

Compositae mix is a more sensitive test for Compositae dermatitis than the sesquiterpene lactone mix

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Over the past 2 decades, Compositae dermatitis has increasingly been recognized as a cause of exposure-pattern dermatitis. The introduction of the sesquiterpene lactone (SL) mix as a screening test has contributed to this improved recognition. However, there is growing evidence that the SL mix fails to detect a substantial number of genuine Compositae allergies. We therefore investigated whether another screening reagent (the Compositae mix) might be more sensitive in detecting cases of Compositae allergy than the SL mix. Over a 1-year period, we tested 656 consecutive unselected patch test patients to both SL mix and Compositae mix. 31 patients were found to have genuine Compositae allergies. Of these, 28 had reacted to the Compositae mix but only 13 had reacted to the SL mix. The Compositae mix failed to detect only 2 genuine Compositae allergies, whereas the SL mix missed 17 such allergies. On the other hand, the Compositae mix led to 9 irritant reactions, while there was only 1 irritant reaction with the SL mix. We conclude that Compositae dermatitis is still being underdiagnosed with the current screening method, and that the Compositae mix is significantly more sensitive in detecting Compositae allergy than the SL mix.

Key words: Compositae dermatitis; sesquiterpene lactone mix; Compositae mix; allergic contact dermatitis; plants; patch testing technique. © Munksgaard, 1999.

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With over 25,000 known species, the Compositae are the 2nd largest family of flowering plants in the world. Many of Britain's most common weeds, such as dandelion, daisy or milfoil but also cultivars such as chrysanthemums or marguerites, belong to this family. It has long been known that about 200 of these plants are able to induce allergies (1). Case reports of contact allergies have appeared in the American literature as early as 1919 (2, 3). In 1939, Shelmire traced the responsible allergens to the oleoresin fraction of the plants (4). Later, these allergens have been identified as the sesquiterpene lactones (SL). Today, over 1350 SLs have been described (5) and, of these, the ones which contain an α -methylene group attached to the lactone ring seem to be most likely to lead to sensitization (6). Some authors distinguish between 6 different classes of sesquiterpene lactones (7), although the majority of them can be classified on the basis of 1 of 4 carbocyclic skeletons: guaianolides, pseudoguaianolides, eudesmanolides and germacranolides. Whereas there is considerable cross-reactivity between SLs within a class, there

seems to be only limited cross-reactivity between members of different classes (7). Despite this, Ben Ezra and Epstein (8) in 1986 suggested a mixture of 4 SLs for the purpose of screening for Compositae dermatitis. Eventually, a mix consisting of only 3 SLs was produced and became known as the SL mix. Following a large multicentre study organized by the EEC DRG, the SL mix has become part of the European standard series (9). In several studies, it has led to reactions in between 1.5–3.5% of tested patients (9–13).

It was soon claimed, however, that the SL mix was not a sufficiently sensitive screening test for Compositae dermatitis. Green & Ferguson (14) reported that it detected only 35% of all cases of Compositae dermatitis, while Goulden & Wilkinson (15) found that the SL mix missed 38% of genuine Compositae allergies.

In 1997, an alternative to the SL mix became commercially available in the UK. It was named the Compositae mix and consisted of extracts of 5 Compositae plants: feverfew, chamomile, tansy, yarrow and arnica. It is obtained by producing

Table 1. Summary of patient characteristics and patch test results

No.	Relevant (Y/N)	Sex	Age (years)	Comp. mix	SL mix	Vesicular reaction	Exposure history	Improvement	Plant series
1	Y	F	40	++	—	Y	Y	Y	Ya, Ta
2	Y	M	19	+	—	Y	Y	Y	not done
3	Y	F	51	+++	++	Y	Y	Y	Ya, Ta
4	Y	M	76	+	—	Y	Y	Y	not done
5	N	F	37	—	+	N	N	N	not done
6	Y	F	50	++	+	Y	Y	N	not done
7	Y	F	51	++	—	Y	Y	N	Fe
8	Y	M	59	++	+	Y	Y	?	Ta
9	Y	F	52	+	—	Y	Y	Y	not done
10	Y	M	86	++	+	Y	Y	N	not done
11	N	F	14	+	—	N	N	N	not done
12	Y	F	38	+	—	Y	Y	N	Fe, Ta
13	Y	F	28	++	—	Y	Y	N	Fe, Cha
14	Y	F	51	+	+	Y	Y	Y	Fe, Ta, Cha
15	Y	F	23	+	—	Y	Y	Y	Ya
16	Y	F	67	++	+	Y	Y	Y	not done
17	Y	M	52	++	++	Y	Y	?	Ta, Fe
18	N	F	27	+	—	N	N	N	negative
19	Y	M	62	+++	++	Y	Y	N	Ta, Fe, Cha, Ya
20	N	F	29	+	—	N	N	N	not done
21	Y	M	39	+	—	Y	Y	?	Ta, Fe
22	Y	M	22	+	—	Y	Y	Y	not done
23	Y	M	55	+	—	Y	Y	?	not done
24	Y	M	25	++	—	Y	Y	?	Ta, Fe, Cha
25	Y	M	83	—	++	Y	Y	Y	not done
26	Y	F	65	+	+	Y	Y	?	not done
27	Y	F	80	+	—	Y	Y	Y	Fe, Ta
28	Y	M	32	+	+	Y	Y	Y	Fe
29	N	F	30	+	—	N	N	N	not done
30	N	F	24	+	—	N	N	N	not done
31	Y	M	71	+	—	Y	Y	N	not done
32	N	M	24	+	—	N	N	N	not done
33	Y	M	71	+	+	Y	Y	Y	Ta, Fe
34	Y	M	40	—	—	Y	Y	Y	Tax
35	Y	F	25	+	—	Y	Y	?	Ya, Ta
36	N	M	48	+	—	N	N	N	negative
37	Y	F	49	++	—	Y	Y	Y	not done
38	Y	M	75	++	++	Y	Y	Y	Ta, Fe, Cha, Ya
39	Y	F	45	+	—	Y	Y	?	not done
40	N	M	79	+	—	N	N	N	not done

Y=yes; N=no; M=male; F=female; Ya=Yarrow; Ta=Tansy; Fe=feverfew; Cha=chamomile; Tax=dandelion.

short ether extracts from the above ground parts of the respective plants. These extracts have been claimed to contain over 90% of the total sensitizing allergens (16, 17). The qualitative determination of the sensitizing constituents of the extracts is controlled by thin-layer chromatography and the irritancy threshold is determined by patch testing in 20 controls (12). In combination, the 5 plants included in the mix contain representatives from each of the SL classes. In addition, the Compositae mix also includes non-sesquiterpene-lactone plant constituents such as polyacetylenes and thiophenes, which may contribute actively to the development of Compositae dermatitis (12). Earlier studies have suggested that the Compositae mix is a useful tool for the purpose of screening for

Compositae allergies (12, 18). So far, there have been no published studies in which the sensitivity of the Compositae mix has been compared against that of the SL mix in a general patch test population.

Materials and Methods

Between July 1997 – June 1998, all patients referred to our patch test clinic were tested to SL mix (Trolab), and to Compositae mix (Trolab) in addition to other tests requested by the referring doctors. Reagents were applied in Finn Chambers on Scanpor tape and removed after 2 days. Readings were after 2 and 4 days according to ICDRG criteria, only reactions scored as $\geq +$ being re-

corded as positive. Positive reactions were retrospectively assessed for relevance based on 4 criteria: (a) the reaction was vesicular; (b) there was a good exposure history; (c) noticeable improvement occurred after exposure reduction; (d) a $\geq +$ reaction to at least 1 constituent of the Compositae mix on repeat testing with a plant series (Trolab). If 2 out of 4 criteria were met, the reaction was deemed to be a true relevant positive.

Results

656 patients were tested altogether. 40 patients showed a positive reaction to at least 1 of the plant-related allergens, namely either the Compositae mix or the SL mix, or on 1 occasion, to an allergen in the plant series where the referring doctor had specifically requested this series. 37 of these (5.6%) were reactions to the Compositae mix, 14 (2.1%) to the SL mix. 1 patient reacted only to 1 of the constituents of the plant series (dandelion extract), but neither to Compositae mix nor to the SL mix. After applying our specified criteria, we deemed 31 patients (4.7%) to have genuine Compositae allergies. Only 13 out of these 31 (42%) had reacted to the SL mix, which thus failed to detect 58% of genuine Compositae allergies. The Compositae mix, on the other hand, detected 28 out of the 32 Compositae allergies (90%). It failed to detect 2 such cases, 1 of which was detected by the SL mix, while 1 was only detected by the plant series. The Compositae mix led to 9 irritant reactions whereas there were no irritant reactions to the SL mix (Table 1).

Discussion

Two key findings in our study deserve particular consideration. One is that the current screening method for Compositae dermatitis by means of the SL mix is insensitive and misses a substantial proportion of genuine Compositae allergies. Our observation that the SL mix fails to detect 58% of Compositae allergies strongly supports previous findings (14, 15). It indicates that, when used on its own, the SL mix will detect only between 1/3–2/3 of all Compositae allergies. It also suggests that Compositae dermatitis is more common than has hitherto been recognized and that, in Northern Europe, it must be expected in around 4% of all patch test patients. This figure puts Compositae dermatitis on a level with colophony allergy (18). It would imply that Compositae allergies need be considered more frequently in the differential diagnosis of any unexplained eczema, and not only where this presents with a typical exposure-pattern dermatitis. It has been recognized for some time

that there may be a substantial degree of variability in the clinical appearance of Compositae dermatitis (10). It is this very difficulty in diagnosing the condition clinically that makes a good screening test such an important instrument.

Our results strongly suggest that the Compositae mix is significantly more sensitive than the SL mix. In our study, the sensitivity of the Compositae mix reached 90% compared with 42% for that of the SL mix. It might thus be argued that the Compositae mix would be better suited as the sole screening agent for Compositae dermatitis and that it should replace the SL mix in the European standard series. Several arguments speak against such a proposal at this time.

(i) Our results will require confirmation from other centres or possibly a multicentre study. Such a study has been conducted in Germany (12), but so far no results are available (personal communication, Hausen).

(ii) Our method for establishing the relevance of positive patchtest reactions is yet unvalidated. More work will be required to determine valid criteria for the recognition of Compositae allergies. Only when this has been achieved can one truly assess the sensitivity and specificity of a screening test.

(iii) As a plant extract, the Compositae mix is more likely to lead to sensitization than the highly purified SL mix. The real risk of such sensitization is still unknown. Neither Hausen (12) nor Paulsen et al. (13) have reported any sensitization in their respective work with the mix, but further experience will be required before a definitive assessment can be made. This also applies to the aspect of irritancy. In our study, 9 out of 656 patients showed an irritant response to the Compositae mix, whereas the SL mix produced only a single irritant result. In the multicentre EECDRG study, the SL mix led to irritant effects in 5 out of 4011 patients (9). This suggests that the SL mix is more specific than the Compositae mix for the detection of Compositae dermatitis.

(iv) A major disadvantage of the Compositae mix compared with the SL mix is that its precise composition is unknown, apart from the total sesquiterpene lactone content. This virtually excludes it from becoming a part of the European standard series, where only substances of a well-defined composition should be used.

The search for an ideal screening agent for Compositae dermatitis thus continues.

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