Concomitant positive patch test reactions in FreeStyle®-allergic patients sensitized to isobornyl acrylate.

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ABSTRACT

Background: Concomitant positive patch test reactions in patients sensitized to isobornyl acrylate (IBOA) have only rarely been documented.

Objectives: To report concomitantsensitizationsinpatients with allergic contact dermatitis (ACD) from the glucose sensor FreeStyleLibre (FL)and sensitized to IBOA.

Patients and methods: In 2019,26patients with suspected ACDfrom FL were patch-testedto a baseline series, and to a (meth)acrylate series containing IBOA and 2-phenoxyethyl acrylate (PEA)1% pet. Diabetes devices and patch test preparations wereanalyzedwith gas chromatography – mass spectrometry (GC-MS)for their presence of IBOA andPEA.

Results: Of the 26 patients 18 (69%) were sensitized to IBOA, and 8 (44%) and 11 (61%) of these were co-sensitized to sesquiterpenelactones and fragrances, respectively.Ten patients (56%) wereco-sensitized to PEA, which, contrary to IBOA,could not be detected in any device. The PEA test material was shown to becontaminated with IBOA.

Conclusions: Contact allergy to IBOAappears to be declining and IBOA-sensitized patients are most often co-sensitized to sesquiterpenelactones and fragrances.Vigilance is required when patch testing (acrylate) materials obtained from industry, as thesemight be contaminated, hence altering the results and their interpretation.

1. Introduction

Cutaneous adverse events (CAE), including allergic contact dermatitis (ACD), from glucose sensors and insulin infusion setshave been extensively reported in recent years (**1**). In many patients ACD from these medical devices has been attributed to (meth)acrylates, and to isobornyl acrylate (IBOA)in particular. The latter is regarded as the main contact allergen present in the FreeStyleLibre(FL) glucose sensor(Abbott Diabetes Care, Witney, Oxfordshire, UK) (**2, 3**).Concomitant sensitizations to acrylates, and other contact allergens, have only rarely been documented in patients sensitized to IBOA(**2, 3**). We here discuss the concomitant sensitizations observed insuch patients and we highlight areas of potential interest for future research.

2. Methods

2.1.Patch tests

At the University Hospital of Antwerp adult and paediatric diabetes patients suffering from CAE, includingACD, from diabetes medical devices are commonly referred by the (paediatric) endocrinologist for an evaluation and allergy work-up (**4**). The latter comprise patch tests with a (selection of) Belgian baseline series allergensand additional series including a(limited or extended) (meth)acrylate series (ChemotechniqueDiagnosticsVellinge,

Sweden).Since IBOA was shown to be a major sensitizer inFL (**2**), our (meth)acrylate series, both limited and extended, contains IBOA0.1% pet., originally as an in-house prepared patch-test preparation (**2**),later onobtained from Chemotechnique Diagnostics (**3**). Additionally,since January 2019,2-phenoxyethyl acrylate (PEA) 0.1% pet. (raw material obtained in the past from the ink industry, namely, AGFA-Gevaert, Mortsel, Antwerp, Belgium, and prepared in-house) has been added to this series, instead of being patch-tested only in selected occupational cases (that is, in workers presenting with suspected ACD from UV-cured inks). Isobornyl methacrylate (IBOMA) has very recently also been added to this series, again as an in-house patch test preparation (raw material from Sigma-Aldrich, Overijse, Belgium). Overall, all 26 patients were patch-tested to IBOA and PEA, both 0.1% pet., and 4 of them also to IBOMA 2% pet. Twenty-six and 23 patients, respectively, were patch-tested to the sesquiterpenelactone mix (SLM; 0.1% pet.) and to its components (alantolactone 0.033% pet., dehydrocostus lactone 0.1% pet. and costunolide 0.1% pet.), whereas 25 patients were patch-tested to both the compositae mix (CM) 2.5% pet. and to parthenolide 0.1% pet. Twenty-one and 18 patients, respectively, were patch-tested to fragrances screeners from the baseline series (ie*Myroxylonpereirae*[MP] 25% pet., fragrance mix I [FM-I]8% pet., hydroxyisohexyl 3-cyclohexene carboxaldehyde 5% pet., fragrance mix II [FM-II] 14% pet., and *Everniafurfuracea* 1% pet.) and from the recommended additions (limonene hydroperoxides[LIM] 0.3% and 0.2% pet., linalool hydroperoxides [LIN] 1% and 0.5% pet.); 23 patients were patch-tested to any of these fragrance sensitizers (**Table 1**).Patch tests were always mounted on Allergeazepatch test chambers (SmartPractice, Calgary, Canada), applied on the upper back (and occasionally also on the upper arm), and occluded for 2 days with

Fixomull (BSN medical, Hamburg, Germany). Readings were performed, according to ESCD guidelines (**5**), on day (D)2 and D4. Patients werealways instructed to report any additional patch test reactions beyond D4, however, were not systematically recalled to the clinic for verification.

2.2.Chemical analyses

Gas chromatography - mass spectrometry (GC-MS) was performed of several brands of glucose sensors and insulin infusion sets (n=6) frequently used by diabetes patients in our hospital.These concernedtwo glucose sensors, FL and DexcomG5 (Dexcom, San Diego, California), and 4 insulin infusion sets,3 from Medtronic (Minneapolis, Minnesota), that is, the MiniMed Sure-T, MiniMedQuick-set Paradigm and MiniMed Silhouette, and 1 from RocheDiabetes Care (Diegem, Belgium), that is, the Accu-chekInsight Flex; other subtypes of Accu-chek(Combo and Aviva Insight) were not available for analysis. The devices were always disassembled into their main parts, that is, the glucose sensors were separated into their adhesive patches and the rest of the sensor, including the circuit boards,whereas the infusion sets were divided into their tubes and infusion sites (i.e. the adhesive patch and the plastic material where the tube is connected to the cannula). All parts were cut into small pieces and placed in test tubes to which acetone was added. The tubes were then placed in an ultrasonic bath for 1h. After removal of the solid parts, the extracts were filtered. Following evaporation under N_2 gas and adding 300 µL of acetone the extracts were analyzed. The GC system consisted of a Trace GC Ultra gas chromatograph (Thermo Fisher Scientific, Waltham, Massachusetts), fitted up with a thirty metres long Restek Rxi-5HT capillary

column (30 m x 0.25 mm, 0.25 µm film thickness) (Chrom Tech, Minnesota,). The carrier gas was helium (Praxair Technology, Danbury, Connecticut) with a flow rate of 1.0 mL/min. The inlet was heated to 250 °C, the splitless injection volume was 1 µL. The temperature program continued as follows: 3 min isothermal at 70 °C, raising the temperature by 8 °C/min to 300 °C and finishing with 10 min isothermal at 300 °C. The MS was performed with a DSQ mass spectrometer (Thermo Fisher Scientific) in scan mode within a *m/z* range of 50 to 600 u, with a run of 41.75min and scanning started after 6 min. The GC-MS interface temperature and the temperature of the ion source were both 250 °C. A total of 0.01% (m/v) IBOA and PEA (both obtained from AGFA Gevaert, with a purity of 96% and ≥83%, respectively) in acetone were used as reference standards (not mixed together in 1 standard solution, but analyzed separately), showing mass spectrum peaks at 13.84 min and 15.15 min, respectively. Of note, the IBOA raw material was still available in-house since a previous report (**2**), but the raw material of PEA had to be re-acquired again from the industry to serve as reference material for the chemical analyses. Also,poly(ethylene glycol) phenyl ether acrylate (PEEA) (obtained from Sigma-Aldrich, Overijse, Belgium) was used as a standard to verify the presence of any PEA oligomers in the devices. Additionally, we analyzed the patch test preparations for their purity, that is, the in-house IBOA patch test material as well as the one recently obtained from Chemotechnique Diagnostics, and the in-house PEA patch test preparation (based on raw material supplied to us in the past by the industry, i.e. different from the PEA reference material used for the current chemical analyses).

3. Results

During the one-yearperiod between January 2019 and December 2019, a total of 26 patients were referred for the evaluation of potential ACD from FL.These concerned 14 females and 12 males, with a median and mean age of 37.5 and 40 years old, respectively (range: 9 to 73 years old.The relevant results of the patch-test investigations are summarized in **Table 1**.

Eighteenof 26 patients (69%) were shown to be sensitized to IBOA, of whom 10 (56%) had a remarkable and unexplained co-sensitization to PEA, the latter with an equal (6 cases) or lower (4 cases) patch-test intensity, suggesting potential cross-reactivity between these acrylates, and with IBOA as a likely primary sensitizer.

GC-MS confirmed the presence of IBOA in FL (**2**), and its absence in DexcomG5 (**6**). Moreover, IBOA was also found in two infusion sets from Medtronic, that is, the MiniMed Quick-set Paradigm (**7**), and the related MiniMed Sure-T infusion set. Interestingly, IBOA was found in their plastic units attached to the actual pump, thus not in the parts directly in contact with the skin; it might not be excluded that IBOA releases and migrates with the insulin flow towards the skin. Based on the chromatographic profiles, an IBOA dilution series and a calibration line, the IBOA content in these devices could be approximatively quantified, i.e. < 1 ppm (“trace amounts”). No IBOA could be demonstrated in the Minimed Silhouette from the same manufacturer. In the Accu-chek Insight Flex device, not previously reported about, the presence of similartrace amounts (< 1 ppm) could also be demonstrated, more specifically in the adhesive and its associated plastic unit. Overall, the levels of IBOA found in these devices are very low compared to the presence of IBOA in FL (range 30-4000

ppm)(**2**). The FL, nor any of the other devices, contained the monomer PEA, nor any of its oligomers.

When the patch test preparations were analyzed, the purity of both IBOA preparations (in-house prepared, and from Chemotechnique Diagnostics) was confirmed. However, the in-house prepared PEA patch test material contained several impurities, notably tetraethylene glycol diacrylate, and, surprisingly, also IBOA. The recently re-acquired PEA raw material, used as a reference to perform the chemical analyses, was shown to be free from these contaminants.

As previously published (**3**), positive patch-test reactions to other (meth)acrylates only rarely occurred in the IBOA-sensitized patients: in 3 of 4 patients (cases 22, 24 and 25) patch-tested to IBOMA 2% pet. positive reactions to this methacrylate were observed, one of whom(case 22) also reacted to methyl methacrylate (MMA). One IBOA-positive patient (case 23) also presented with a patch test reaction to triethyleneglycoldimethacrylate (TEGDMA), whereas an IBOA-negative patient (case 7) had a reaction to butyl methacrylate (BMA).

Interestingly, 8 of 18 (44%) IBOA-sensitized patients showed a doubtful (?+) or weak (+) positive patch test reaction to SLM 0.1% pet., and all of themwere equally or stronger sensitized to IBOA 0.1% pet. Conversely, all 8 patients not sensitized to IBOA, neither reacted to SLM ($p=0.031$), indicating a statistically significant concomitant reactivity toboth

substances. The 3 SLM components were patch-tested in 23 patients, of whom 16 were sensitized to IBOA, and 5 of the latter showed positive, concomitant reactions to SLM and to both alantolactone 0.033% pet. and costunolide 0.1% pet. All patients with a negative patch test to SLM, or a doubtful one (case 6), hadnegative reactions to the components of the mix, and none of the IBOA-negative patients reacted to the SLM components separately.CM2.5% pet. gave a positive reaction in 5 patients, 4 of whom were co-sensitized to SLM and IBOA. One patient (case 7), with suspected CAE from FL, was negative to IBOA and SLM, but positive to CM. In 3 IBOA-sensitized patients (cases 6, 8, 13) the CM remained negative, whereas the SLM was positive. Parthenolidewas only positive in 2 IBOA-positivepatients, the first being positive to SLM (case 13) and the second(case 9) reacting to both SLM and CM. In 6 cases parthenolideremained negative, whereas these patients (IBOA positive or negative) had reacted to SLM and/or CM.

Of the 18 IBOA-sensitized patients, 11 (61%) had positive patch-test reactions to fragrance markersfrom the baseline series and/or recommended additions. More specifically,4 and 3 IBOA-sensitized patients reacted to MP and FMI, respectively, whereas 9patients (cases 1, 8, 9, 11, 13, 17, 22, 24 and 25) reacted to LIM and/or LIN, that is, 2 only to LIM, another 2 only to LIN, and 5 to both. Interestingly, in only 4 of these 11 fragrance-sensitized patients relevance could be found for these particular positive tests; in the remaining 7 no evident ACD had ever occurred with regard to the use of scented (skin care) products. Only one IBOA-negative patient (case 7) reacted to MP and FM-II, and another two IBOA-negative patients (cases19 and 26) reacted to LIM, and to LIM, FM-I, and MP, respectively.

Other remarkable positive patch test reactions in the group of IBOA-sensitized patients concerned: colophonium (2 cases), sulfites (2 cases), methyldibromoglutaronitrile (2 cases), and benzisothiazolinone(2 cases), some of which might be potentially present in glues and adhesives.

Less than half of the patients (11/26; 42%) had used, or were using, other glucose sensors and/or insulin infusion sets. Some of these devices, known to contain this acrylate, had also resulted in CAE, possibly ACD, in these patients (**Table 2).**

For example, some patients with ACD from FreeStyleLibreand sensitized to IBOA (cases 9and 23)had also tried using the Enlitesensor, known to containIBOA (**8**), which provokedACD in them, whereas the Dexcom sensor, known to be free from IBOA (**6**), was a good alternative, also for 2 other patients (cases 10 and 12). One IBOA-negative patient (case 7) showedskin reactions to Enlite, perhapsbecause of the colophonium it contains and to which this particular patient was sensitized (**7**).

Eight patients (cases1, 7, 8, 9, 17, 19, 22 and 26) had used an insulin infusion set, and 4 of them (cases7, 9, 19 and 26) had developed CAE, possibly ACD, from these devices, the culprit sensitizers remaining largely unidentified. Although some infusion sets were shown to contain (trace amounts of) IBOA, hence explaining ACD in case 9, this could not explain the CAE that developed in 3 other (IBOA-negative) patients (cases 7, 19, 26).

4. Discussion

Manycasesof ACD from diabetes devices have been attributed toIBOA (**2,9,10**), an acrylate recently elected as the U.S. “Contact Allergen of the Year 2020” (**3**). In our patch-test clinic, 1 out of 20 (5,5%) diabetes patients is referred for suspected ACD from FL (**4**).Of the 26 patients with potential ACD from FL reported herein18 (69%) were sensitized to IBOA. Although thissensitization rate appears to be lower than previously reported (~80%) (**2, 11**), perhaps explained by a change in the composition of this device in more recent years (**4**), it concurs well with the overall IBOA-sensitization rate observed in the Antwerp diabetes patient population since 2016 (68%; **4**). Although one might argue that the 0.1% pet. preparation of IBOA might underestimate sensitization to this chemical (**12**), we have always used (from 2016 till now) this same test concentration, indicating that the “relative” decline in sensitization may truly represent a decreased overall sensitization rate. In Belgium some of our patients sensitized to IBOA are now able to use newer, IBOA-free versions of FL (data on file), but, as shown by the current report, in 2019 patients were often still affected by primary sensitization to IBOA due to its presence in this particular glucose sensor.

Patients with CAE from FreeStyleLibre, not shown to be sensitized to IBOA (n=8), might have been affected by irritant contact dermatitis (ICD), or by ACD from currently unidentified or untested contact allergens present in the device (**13-15**).Alternatively, some weakly sensitized patients might have been missed, as we did not patch test IBOA in a higher concentration (e.g. 0.3% pet.), nor were patients systematically recalled to the clinic for a reading on D7(**12**).

Although concomitant positive patch test reactions have occasionally been observed to other (meth)acrylates (**2**),and to acrylic acid (**16**), itremainsdifficultto delineate a clear cross-reactivity profile of IBOA. Alsoin this study, concomitant reactions to(meth)acrylates were only rarely observed, although not all patients were always patch-tested with an extended (meth)acrylate series. Three of 4 IBOA-sensitized patients (75%) co-reacted to IBOMA,the corresponding methacrylate of IBOA, although the numbers are low. The co-reaction between these 2 acrylates might be explained by cross-reactivity, although it has been argued that, in general, patientsprimarily sensitized to the (weaker) methacrylate develop cross-reactions to the (stronger) acrylate counterpart, ratherthan the other way around (**17**).In the one IBOA-sensitized patient reacting to TEGDMA, no relevance could be detected for this particular methacrylate, although ithas beenincriminated in a patient with ACD from an insulin infusion set(**18**). Since the devices used by our patients were not specifically analyzed for their presence of IBOMA, and given that this methacrylate can also be found in certain consumer items (eg gel nail polishes), concomitant sensitization can probably not be entirely ruled out.

Only two reports have highlighted 2-phenoxyethyl acrylate (PEA; CAS no. 48145-04-6) as a contact allergen in diabetes medical devices, namely, insulin infusion sets, together concerning three patients of whom twoshowedconcomitant sensitizations to IBOA and PEA (**19,20**). Based on these observations, we addedPEA 0.1% pet.based on raw material obtained from the ink industry in the past, to our (meth)acrylate series. Before 2019 this contact allergen had only sporadicallybeen patch tested in workers suspected to have ACD from UV-cured printing inks, but who never reacted positively to it(**17,20, 21-22**).

Quite strikingly,10 of 18 patients (56%),primarily sensitized to IBOA from its presence in FL, showed concomitant positive patch test reactions to PEA (**Figure 1**), with an equal or less pronounced patch-test reactivity to the latter, suggesting cross-reactivity, with IBOA as the primary sensitizer. This hypothesis was further supported by chemical analyses (GC-MS) that could not demonstrate the presence of PEA (nor any of its oligomers) in FL, nor in any other diabetes device (n=6) often used by patients in our clinic.Given that the devices were only qualitatively analyzed("screened") for their presence of PEA and its oligomers, we cannot fully exclude that very low amounts may not have been picked up. Upon verification of the patch-test preparations of IBOA and PEA, the latter was, however, shown to contain several contaminants, among which tetraethylene glycol diacrylate, and, surprisingly, also IBOA. The (newly,re-acquired) PEA raw material, used as a reference material for the chemical analyses, did not contain these impurities, the origin of which remains elusive (contamination of the raw material?). The presence of IBOA impurities in the PEA test material does explain the observed co-reactivity profile (PEA < IBOA). As we performed a retrospective review of

patch-tested patients, we were, unfortunately, not able to re-test anew PEA 0.1% patch test preparation,based on the re-acquired and purer PEA raw material. Notwithstanding that no PEA, nor any of its oligomers, could be detected in any of the diabetes devices analyzed (n=6), some devices might still contain it (**19,20**); hence, its inclusion in a medical device series seems justified (**12).** Future investigations will undoubtedlyshed more light on the potential relevance this acrylate may have in the setting of ACD from medical devices. Of note, our experience illustrates that “in-house prepared”(acrylate) patch test preparations, based on raw materialsfrom the industry (often needed to accomplish a diagnostic work-up), may not always be fully reliable in terms of potentially containing impurities that influence the final patch test reactions observed.

Diabetes devices other than FL may also contain IBOA and provoke skin problems. For example, the IBOA-containing glucose sensor Enlite provoked ACD in some of our IBOA-sensitized patients, whereas the IBOA-free Dexcom G5 sensor did not (**6,7**).Insulin infusion sets, such as Accu-ChekInsight Flex,MinimedQuick-Set and Sure T)(**7**), equally shown to contain (trace amounts of) IBOA, mayoccasionally alsoprovoke ACD in IBOA-sensitized patients (e.g. case 9, severely sensitized to IBOA), although other patients could apparently tolerate these devices. For example, cases 1 and 8, weakly sensitized to IBOA, did not react to their own insulin infusion sets(Accu-Chek Insight Flex and Minimed, respectively), in spite ofthe presence of (trace amounts of) IBOA. Similarly, in cases 17 and 22, doubtfully and weakly sensitized to IBOA, respectively, it may not be excluded that their insulin infusion sets, causing no skin reactions at all, still contained low levels of IBOA; these devices (e.g.

Accu-chekAviva Insight) were, however, not available for analysis. Conversely, some patients (cases 7, 19 and 26), not sensitized to IBOA, did show CAE when using certain insulin infusion sets, such as Accu-chekCombo and Minimed, the latter known to contain IBOA.This indicates that other, hitherto unidentified contact allergens might still be present in these diabetes devices; alternatively, as mentioned above, false-negative patch test reactions to IBOA 0.1% pet. might be an alternative explanation (**12).**Overall, these observations also illustratethat, beside the actual sensitization to an allergen (egIBOA), also other variables may be important when it comes to developing ACD from a device containing that allergen, such asthe strength of sensitization, the dose and concentration of the allergen present in the device, and the exposure time, the latter being for insulin pumps usually shorter (a few days) as opposed to glucose sensors (1-2 weeks).

As previously reported (**23**), IBOA-positive patients frequently show concomitant positive reactions to SLM (**Figure 1**). In the current series, 8 of 18 (44%) patients sensitized to IBOA showed a positive reaction to SLM 0.1% pet., whereas all 8 patients not sensitized to IBOA neither reacted to SLM (p=0.031). As all SLM-positivepatients were equally or stronger sensitized to IBOA 0.1% pet, it is tempting to suspect potential cross-reactivity between these substances, with the latterthen acting as a primary sensitizer (**23**).

Both the sesquiterpene lactones and IBOA contain a reactive Michael acceptor (*i.e.* the α-methylene-γ-butyrolactone (**Figure 2a**) and the acrylate respectively) susceptible to nucleophiles which could explain their cross-reactivity with skin proteins (**24**). Although

energetically disfavored, rotations about single bonds (**Figure 2b**) allow IBOA to be present in a conformation that could be seen as an open chain analogue of the butyrolactone moiety present in the sesquiterpene lactones. In this conformation the bulky hydrophobic parts of the molecule point in the same direction as can be seen in a 3D model of these two compounds (**Figure 2c**). The geometrical disposition of the corresponding molecular features canfavor a similar binding mode and reactivity with skin proteins. However, this remains speculation in absence of information of the protein target(s).

When considering IBOA-sensitized patients reacting to sesquiterpenelactones, it is of interest to note that 3 IBOA-sensitized patients (cases 6, 8, 13) remained entirely negative to CM although SLM was positive. Similarly, in 6 cases,parthenolide remained negative, although these patients had reacted to SLM and/or CM. Overall, it appears that the use of CM, and especially parthenolide, the latter suggestedby some to screen for sesquiterpenelactone sensitization (**25**), is of limited value, at least in this particular setting.

Ahigh number of IBOA-sensitized patients (11 out of 18; 61%) were also co-sensitized to fragrance chemicals,particularly to terpenes, such as LIM and LIN.Also a Swedish study showed that 5 of their 12 IBOA-sensitized patients (42%) co-reacted to fragrance screening agents, including LIM, LIN, FMI and II, and MP (**26**). Interestingly, in only a minority of our fragrance-sensitized patients (4/11) relevance could be found, suggesting that other, fragrance-containing materials might be of importance. For example, LIMmaybe industrially used in adhesives (**27).** In the same line it is noteworthy that some of our patients also reacted

to other chemicals, some of which potentially present in glues and adhesives (e.g. colophonium, benzisothiazolinone).

In conclusion, we have shownthat, in the course of 2019,ACD from FLcould still be largely attributed to IBOA, although the sensitization rate appears to be declining.Moreover, we confirm that thesepatients rarely show positive patch test reactions to other (meth)acrylates, but areremarkably co-sensitized, not only to SLM,butalso to fragrance chemicals, terpenes in particular. These observations suggest that future research might also need to focus on non-acrylatesensitizersinmedical devices and adhesives.

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Table legends

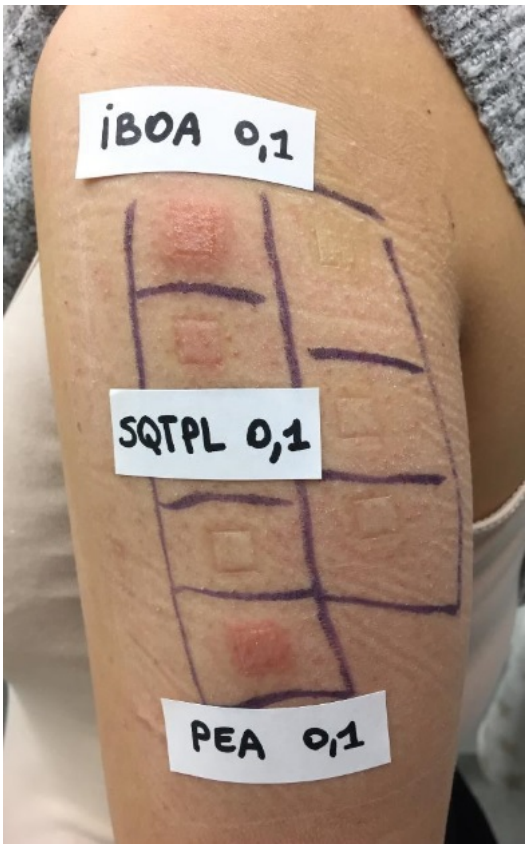
Table 1. Overview of the patch test results of 26 patients, of whom 18 sensitized to IBOA, with suspected allergic contact dermatitis(ACD) from the glucose sensor FreeStyleLibre (FL).

Table 2. The IBOA content of diabetes devices, used with* or without° skin reactions, by 11/26 patients with cutaneous adverse events, including possible allergic contact dermatitis (ACD), from FreeStyleLibre (FL).

Figure legends

Figure 1. Positive patch-test reactions,on day 4,in case12,to isobornyl acrylate (IBOA) 0.1% pet. (++)[upper patch test], sesquiterpenelactone mix (SQTPL; SLM) 0.1% pet. (+)[second patch test], and 2-phenoxyethyl acrylate (PEA) 0.1% pet (++)[lower patch test].The PEA patch test preparation was later shown to be contaminated with IBOA.

Figure 2.(**A**) the α-methylene-γ-butyrolactone ring required to allow cross-reactivity between sesquiterpene lactones, (**B**) rotations about single bonds allow interconversion betweenisobornyl acrylate (IBOA) conformers, giving rise to a conformation that can be seen asthe open chain analogue of theα-methylene-γ-butyrolactone ring, and (**C)**3D models of alantolactone (left) and IOBA (right) showing a similar disposition of molecular features in the molecule.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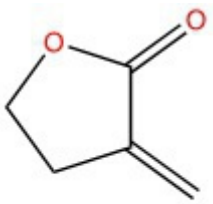
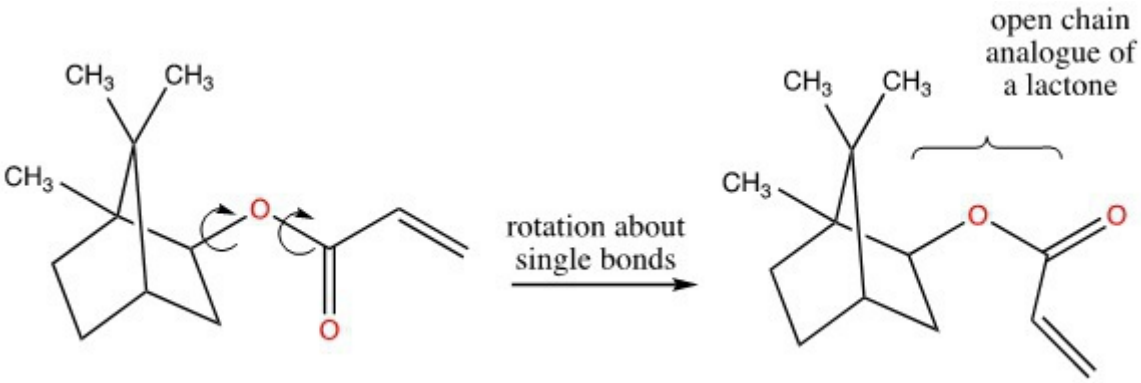
SQTPL 0,1
PEA 0,1


O
O


CH3
CH3
CH3
O
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rotation about
single bonds
open chain
analogue of
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CH3
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O
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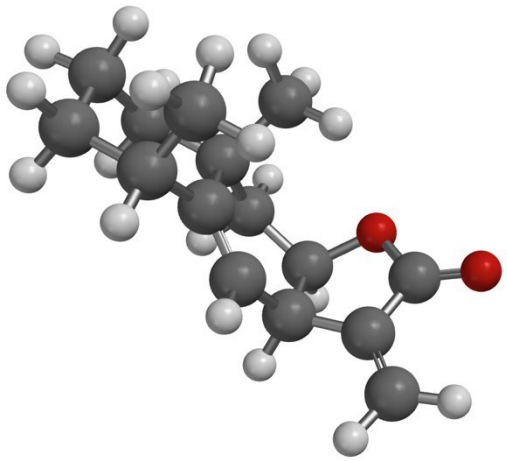

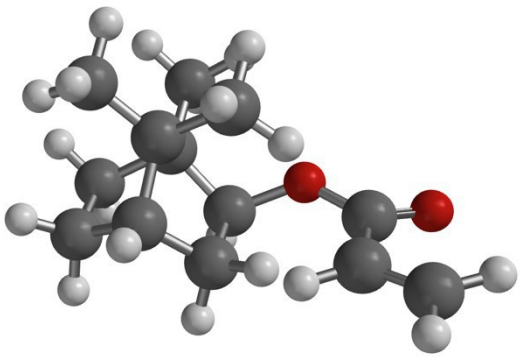

Table 1. Overview of the patch test results of 26 patients, of whom 18 were sensitized to IBOA, with suspected allergic contact dermatitis (ACD) from the glucose sensor FreeStyle Libre (FL).

Patient	IBOA 0.1%	PEA 0.1%	IBOMA 2%	SLM 0.1%	SLM components*	CM-II 2.5%	Parthe-nolide 0.1%	Fragrances from the baseline series**	Fragrances from the recommended additions***	Any fragrance positive	Relevance of fragrance allergy	Other positive patch test reactions
1	+	+	NT	-	-	-	-	-	+ (LIM, LIN)	+	No	Nickel
2	+	+	NT	+	+ (A, C)	?	-	-	NT	-	NA	Colophonium
3	-	-	NT	-	-	-	-	NT	NT	NT	NA	-
4	-	-	NT	-	-	-	-	-	NT	-	NA	-
5	?	-	NT	-	-	-	-	NT	NT	NT	NA	-
6	++	+	NT	?	-	-	-	+ (MP)	NT	+	Yes	Propolis, formaldehyde, chromium
7	-	-	NT	-	-	+	-	+ (MP, FM II)	+	+	Yes	BMA, colophonium, formaldehyde, IPBC, chromium, cobalt, MCI/MI, PPD, MDBGN, formaldehyde
8	+	+	NT	+	+ (A, C)	-	-	-	+ (LIM)	+	No	Caine mix, formaldehyde
9	+++	++	NT	+	+ (A, C)	+	+	+ (MP)	+ (LIN)	+	Yes	Chromium, nickel, decyl-and lauryl glucoside
10	++	-	NT	-	-	-	-	-	-	-	NA	-
11	+	-	NT	-	-	-	-	+ (FM I)	+ (LIM, LIN)	+	Yes	-
12	++	++	NT	+	NT	NT	NT	-	NT	-	NA	-
13	++	+	NT	+	+ (A, C)	-	?	+ (FM I)	+ (LIN)	+	Yes	Nickel, MDBGN, BIT, sodium metabisulfite
14	-	-	NT	-	-	-	-	-	-	-	NA	MCI/MI, nickel, bromonitropropane

												diol, decyl- and lauryl glucoside
15	-	-	NT	-	-	-	-	NT	NT	NT	NA	-
16	?	-	NT	-	-	-	-	-	-	-	NA	-
17	?	-	NT	-	-	-	-	-	? (LIM)	+	No	-
18	-	-	NT	-	-	-	-	-	-	-	NA	-
19	-	-	NT	-	-	-	-	-	+ (LIM)	+	Yes	-
20	?	?	NT	-	-	-	-	-	-	-	NA	Cobalt
21	+	-	-	-	-	-	-	-	-	-	NA	Methylhydroquinone, formaldehyde
22	+	-	+	-	-	-	-	+ (FM I)	+ (LIM, LIN)	+	No	MMA, Sodium metabisulfite, MDBGN
23	++	+	NT	+	NT	+	-	+ (MP)	-	+	No	TEGDMA, Colophonium
24	++	++	+	+	+ (A, C)	+	-	-	+ (LIM, LIN)	+	No	-
25	+++	-	+	-	-	-	-	+ (MP)	+ (LIM, LIN)	+	No	BIT, MDBGN, benzoic acid, sodium benzoate
26	-	-	NT	-	NT	-	-	+ (MP, FM I)	+ (LIM)	+	No	-
#positives/# tested	**18/26**	**10/26**	**3/4**	**8/26**	**5/23**	**5/25**	**2/25**	**10/21**	**11/18**	**13/23**	**NA**	**NA**
#positives/# tested <u>and</u> IBOA-positive	**18/18**	**10/18**	**3/4**	**8/18**	**5/16**	**5/17**	**2/17**	**7/17**	**9/14**	**11/18**	**NA**	**NA**

All patch test reactions concern those observed on day (D) 4 following the application of the tests.
*SLM (sesquiterpenelactone mix) components: alantolactone [A] 0.033% pet., dehydrocostus lactone 0.1% pet., costunolide [C] 0.1% pet.
**Fragrances from the baseline series: *Myroxylon Pereira* [MP] 25% pet., fragrance mix I [FM-I] 8% pet., Lyral® 5% pet., fragrance mix II (FM-II] 14% pet., Evernia furfuracea 1% pet.
***Fragrances from the recommended additions: limonene hydroperoxides (LIM) 0.3% and 0.2% pet., linalool hydroperoxides (LIN) 1% and 0.5% pet.

IBOA= isobornyl acrylate 0.1% pet.
IBOMA= isobornyl methacrylate 2% pet.
PEA= 2-phenoxyethyl acrylate 0.1% pet.
SLM= sesquiterpene lactone mix 0.1% pet.
CM-II= compositae mix II 2.5% pet.

PPD = *p*-phenylenediamine 1% pet.
MCI/MI = methylchloroisothiazolinone/methylisothiazolinone 0.02% aq.
MMA = methylmethacrylate 2% pet.
BMA = butyl methacrylate 2% pet.
TEGDMA = triethyleneglycol dimethacrylate 2% pet.
BIT= benzisothiazolinone 0.1% pet.
MDBGN = methyldibromo glutaronitrile 0.5% pet.
IPBC = iodopropinyl butylcarbamate 0.2% pet.

Table 2. The IBOA content of diabetes devices, used with* or without° skin reactions, by 11/26 patients with cutaneous adverse events, including possible allergic contact dermatitis (ACD), from FreeStyle Libre (FL).

Patient n°	**IBOA 0.1% pet.**	**Diabetes devices used, with*/without° skin reactions**	**IBOA content of the devices****
1	+	Insulin infusion set° (Accu-Chek Insight Flex)	+ (traces)
7	-	Glucose sensor* (Enlite) Insulin infusion set* (Minimed)	+ + (some subtypes)§
8	+	Insulin infusion set° (Minimed)	+ (some subtypes)§
9	+++	Glucose sensor* (Enlite) Glucosesensor° (Dexcom G5) Insulin infusion set* (Minimed)	+ - + (some subtypes)§
10	++	Glucose sensor° (Dexcom G5)	-
12	++	Glucose sensor° (Dexcom G5)	-
17	?	Insulin infusion set° (type unknown)	?
19	-	Insulin infusion set* (Accu-chek Combo)	?
22	+	Insulin infusion set° (Accu-chek Aviva Insight)	?
23	++	Glucose sensor* (Enlite) Glucose sensor° (Dexcom G5)	+ -
26	-	Insulin infusion set* (type unknown)	?

+ : contains IBOA
- : contains no IBOA
? : IBOA content unknown
* : with skin reactions, °without skin reactions
** : IBOA content of diabetes devices based on the literature and/or on the current study
§ : Minimed® Quick-Set and Minimed® Sure-T contain trace amounts of IBO, whereas Minimed® Silhouette does not contain IBOA.