

“Re-testing” suggests that co-sensitizations to isobornyl acrylate and sesquiterpene lactones may be due to cross-reactivity.

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Patients with allergic contact dermatitis (ACD) from the glucose sensor FreeStyle Libre (Abbott Diabetes Care, Witney, U.K.) are often (strongly) sensitized to isobornyl acrylate (IBOA)(1,2). About 40 to 60% of these patients also have a concomitant positive patch test to the sesquiterpene lactone mix (SLM; 0.1% pet.), an observation for which an explanation is lacking (3,4).

Case report

A 19-year-old male patient with diabetes mellitus type 1 developed severe ACD from FreeStyle Libre several weeks after starting its use. Patch tests, performed as described elsewhere (4), and including the application of IBOA 0.3% pet. (in-house prepared from raw material obtained from Sigma-Aldrich, Overijse, Belgium) and 0.1% pet. (Chemotechnique Diagnostics, Vellinge, Sweden) on the right upper arm confirmed sensitization (++ and +, respectively) to both patch test preparations on day (D)3 and D7. A patch test to SLM 0.1% pet. gave a doubtful reaction (?+) on D3 and D7. The patient was instructed to mark the skin reactions to both IBOA preparations on his arm, and 6 weeks later, when all reactions had disappeared leaving only mild residual erythema (**Figure 1A**), patch tests with SLM 0.1% pet. were again applied onto his skin: one of each on the two previously positive skin test sites of IBOA (0.1% and 0.3% pet.) on the right upper arm, and also one on the (control) left upper arm. Readings now showed, already on D2, a strong (++)

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reaction to both SLM 0.1% pet. patch tests on the right upper arm (**Figure 1B**), whereas on the left upper arm SLM 0.1% pet. again only gave a doubtful (?+) reaction (**Figure 1C**). On D3 the same patch test reactivities were present, diminishing again by D7. The patient tried the use of the FreeStyle Libre 2 device, no longer containing IBOA, which was well tolerated (**5**). No relevance was found for the positive patch tests to SLM 0.1% pet.

Discussion

Concomitant sensitization to IBOA and SLM cannot be explained by concomitant exposure as chemical analyses could not demonstrate the presence of sesquiterpene lactones (SL) in the FreeStyle Libre sensor, and the presence of SL could not be shown in the patch test material of IBOA either, nor vice versa (**3**). Although cross-reactivity has been coined as an alternative explanation, its existence remains debated. However, clinical, patch test and chemical data might point towards such cross-reactivity: (i) positive patch test reactions to SLM in IBOA-sensitized patients often seem to lack relevance, as in our patient, potentially indicating non-relevant cross-reactivity (**3**), (ii) in many of these patients the patch test reactivity to IBOA is more pronounced than to SLM, suggesting that, in the event of cross-reactivity, IBOA acts as the primary (relevant) sensitizer, whereas SLM is only a secondary (possibly irrelevant) co-sensitizer (**4**), and, finally, (iii) it was recently suggested that rotation about single bonds may allow IBOA to present itself in an albeit energetically disfavored conformation that can mimic the α -methylene- γ -butyrolactone ring present in SL. In this respect, it then seems to behave as an open chain analogue of the ring system present in SL. The latter is required for cross-

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reactivity between SL, and, possibly, also between SL and IBOA. However, this remains a hypothesis as we do not know if (protein-bound) IBOA will effectively behave as such in front of the T-cell receptor (**Figure 2**) It would, however, also concur with observations that IBOA only rarely cross-reacts with other acrylates (**4**).

The re-test model offers an in vivo possibility to evaluate potential cross-reactivity (**6**): when a patient shows a positive patch test to a hapten (i.e., IBOA), persisting allergen-specific T cells that reside in that particular part of the skin will provoke a faster and/or stronger reaction upon re-exposure to the same chemical, and also to a cross-reactive substance. In the present case the reaction to SLM 0.1% pet. upon re-testing was indeed much stronger at the previously positive patch test sites to IBOA as compared to the same patch test performed on normal (previously patch-test uninvolved) skin. Similar to its value in demonstrating the existence of cross-reactivity to octylisothiazolinone (OIT) in patients primarily and strongly sensitized to methylisothiazolinone (MI)(**7**), the same method now also suggests that immunological cross-reactivity to SL occurs in patients primarily and strongly sensitized to IBOA. Future studies, with more patients, and including separate SL components, might not only confirm the cross-reactivity hypothesis, but may also shed more light on which particular SL component(s) most likely cross-react(s) with IBOA.

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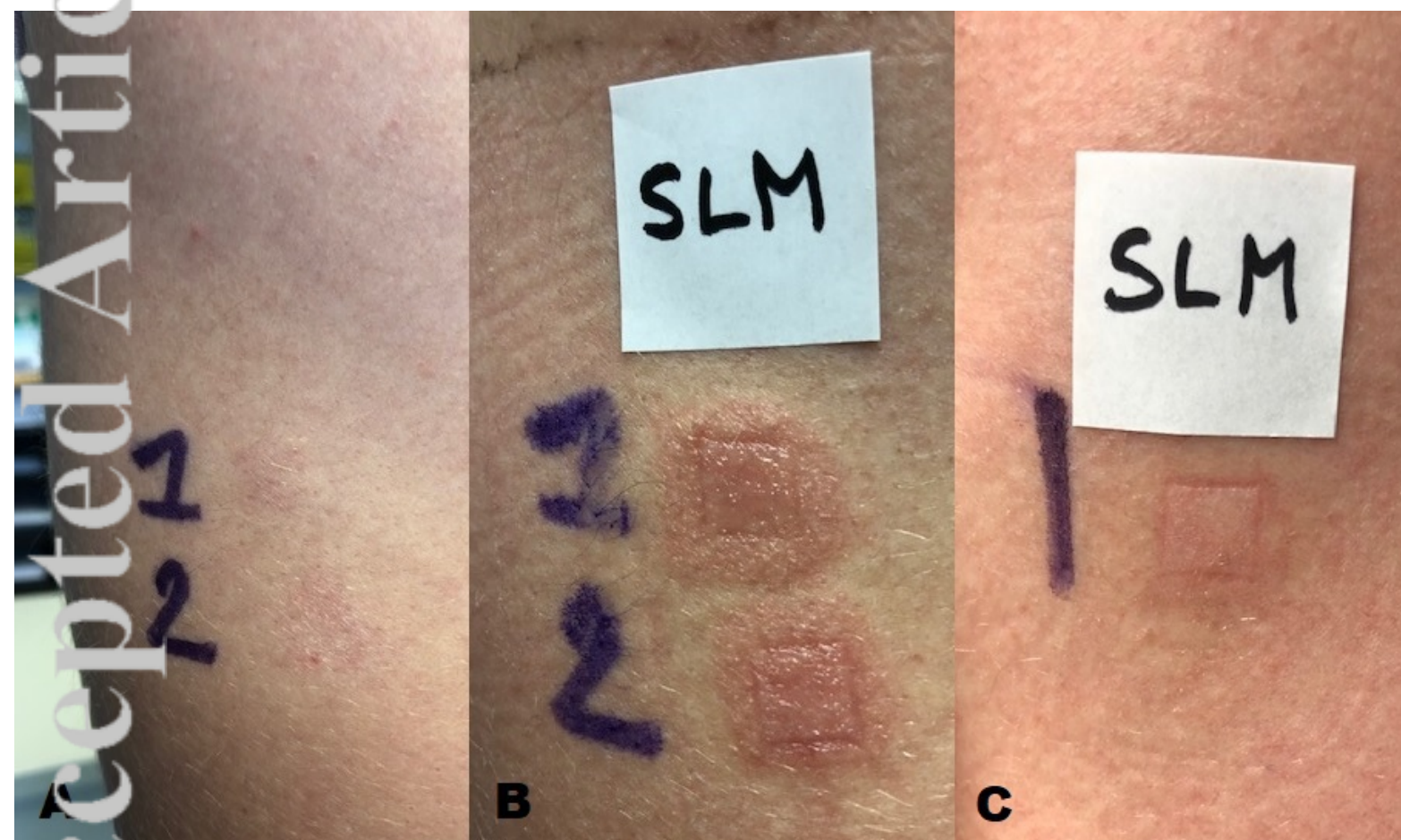
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Fig. 1A: Day (D)0: residual erythema 6 weeks after positive patch tests to isobornyl acrylate (IBOA) 0.1% pet. (no. 1) and 0.3% pet. (no. 2) on the right upper arm.

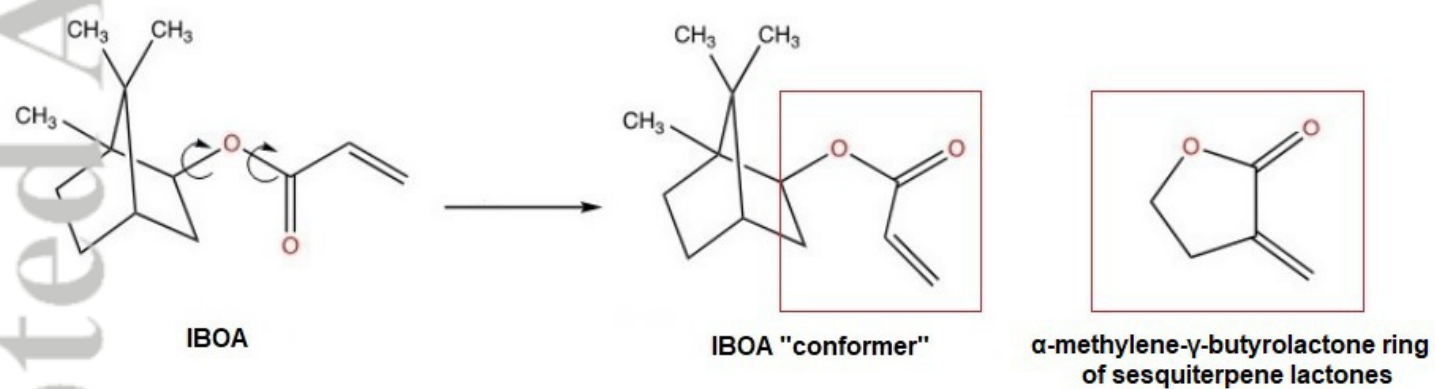
Fig. 1B: Day (D)2: strong positive patch test reactions (++) to sesquiterpene lactone mix (SLM) 0.1% pet. on the previous positive patch tests sites of IBOA (no. 1 = 0.1%, no. 2 = 0.3%) on the right upper arm.

Fig. 1C: Day (D)2: doubtful positive patch test reaction (?+) to sesquiterpene lactone mix (SLM) 0.1% pet. on a normal (previously patch-test uninvolved) skin site on the left upper arm.

Fig. 2: Isobornyl acrylate (IBOA), by rotating around single bonds, can form a “conformer” displaying a chemical structure that closely mimics the α -methylene- γ -butyrolactone ring of sesquiterpene lactones (SL). The ring structure allows cross-reactivity between different SL, and, presumably, also between IBOA and SL.



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