocortisone allergy (3). In a corticosteroid patch test series, reactions to hydrocortisone (2.5% eth.), hydrocortisone-17-butyrate (1% eth.) and Pivalone containing tixocortol

pivalate (as is and as a 1:10 mixture in eth.) were seen. Intradermal (i.d.) tests with 0.05 ml of hydrocortisone succinate (20 mg/ml), methyl prednisolone (12.5 mg/ml) and prednisolone (25 mg/ml) resulted in allergic reactions (4). I.d. tests with 0.05 ml betamethasone (4 mg/ml), dexamethasone (5 mg/ml) and triamcinolone (10 mg/ml) were negative.

Based on these results, the patient was challenged orally with 0.75 mg, 2.5 mg and 8 mg betamethasone on 3 consecutive days. No reactions occurred and she was advised to use betamethasone if there was a need for topical, intralesional, oral or intravenous corticosteroids. Her current work did not require handling of corticosteroid creams or ointments and she was advised not to handle them any more.

Discussion

This case demonstrates the possibility of occupational contact sensitization to topical corticosteroids in pharmacy work. It seems that hydrocortisone, which showed allergic reactions in this patient, is one of the most allergenic corticosteroids (5). Handling of corticosteroids, or other biologically active or potentially allergenic medicaments and bases, should not be done with direct skin contact.