

Patch testing and diagnosis when suspecting allergic contact dermatitis from medical devices

To the Editor:

In two interesting articles recently accepted for publication in *Contact Dermatitis*,^{1,2} a high proportion (32.7%¹ and 43%,² respectively) of patients with adverse cutaneous reactions suggestive of allergic contact dermatitis (ACD) from their glucose sensor and/or insulin pump had no relevant positive patch test reactions. In the article by Herman et al,¹ patch testing included isobornyl acrylate (IBOA) and *N,N*-dimethylacrylamide (DMAA), both tested at 0.1% pet.,^{3,4} colophonium, a (meth)acrylate series, and a piece of the adhesive of the device tested "as is." In the article by Vidal-Albareda and Yelmo-Valverde et al,² testing included ethyl cyanoacrylate, colophonium, IBOA 0.1% pet., an acrylate series, and in some cases a piece of the adhesive of the implicated sensor tested "as is." Patch test readings in both studies were performed on day (D) 2 and D4. Herman et al¹ discuss reasons for possible false-negative reactions. Nevertheless, they conclude "This may be due to other culprit allergens having not yet been identified, or a more likely diagnosis of ICD." We agree on the false-negative reactions but think that ICD (irritant contact dermatitis) is an unlikely, although at least theoretically possible, diagnosis in many of the reported patients for the following reasons:

1. In accordance with the ESCD guidelines for diagnostic patch testing,⁵ in Malmö mandatory patch test readings on D3 or D4 and D7 have been performed for nearly 30 years.⁶ Paired patch test readings on D4 and D7 have been shown to be more reliable than those made on D2 and D4.⁷ Furthermore, by adding a patch test reading on D7 to the D3/D4 reading, an additional 3%-34% of sensitized cases can be identified.⁸ When it comes to (meth)acrylates, late reactions are well known, with about 10% of positive reactions occurring first on reading D7 or later,⁹⁻¹¹ without being cases of active sensitization.¹⁰ Thus, a patch test reading on D7 is mandatory to increase diagnostic accuracy.
2. It is generally acknowledged that the amount of molecules/cm² has a significant impact on patch test reactions.¹² When the amount of each patch test preparation applied on the chamber is standardized, the patch test concentration and the molecular weight of the tested substance are the decisive factors determining the number of molecules/cm². In a recent study,¹³ 15 patients with suspected ACD caused by FreeStyle Libre were patch tested with IBOA and DMAA, both at 0.1% and 0.3%, respectively. Thirteen patients were sensitized to IBOA, with 2 of the patients (15%) presenting positive reactions only on D7 and when tested with 0.3%. Four patients had positive patch test reactions to

DMAA, one of whom presented positive only to DMAA 0.3% on D7. Furthermore, 100 consecutive dermatitis patients in Malmö were patch tested with IBOA 0.3% with neither doubtful nor irritant reactions observed, and without indications of patch test sensitization. Because a low dose/cm² increases the risk of false-negative reactions, we suggest that IBOA and DMAA at 0.3% concentration should be included when patch testing with these substances.¹³

3. Diagnosis of ICD requires demonstration of no clinically relevant contact allergies in an individual with exposure to irritant factors and of a relationship between this exposure and the dermatitis, temporally and with regard to localization and morphology of the dermatitis. Indeed, there is exposure to potential irritant factors, and the localization and morphology of the dermatitis are consistent with ICD.^{1,2} However, is there a temporal relationship? The time between first symptoms and first use between those with and without clinically relevant contact allergies was virtually the same.¹ For those "with a possible ICD" the average time was 6.3 months and with at least one patient "contracting the ICD" after 29 months.¹ After having experienced skin problems under the medical devices for the first time, the subsequent exposures on nondamaged skin resulted in dermatitis after few days, indicating a possible ACD but with the subsequent patch testing being negative. We are not aware of evidence that repeated exposure to the same irritants on various areas of nondamaged skin will result in a substantial increase in sensitivity to irritation. Thus the same clinical pattern and temporal relationship between first symptoms and first use on the one hand and symptoms after a few days on subsequent exposures on the other hand in those with and without clinically relevant contact allergies argue in favor of the same mechanism for the contact dermatitis in both groups. A similar temporal relationship as described above can of course theoretically be seen in cases of ICD, taking into account the possibility of a sudden modified content of the device used increasing its irritating potential.
4. If ACD is the most likely diagnosis in the majority of those testing negatively, how is the diagnosis established? We agree with Herman et al¹ that the manufacturers of the medical devices should be more cooperative and that ingredient labeling of the products is desirable. With knowledge on the composition, the individual ingredients can be tested at a higher dose than the dose the patient is exposed to when using the device to avoid false-negative reactions. In general, IBOA and DMAA are present at a lower

concentration in medical devices than those being patch tested.^{3,4,14} However, how does one test possible sensitizers in products with unknown ingredients/composition at a higher concentration? This can be done with ultrasonic bath extracts.^{15,16} The rationale behind the use of ultrasonic bath extracts is a quick extraction in a sonicator using an appropriate extracting solvent from a substantially bigger area of the suspected product than what is used when testing the product "as is." Thereafter, the solvent is evaporated and a minute volume in the same solvent or a different vehicle is used for patch testing. By this procedure, a possible sensitizer in the suspected product might have been concentrated, and thus a weak contact allergy may be discovered.

Actually, when the first patient was seen in Malmö with dermatitis corresponding to the contact area of FreeStyle Libre, a patch test was performed on the first test occasion with ultrasonic bath extracts of the whole sensor, because occlusive exposure to the sensor for 10 days was needed to elicit dermatitis under the sensor. Positive reactions consistent with an allergic morphology were noted in response to the extracts. To substantially diminish the possibility of false-positive reactions to the extracts, 20 dermatitis controls were tested, and all had negative test results. The diagnosis was thus ACD caused by the sensor. A collaboration between the department in Malmö and departments in Belgium could subsequently identify IBOA as a major sensitizer in FreeStyle Libre.³

We suggest the following investigative procedure for patients with suspected ACD caused by medical devices:

- I. Patch testing with a baseline series supplemented with a relevant and updated medical device series including IBOA and DMAA tested at concentration 0.3%¹³ and, if possible, the medical device, or parts of it, tested "as is." A test reading after 1 week is mandatory.⁵
- II. If a strong reaction is expected to, for example, IBOA, patch testing can start with the concentration 0.1%.
- III. Occasionally, such an approach (II) may result in a negative reaction to the sensitizer (IBOA, for example), having been expected to give a strong reaction at the first reading. When this happens, the higher dose should be tested at the reading 3 or 4 days after the application of the initial test. This retest shall also be read twice with the last reading 1 week after the application unless the test is positive already at the first reading.
- IV. If the results of the above-mentioned patch tests are all negative in a patient with a strong suspicion of ACD, additional patch testing with ultrasonic bath extracts of the involved device is recommended^{15,16} for those patch test clinics that have access to the technique. According to the description of the technique, many devices of the same type should preferably be used for the extraction. Obviously, this is virtually impossible in the clinic when investigating individual cases with suspected ACD from a medical device. Furthermore, to increase the likelihood of extracting both polar and non-polar sensitizers from the device, three extracting

solvents with different physicochemical properties can be used—water, ethanol, and acetone. Again, a test reading after 1 week is mandatory unless positive reactions are noted already at the first reading. A positive reaction can be false-positive; therefore, patch testing in 20 consecutive dermatitis patients with a negative result is required to substantially diminish the possibility of a false-positive reaction.

When the history suggests ACD from a medical device, the following diagnoses are recommended based on the patch testing according to I-IV above:

ACD – a relevant positive patch test reaction according to I and/or II and/or III and/or IV.

ACD? – negative patch test reactions to I; III, and possibly IV (particularly if the extraction is based on only one device) but where the time between first symptoms and first use is substantially longer than the exposure time needed on subsequent exposures on nondamaged skin to a medical device for which the composition has not changed over the years when the patient has used the device.

A changed composition may imply a different exposure to sensitizers and also an increased exposure to irritant factors that may cause ICD. Such an ICD from "a new product," will obviously be accompanied by a negative patch test result and a temporal relationship with regard to the old medical device suggesting ACD. Thus, if the investigating dermatologist is not aware of the exposure to "the new product," the diagnosis ACD? may incorrectly be set instead of UCD.

UCD (unspecified contact dermatitis) – negative patch test reactions to I; III, and possibly IV, but where the time between first symptoms and first use is virtually the same as the time needed on subsequent exposures on nondamaged skin. This diagnosis includes both ICD and ACD. The latter diagnosis is based on the situation, although unlikely but still theoretically possible, when a patient already has a preexisting contact allergy to a sensitizer in the device but where its presence in the device is unknown.

ICD – negative patch test reactions to I; III, and possibly IV but where the time between first symptoms and first use is virtually the same as the time needed on subsequent exposures on nondamaged skin. The possibility of a preexisting hidden contact allergy to a currently unidentified sensitizer in the device according to what is described for **UCD** above is considered unlikely.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest

AUTHOR CONTRIBUTIONS

Josefin Ulrikssdotter: Conceptualization; writing-original draft; writing-review and editing. **Martin Mowitz:** Conceptualization; supervision; writing-review and editing. **Cecilia Svedman:** Conceptualization; resources; supervision; writing-review and editing. **Magnus Bruze:** Conceptualization; supervision; writing-original draft; writing-review and editing.

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