

Sesquiterpene lactone mix contact sensitivity and its relationship to chronic actinic dermatitis: a follow-up study

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In a retrospective case note analysis over a 4-year period, 0.9% of all patients tested with a standard patch test series (65 of 7600) were demonstrated to have clinically relevant responses to a sesquiterpene lactone (SQL) mix. Of these patients, 11 (17%) also had a diagnosis of chronic actinic dermatitis. This group made up 25% of all patients diagnosed as suffering from CAD in this 4-year period. These figures differ somewhat from those reported by our group in an initial 4-year period immediately following the introduction of the mix into our standard patch test series, when 1.5% of all patients tested had a clinically relevant response to the SQL mix, including 36% of all patients with a diagnosis of CAD. It is not uncommon for the prevalence of sensitivity to an allergen to be overestimated immediately following its introduction into routine testing. Possible reasons for our findings are discussed.

Key words: allergic contact dermatitis; chronic actinic dermatitis; Compositae; patch testing; photosensitivity; sesquiterpene lactones; plants. © Munksgaard, 1998.

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Chronic actinic dermatitis (CAD) (1), also known as the photosensitivity dermatitis and actinic reticuloid syndrome (2), is a rare, chronic and disabling photodermatosis which is more common in men. It is characterized by eczema predominantly of the light-exposed sites, with or without lymphoma-like changes, and increased photosensitivity with altered morphological responses to UVB (280–315 nm), sometimes also UVA (315–400 nm) and occasionally also visible radiation.

The pathogenesis of CAD is poorly understood, but is likely to be immunologically based, both clinically and histologically resembling allergic contact dermatitis. Of patients with CAD, some have no apparent predisposing factors, while others have had a preceding photoallergic contact dermatitis, some atopic or other endogenous eczema, and many have associated, often multiple, contact allergies (3). In particular, attention has been drawn to a possible association between CAD and allergic contact dermatitis from Compositae (4, 5).

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Plants of the Compositae (Asteraceae) family have long been recognized as an important cause of contact dermatitis. They are commonly found in gardens and as house plants, as well as being widely distributed in nature, and include chrysanthemums, dahlias, sunflowers, dandelions, thistles and cornflowers, and the vegetables lettuce, endive and artichoke. The main allergenic constituent of these plants, accounting for cross-sensitization between the different species, are the sesquiterpene lactones (SQLs) (6). SQLs are also found in plants of the Lauraceae (bay tree) and Jubulaceae (liverwort) families. Although there are many SQLs, a 0.1% mix of 3, costunolide, dehydrocostus lactone and alantolactone, each with different sesquiterpene lactone skeletons, are now included in the European standard series as a probe for Compositae dermatitis, with a low risk of provoking an irritant response or active sensitization (6). The prevalence of Compositae dermatitis as detected by this mix is, however, lower than that detected by non-commercially available plant extracts and Compositae mix (7–9).

In a previous report we looked at results of patch testing with this mix over the 4-year period

immediately following its introduction into the St John's Institute of Dermatology standard series (1988–1992), and found that 36% of all patients with a diagnosis of CAD also had a positive response to the SQL mix (10). This confirmed previously reported associations (4, 11). The prevalence was less than that reported with testing with oleoresin extracts, where positive responses were found in 47 of 55 patients with CAD (4), although the use of occlusive patch tests with oleoresin extracts in this study may have caused false-positive irritant responses (12). The prevalence was also less than that reported on testing with plant extracts, where 8 of 16 patients with summer-exacerbated dermatitis had positive responses (10 patients in this group had abnormal broad band tests to UVB±UVA, and thus presumed CAD, of whom 4 of these had positive patch test responses to plant extracts) (11).

Patterns of Compositae dermatitis include the airborne pattern which may mimic (13) or precede the onset of (14) photosensitivity. Other clinical patterns are widespread eczema or hand dermatitis alone, generally not associated with photosensitivity. In a parallel study of all contact dermatitis patients tested with the SQL mix as part of the standard series during this initial 4-year period (1988–1992), we found that 1.5% (114 of 7420 patients) had a clinically relevant response to the mix (5).

The aim of this present study was to review our findings over a subsequent 4-year period (1992–1996).

Patients and Methods

Patch tests

The sesquiterpene lactone mix (prepared and supplied by Hermal, Reinbeck, West Germany), consisting of a 0.1% dilution in petrolatum of an equal mixture of 0.033% each of the 3 purified lactones, costunolide, dehydrocostus lactone and alantolactone, was included in our standard patch test series. Patch tests were performed with 8 mm Finn Chambers under Scanpor tape applied for 2 days before removal for readings at 2 and 4 days.

The total number of patients patch tested between February 1992 and 1996 were identified by

computerized records, as were the number with responses to the SQL mix deemed to be of current clinical relevance.

CAD patients

Patients with a diagnosis of CAD referred for patch testing between February 1992–1996 were identified through their manual records and their patch test results were counterchecked against contact dermatitis clinic computerized records. The diagnosis of CAD had been made in all cases by the clinical features in association with a reduction in the minimal erythema doses to UVB and/or UVA and/or visible radiation as determined by phototesting of the unaffected skin of the back with graded doses from an irradiation monochromator (Applied Photophysics, London, model 498/01) at wavelengths between 300 and 600 nm. Incisional biopsy of lesional skin for histological analysis was not routinely performed.

Results

SQL mix positive responses

7600 patients were identified as having been patch tested over this 4-year period (Table 1). Of these, 65 had been noted to have clinically relevant responses to the SQL mix, making up 0.9% of all patients tested.

SQL mix positive responses and chronic actinic dermatitis

11 of the patients with clinically relevant responses to the SQL mix were noted to have had an additional diagnosis of CAD, making up 17% of all those with clinically relevant responses. 44 patients with a diagnosis of CAD were identified as having undergone patch testing during this 4-year period; thus, those with a positive result to the mix made up 25% of all CAD patients.

Discussion

We have shown that the prevalence of Compositae dermatitis, as assessed by a positive and clinically relevant result to testing with a SQL mix, in the 4

Table 1. Prevalence of SQL mix positive responses: initial (5, 8) and follow-up findings

	1988–1992	1992–1996
patients patch tested	7420	7600
SQL-clinically relevant response	114 (1.5%)	65 (0.9%)
patients with CAD	80	44
CAD+SQL-clinically relevant response	29 (36%)	11 (25%)
% of SQL+ve patients with CAD	25%	17%

years immediately following introduction of the mix and in a subsequent 4-year period, appears to have diminished. This reduction is not due to a reduction in the number of patients undergoing patch testing, which remains comparable in these 2 periods, but represents a true drop from 1.5% to 0.9% of all those tested (5). Although this may reflect a genuine decrease in the incidence of SQL sensitivity in the general population, intuitively, this appears unlikely.

In addition, we have shown a reduction in the number of patients with both a diagnosis of CAD and a positive patch test response to the SQL mix. Although a reduction is also observed in the total number of CAD cases diagnosed, this does not account for these observations, as a fall in the proportion of patients with CAD to have a positive patch test response to the SQL mix from 36% to 25% is also observed (not statistically significant) (10). Similarly, when one looks at all patients observed to have clinically relevant responses to the mix, the % of those with CAD is shown to have diminished from 25% to 17% (not statistically significant) (5).

Following introduction of a new (so called "new-comer") allergen into a standard series, the prevalence of sensitivity in the general population tends to be overestimated (observations reported by P. J Frosch at the Jadassohn Centenary Congress, London, October 1996). There are 2 possible explanations for this: the 1st is the possibility of observer bias in interpretation of results, as a result of enhanced interest in the particular allergen and an inadequate interpretation of results with regards to clinical relevance. This, however, is unlikely to have been the case in our studies where reactions were generally strong (rarely less than ++ in the international system). A more likely explanation for our findings is a selection phenomenon, the St John's Institute of Dermatology being a national referral centre for patients with cutaneous photosensitivity, of whom patients with suspected CAD routinely undergo patch testing. Thus, as there is a recognized association between CAD and allergic contact dermatitis and, in particular, allergic contact sensitivity to Compositae (4), this is likely to be reflected in our patch test results. Indeed, our initial studies included CAD patients referred for reinvestigation following introduction of the SQL mix as a marker for Compositae sensitivity into our standard series, thus introducing recall bias into our original cohort and likely to account for the different findings between the 2 cohorts.

25%–36% of CAD patients have been found in our studies to have allergic contact sensitivity to the sesquiterpene lactone mix. A much stronger association between CAD and Compositae dermatitis has

previously been suggested, namely in up to 86% of patients with CAD (4). It is likely that the use of unpurified plant extracts in that study may have led to false-positive irritant responses in some cases. However, it is also possible that the 0.1% sesquiterpene lactone mix may not detect all patients with Compositae dermatitis. Lovell & Rowan (8) suggested that the mix may fail to detect sensitivity to some Compositae such as dandelion. Green & Ferguson (7) found 9 of 70 patients studied to have clinically relevant responses to Compositae oleoresins, but negative responses to the sesquiterpene lactone mix. Hausen (9), reporting on the results of testing with ether extracts of Compositae plant over a 6-year period, found that 3.1% of the population in general undergoing patch testing had relevant responses, in contrast to our findings of 1.5% and 0.9%. Thus the true prevalence of Compositae dermatitis in CAD may lie somewhere between our figures and those detected by testing with plant extracts (4). Alternatively, the differences may simply reflect different exposure to Compositae; of interest, no association with Compositae dermatitis has been found in North American patients with CAD, possibly related to less exposure to Compositae plants (15).

The significance of the association between CAD and contact sensitivity to the SQL mix and other allergens is unknown. Indirect evidence suggests that CAD may reflect a delayed hypersensitivity response, conceivably to a light-induced antigen, and one may speculate that stimulation of cutaneous immune responsiveness during airborne allergen exposure may encourage simultaneous recognition of a weak endogenous photo-induced antigen formed during concomitant light exposure. A more specific rôle for Compositae in the pathogenesis of CAD is also possible: isoalantolactone has been shown to be highly reactive with DNA in solution during UVA irradiation (observations reported by V Berl, E Gimenez-Arnau and J-P Lepoittevin at the Jadassohn Centenary Congress, London, October 1996), and indirect support for a rôle for DNA in the pathogenesis of CAD has been provided by studies of the action spectrum for the induction of CAD lesions, showing it to resemble that for UV erythema where DNA is suspected to be the chromophore (16). Thus, one might speculate that an interaction between Compositae allergens and DNA in the presence of UV irradiation may alter DNA in such a way as to make it antigenic and trigger the CAD response. Further study is required to test this hypothesis.

In conclusion, this follow-up study shows a reduction in the prevalence of sensitivity to SQL mix compared to findings in the 4 years immediately after its introduction into our standard series, al-

though there remains a significant association with the presence of CAD in those who do react. We consider the present figures to be more representative of the true prevalence of SQL mix sensitivity in our population.

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