

Isobornyl Acrylate

Olivier Aerts, MD, PhD,* Anne Herman, MD,† Martin Mowitz, MSc, PhD,‡ Magnus Bruze, MD, PhD,§ and An Goossens, PhD§

Multidisciplinary collaboration between several European dermatology departments has identified isobornyl acrylate (IBOA; CAS 5888-33-5), once deemed a low-risk sensitizer, as a major culprit contact allergen in glucose sensors and insulin pumps, medical devices used by diabetes patients worldwide. Although the patch test modalities of IBOA have been fairly well characterized, intriguing questions remain. For example, its cross-reactive profile to other acrylates remains to be determined, and the striking occurrence of concomitant positive patch test reactions to sesquiterpene lactones needs to be further elucidated. Importantly, the path to its discovery as a contact sensitizer in diabetes devices and the difficulties that were associated with this quest illustrate that apparent difficulties in obtaining sufficient cooperation from the medical device industry may seriously hamper the correct workup of cases of allergic contact dermatitis. The IBOA saga will convince companies to lend more cooperation to dermatologists and policymakers to side with patients and physicians when it comes to updating medical device regulations, including the compulsory labeling of medical devices in general and of diabetes devices in particular.

In the past few years, the development of high-tech medical devices has revolutionized the diagnosis and treatment of human diseases. In the field of diabetology, the surge of continuous and flash glucose monitoring systems and insulin pumps can be considered a real game changer: these innovative instruments allow diabetes patients to monitor and respond to their glycemia levels without the hurdle of repeated skin pricks. It is against this background, during 2017, after the wide adoption of a newly introduced glucose sensor, that a worldwide epidemic of allergic contact dermatitis (ACD) was born.¹ The search to find the culprit sensitizer(s) proved to be a successful example of international and multidisciplinary collaboration between Belgian and Swedish dermatologists, pharmacists, and chemists.

The Calm Before the Storm: IBOA, A Rare Skin Sensitizer?

Isobornyl acrylate (IBOA; CAS 5888-33-5), or the isobornyl ester of acrylic acid, can be obtained by a chemical reaction between acrylic acid and camphene, a bicyclic monoterpene. The raw material of IBOA, besides containing several, unidentified impurities, might also contain acrylic acid and/or camphene residues (<1%).² Isobornyl

acrylate, a photopolymerizable acrylate monomer, is available as a liquid substance. It is used in coatings, sealants, glues, adhesives, paints, and inks and, according to some sources, also as a plasticizer in various plastic materials.³ It has also been claimed to be a potential impurity in preparations containing alkyl glucosides³; however, a Belgian study was unable to confirm this.⁴

Isobornyl acrylate displays qualities of hardness combined with flexibility and impact resistance, making it also an ideal substance in medical devices. According to material safety data sheets, it is foremost a skin irritant, but not an important skin sensitizer.⁵ Historically, IBOA has indeed rarely led to any significant cases of skin sensitization and thus managed to stay under the radar for quite some time. For example, despite the fact that IBOA has repeatedly been identified as a highly concentrated component (>60%) in different work-related, UV-cured, and bicomponent acrylic glues, it was hardly ever the cause of ACD in this context. In Poland, Kiec-Swierczynska et al⁶ reported on a miniepidemic involving 12 laborers experiencing occupational ACD from such a glue, a similar case having been observed by Kanerva et al⁷ in Finland. In all these patients, despite skin contact with IBOA, other (meth)acrylates were identified as the responsible sensitizers. More recently, in 2013, Christoffers et al⁸ reported an industrial process operator experiencing hand dermatitis while working in a glass fiber-producing factory; although he was effectively shown to be sensitized to IBOA, 14 other acrylate-sensitized patients failed to show cross-reactions to this particular component, leading the authors to conclude that there was insufficient support to include IBOA in a (meth)acrylate test series. Similarly, reassuring occupational experience with IBOA also led researchers of the Finnish Institute of Occupational Health to cease its routine testing in their (meth)acrylate series.⁹ However, a publication from the Leuven department, dating back to 1995, detailed 2 young female diabetes patients, who had developed eczema and abscesses at and around the injection site of several portable insulin pumps (Cliniset and Clinisoft

*From the *Department of Dermatology, University Hospital Antwerp (UZA) and University of Antwerp; and †Department of Dermatology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ‡Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö, Sweden; and §Department of Dermatology, University Hospitals, KU Leuven, Belgium.*

Address reprint requests to Olivier Aerts, MD, PhD, Department of Dermatology, University Hospital Antwerp (UZA) and University of Antwerp, Wilrijkstraat 10, B-2650 Antwerp, Belgium. E-mail: olivier.aerts@uza.be.

The authors have no funding or conflicts of interest to declare.

DOI: 10.1097/DER.0000000000000549

© 2020 American Contact Dermatitis Society. All Rights Reserved.

[Pharmaplast, Vaerloese, Denmark] and Disetronic [Disetronic Medical Systems, Burgdorf, Switzerland]).¹⁰ Patch tests were positive to scrapings of the plastic surrounding the needle, and it was subsequently shown that several acrylates, all components of the UV-cured glue (Loctite 302; Loctite International, Dublin, Ireland), used to fix the needle into the plastic, were responsible. It was hypothesized that these acrylates had somehow diffused into the surrounding plastic; hence, these had been capable of inducing sensitization and subsequent ACD. Among other components, IBOA, patch tested at 0.1%, 0.01%, and 0.001% in petrolatum (pet.), had been identified as one of the major culprit sensitizers. Both patients were successfully switched to an alternative insulin infusion set, manufactured by using a process called “heat staking,” a procedure in which the plastic is melted around the needle and no glue is used. In the years, thereafter, similar cases of ACD from diabetes devices were observed, and most of these were attributed to (meth)acrylates other than IBOA.^{11–14}

Cutaneous Adverse Events Related to the Use of Diabetes Medical Devices

From 2014 onward, several cases of ACD related to the use of newly launched glucose monitoring devices (eg, Enlite; Medtronic, Fridley, MN; FreeStyle Libre; Abbott Diabetes Care, Alameda, CA; Dexcom; Dexcom, San Diego, CA) were observed throughout Europe. For example, in Germany, more than two-thirds of the FreeStyle Libre glucose sensor users seemed to experience “unspecified skin reactions.”¹⁵ Dermatologists cooperating in allergy vigilance networks (eg, the French Réseau de Vigilance en Dermato-Allergologie) and also communications at medical conferences (eg, the Groupe d'Études et de Recherche en Dermato-Allergologie) highlighted that in some of these patients patch tests with pieces of the adhesives contained in the diabetes devices had resulted in morphologically contact-allergic skin reactions, indicating ACD rather than irritant contact dermatitis (ICD). Associated itch, progressive worsening, and distant spreading reactions further argued for a contact-allergic mechanism. Contrary to earlier suggestions that the observed cutaneous adverse events might just be a reflection of ICD or relate to a preexistent contact allergy from acrylates,^{16,17} the rather late onset of the dermatitis (ie, 2 weeks or later after the first use of most of the devices) not only favored ACD but also even indicated primary sensitization to 1 or more components contained in them.

Given that nowadays (meth)acrylates, the main suspected sensitizers in medical adhesives, are hardly ever specified on the respective packagings or accompanying leaflets, many dermatologists have already pursued allergy investigations with extended, commercially available (meth)acrylate series. These, however, have in most cases yielded no results. Many colleagues mentioned frustrating and time-consuming interactions with the industry, including difficulties in obtaining basic information on the type of adhesives used and lack of cooperation when (raw) materials were requested to perform customized, in-house prepared patch tests. Whenever manufacturers did lend some cooperation, it was sometimes negotiated within the frame of confidentiality agreements, not allowing the respective physicians to report about potential skin sensitizers

contained in their products. Kamann et al,¹⁸ although bound by such agreement, communicated that the acrylates used in medical adhesives clearly differ from the ones nowadays present in commercially available patch test trays, hence explaining why most workups remained unsuccessful. Equally troublesome was the fact that even the registration of cases at national EU and US pharmacovigilance authorities did not seem to contribute to a solution either.¹⁹ As evidenced by the organization of online petitions and numerous testimonials of patients on social media and Internet forums (eg, <http://diabeteetmechant.org/>, <https://www.diabetes.co.uk/>), the problem of ACD caused by diabetes devices is certainly not limited to some isolated cases. The problem was truly a “catch 22” for many patients, as they clearly experienced great benefit from these devices in controlling their diabetes but, eventually, had to stop using them because of the sometimes severe cutaneous adverse effects. The need to rely again on skin pricks inevitably meant a step backward and a serious decrease in their quality of life. Ironically, when these patients contacted customer care services, they were often referred to their treating physicians, who, themselves, in view of the insufficient cooperation from manufacturers, were unable to offer any help.

Together with the steep increase in the number of cases observed by many dermatologists, the identification of the culprit sensitizer(s) became more urgent every day, but efforts to identify it remained unsuccessful until the end of 2016.

The Discovery of IBOA in a Popular Glucose Sensor: The Story Behind

Many discoveries in medicine have been made by accident, and the finding of IBOA as a major culprit sensitizer in diabetes devices was no exception to this. During 2016, an adult female patient was referred to the Antwerp (UZA) department because of a suspicion of occupational ACD after the manipulation of several chemicals, including IBOA. However, patch tests with this acrylate at 0.1%, 0.05%, and 0.01% in pet. (in-house diluted from raw material obtained from Kowa Europe, Düsseldorf, Germany) remained completely negative, whereas the culprit sensitizer was shown to be a limonene-related solvent. Shortly thereafter, in November 2016, a 9-year-old adolescent boy presented at the UZA department with ACD from his FreeStyle Libre glucose sensor. Patch tests with IBOA and an acrylate series containing more than 30 commercialized (meth)acrylates (Chemotechnique, Vellinge, Sweden) were performed, showing positive results only to IBOA 0.1% and 0.05% pet. (both ++), and 0.01% pet. (+) on days (D) 2 and D4. Although, as stated previously, IBOA was known to be a potential contact allergen in diabetes devices,¹⁰ it had been applied accidentally by the patch test nurse, who was unaware this contact allergen was not a part of the standard UZA patch test tray of (meth)acrylates.

After this observation, the contact allergen was also patch tested by the Leuven and Brussels departments, where several patients, experiencing ACD related to the use of the same glucose sensor, had been observed. Patch tests in these patients confirmed IBOA as a potential culprit. Although a strong suspicion was thus raised,

the presence of IBOA in the culprit device remained to be shown. At this point, input from the industry manufacturing and distributing medical devices again proved disappointing; the company could not confirm whether IBOA had specifically been used in the manufacture process. Instead, and quite ironically, a long list of potential allergens “not” contained in the adhesive was provided, seemingly compiled by notifications of results of allergy tests previously performed by other dermatologists, who tried to manage similar problems in their patients. As evidenced by some messages on social media, also patients were sometimes sent the very same “negative” list, which, obviously, was of no help to them either. When, in Malmö, a similar patient was observed, a patch test with an acetic ultrasonic bath extract of the whole glucose sensor revealed a positive reaction, whereas 20 controls showed no reactions to it. None of the usual suspect acrylates was shown to be the culprit, and gas chromatography–mass spectrometry (GC-MS) screening of the extract, to search for acrylates, did not result in a positive match either. Similar to the Belgian experience, approaching the manufacturer for help proved unsuccessful and other affiliates of the same company, in and outside Europe, did not contribute to a solution either. However, when the Belgian patch tests results with IBOA were communicated to the Swedish group, the chemical analyses, by means of GC-MS, were focused more precisely on this particular acrylate, which subsequently could be detected in the extract of the device. Approximately 80% of patients experiencing ACD caused by that particular glucose sensor were eventually shown to be sensitized to IBOA.¹ French and German dermatologists confirmed, also in their patients, that IBOA was often the culprit sensitizer provoking ACD from the same glucose sensor.¹⁸

Interestingly, and similar to earlier observations with insulin pumps,¹⁰ the GC-MS investigations at the Swedish laboratory showed that the adhesive patch itself was not the actual source of IBOA, but rather it was suspected that IBOA was released from a glue used to join the top and the bottom part of the glucose sensor housing, which subsequently migrated into other parts of the sensor. This finding was later on confirmed by German researchers, who, after contacts with the suppliers of the adhesive material to be used in the glucose sensor's adhesive patch, were able to patch test the finished adhesive components, which, surprisingly, gave no positive reactions.¹⁸ Their patient, however, had shown contact-allergic skin reactions to the glucose sensor itself and to IBOA 0.1% pet. The authors thus confirmed that IBOA was indeed foremost contained in the plastic part of the sensor. This finding also explains why some patients reacted to their glucose sensor as a whole but showed no reactions when a small piece of (only) the adhesive part, containing little to no IBOA, was patch tested. Similar observations have previously been made with regard to ethyl cyanoacrylate, shown to be a sensitizer in another glucose sensor.^{20–22}

Contact Allergy to IBOA: A New Epidemic

Besides in Belgium and Sweden, cases of ACD from IBOA in diabetes devices were also reported in France, Germany, Italy, Spain, Finland, and Japan,^{18,23–26} both in adults and children. Dermatologists from various other countries also expressed concerns on similar cases

and highlighted the additional problem that after the initial publication¹ no commercialized patch test material of IBOA 0.1% pet. existed, rendering a correct allergy workup difficult.

Up until now, only limited information exists on the true scope of the epidemic, that is, the actual number of patients sensitized to IBOA from its presence in the previously mentioned glucose sensor and related diabetes medical devices. According to the French governmental agency ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), the number of cutaneous adverse events arising from the particular glucose sensor FreeStyle Libre has been stable since June 2018 with approximately 0.2% (or 2 of 1000) patients requiring a medical follow-up.²⁷ Such figures, relating to the general population, are evidently lower than the experience in highly specialized patch test clinics, where easily 1 or 2 patients are evaluated every week for ACD from potentially IBOA-containing diabetes devices. For example, in Finland, of 6567 FreeStyle Libre users, 63 (1.0%) developed cutaneous adverse reactions,²⁴ with 51 (81%) of them shown to be sensitized to IBOA, equaling a 0.8% prevalence of IBOA sensitization in the whole population of FreeStyle users. The 81% IBOA sensitization in the group of FreeStyle users is in agreement with data from the initial publication.¹ Some centers (eg, the Antwerp UZA department) have nowadays noted slightly lower figures of IBOA sensitization (68%) in FreeStyle users, indicating that other contact sensitizers may still be of importance.²⁸ Alternatively, the device may recently have been modified (see hereinafter). Furthermore, the Finnish authors stipulated that 1% of patients experiencing skin problems are actually referred patients, mostly experiencing severe dermatitis, whereas the real number of patients experiencing “any” type of skin adverse effect is probably much higher, that is, in the magnitude of 5.0%. The latter figure concurs well with experience at the Antwerp UZA patch test clinic where, notwithstanding, a potential referral bias that might overestimate the true occurrence of IBOA-related dermatitis, approximately 5.5% of patients are referred for patch tests because of adverse cutaneous reactions due to the use of diabetes medical devices, mostly FreeStyle Libre (data on file²⁸). Danish studies reported even far higher rates of cutaneous adverse effects caused by diabetes medical devices, that is, in 35% to 46% of the patients, although these did not only concern potential ACD and patch tests were not performed.^{29,30} Care, in any case, must be taken not to underestimate the occurrence of IBOA contact allergy, especially considering that (a) there are millions of diabetes patients across the globe eligible for the use of IBOA-containing medical devices; (b) more than 1.3 million people are currently using such a device (ie, FreeStyle Libre)³¹; (c) not all cutaneous adverse effects, especially the minor ones, are necessarily reported to the manufacturer, authorities, or treating physicians; (d) not all patients are able or willing to undergo patch tests; and (e) in those in whom patch tests could be applied, IBOA, until recently not commercially available, was often not patch tested.

Broadening of the Epidemic

Shortly after ACD from IBOA in FreeStyle, the first cases of ACD from IBOA in Omnipod (Insulet Corporation, Billerica, MA), an

innovative, tubeless insulin pump, were reported.^{32,33} In 2 of the 4 patients reported by Raison-Peyron et al,³² initial IBOA sensitization had occurred from its presence in the FreeStyle sensor, whereas in the other 2 patients, primary sensitization to IBOA was caused by the Omnipod device itself; one of the latter patients later also showed ACD from the FreeStyle sensor. Similar to experience with the FreeStyle device, the highest IBOA concentrations were again found in the Omnipod unit itself, as opposed to the adhesive patch, which, in all 4 patients, gave negative patch test results.

Interestingly, also other sources of IBOA, and of the related isobornyl methacrylate (IBOMA), exist nowadays. Notably gel nail polishes may contain both allergens, and IBOA-based copolymers are also used in sun-protecting creams (personal observation by O.A.). Moreover, these (meth)acrylates might also be present in other medical adhesives (eg, other diabetes devices, adhesive tapes, etc). Whether such sources are capable of inducing sensitization to IBOA, or elicit ACD in already sensitized subjects, remains to be demonstrated.

Patch Testing IBOA and Potentially IBOA-Containing Medical Devices

Similar to other acrylates, IBOA has often been patch tested at 0.1% pet.¹ Initially, further dilutions, such as 0.05% and 0.01% pet., were used as well, although the latter, and certainly even lower concentrations (eg, 0.001% pet.), bear the risk of resulting in false-negative reactions.³² Christoffers et al⁸ demonstrated that higher test concentrations, such as 0.3% pet., frequently result in irritant skin reactions and thus should be avoided.⁸ Hyry et al²⁴ argued that given the sometimes strong patch test reactions to IBOA 0.1% pet. observed, often already on D2, an intermediate test concentration of 0.032% pet. might be more suitable.²⁴ The latter, however, again bears the risk of missing contact allergy; in case the reading of the lower concentration on D2 remains negative, this might then be overcome by additional patch testing with the 0.1% pet. preparation. Acetone is equally possible as a vehicle for IBOA,¹ but comparative studies on the most optimal vehicle for IBOA are lacking. Overall, in daily practice, the 0.1% pet. preparation, which was recently commercialized (B. Niklasson, e-mail communication, June 21, 2019), and for which numerous negative controls have been established in the literature, is usually feasible. Negative or doubtful (?) patch test reactions to IBOA 0.1% pet. might exceptionally occur during the first readings, especially in weakly sensitized individuals, making later readings (eg, on D7), as for other (meth)acrylates, necessary. Furthermore, IBOA, like other acrylates, is a volatile substance, and preloading on patch test chambers should be avoided, whereas adequate (refrigerated) storing is necessary. If sensitization to IBOA is suspected, it should be specifically patch tested for, as cross-reactions to other acrylates seem relatively rare (see hereinafter). In line with this, it is important to realize that 2-hydroxyethyl methacrylate, recently added to the European baseline series,³⁴ nor any other (meth)acrylates contained in national baseline series currently serve as a marker for contact allergy to IBOA.

In the workup of ACD from diabetes devices, besides a baseline series (containing colophonium 20% pet.), most physicians also test

commercialized patch test trays containing a limited or extended selection of (meth)acrylates, plastics and glues allergens, epoxy resins, isocyanates, plant allergens (see hereinafter), as well as the colophonium derivatives abitol and abietic acid (both 10% pet.), and personal care products (eg, disinfecting wipes). As the adhesive patches contained in diabetes devices (eg, FreeStyle, Omnipod), as opposed to the devices themselves, have been shown to contain little to no IBOA, it should be anticipated that patch testing these adhesives “as is” may result in false-negative reactions.¹⁸ If performed, large enough pieces should be patch tested, or if feasible, (acetonic) extracts should be made, preferably from the different parts of the device (eg, the adhesive part vs the plastic unit).

Risk Factors, Clinical Presentation, and Consequences of Contact Allergy From IBOA

Contact allergy to, and ACD from, IBOA contained in medical devices, such as the FreeStyle Libre sensor, has been reported to occur regardless of age, sex, and atopy status.²⁴ Nevertheless, in some series, a relative overrepresentation of female patients has been noted,² and some authors have stressed the large number of children involved.¹⁹ Most patients reported so far were experiencing diabetes type 1, although occasionally also diabetes type 2 or other endocrinological diseases have been involved.

Why did sensitization to such an innocuous acrylate, such as IBOA, suddenly occur in these patients? Possible explanations relate to the specific exposure conditions: the long wearing time of the IBOA-containing devices on the skin (eg, 14 days in case of the FreeStyle Libre sensor), possibly with preexistent ICD enhanced by sweating and friction, thus facilitating primary sensitization. Previously, unsensitized patients presented with symptoms of ACD after various delays, some already after 2 weeks, others only after 1 year, with the gross majority after approximately 6 months. As stipulated previously, this long lag time effectively indicates ACD, and even primary sensitization, and not ICD. Upon re-exposure, ACD develops more rapidly and more pronounced, and an initially mild dermatitis may transform into a progressively worse one, often making further use of a culprit device impossible.

Some patients developed reactions to an IBOA-containing device already after its first use, indicating preexistent sensitization from another source. Besides other medical devices (eg, insulin pumps, glucose sensors), Raison-Peyron et al³² also questioned whether the previous use of long-lasting nail gel polishes might be a risk factor for IBOA sensitization, although this remains to be demonstrated.

With regard to the clinical presentation, many patients develop an (intractable) itch, sometimes accompanied by burning sensations, erythema, edema, (severe) vesiculation, blistering, oozing, bleeding, and/or pus formation (Figs. 1, 2). Skin erosions and even ulcers, sometimes referred to as “burn wounds” by patients, may develop, which, given their diabetes status, may bear an additional risk of superinfection. Evidently, the further use of such device then becomes virtually impossible, and in some patients, the strong suppuration even makes the device come off spontaneously. Residual hyperpigmentation



Figure 1. Mild ACD caused by a previously applied IBOA-containing FreeStyle Libre glucose sensor.

may occur, and recently, a first case of acquired leukoderma has been reported, attributed to the presence of the polymerization inhibitor hydroquinone monomethyl ether.³⁵

Some patients noticed skin reactions from other acrylate-based (barrier) adhesives, whereas others, who previously tolerated a concomitantly used insulin pump, all of a sudden, after the occurrence of IBOA sensitization from a newly introduced IBOA-containing glucose sensor, noticed (strong) skin reactions to the insulin pump as well. The presence of a lower amount of IBOA or a cross-reacting acrylate in the pump or another concomitantly present sensitizer in both the glucose sensor and pump might be possible explanations.

Equally intriguing is the fact that some patients, although reacting to IBOA-containing glucose sensors, were still continuing the use of other IBOA-containing devices (eg, insulin pumps), which is possibly explained by a lower IBOA content (ie, too low to elicit skin reactions) and/or a shorter exposure time, although changes in the manufacture process of the latter might not be excluded.³⁶

Patients have occasionally highlighted that with the occurrence of strong local skin inflammation and edema, glycemia measurements became unreliable (eg, indicating a lower glycemia level than actually present, possibly because of a too strong interstitial fluid dilution), although this has not been scientifically evaluated; indeed, such an end point has hitherto not been included in studies dealing with ACD from glucose sensors.

Besides local spreading of the dermatitis, also the development of the contact dermatitis syndrome, with generalized eczema and/or vesiculopustular palmoplantar involvement, has been induced by the IBOA-containing FreeStyle sensor.³⁷

Concomitant Sensitizations and Cross-reactions

Despite IBOA being an acrylate, most sensitized patients seem to have negative patch test results to other acrylates. However, concomitant reactions to acrylates, diacrylates, and methacrylates have occasionally been observed, notably to ethyl acrylate and hydroxyethyl acrylate and to a lesser extent to hydroxypropyl acrylate and ethylhexyl acrylate.^{1,2} Simultaneous patch test reactions to acrylic acid 0.1% in saline solution have been observed as well.²³ Whether all these

reactions represent concomitant or cross-reactions remains to be determined. It should be noted that in most patients reported so far only a limited number of additional (meth)acrylates have been patch tested; results from patch tests with all commercially available (meth)acrylates, in larger groups of patients, might shed some more light on the exact cross-reactivity profile of IBOA. In view of the previous observations made by occupational dermatologists, who often patch test larger (meth)acrylate series, it does seem rather unlikely that IBOA easily cross-reacts with other acrylates.

A study by researchers from Malmö and Brussels showed that 7 patients reacting to the FreeStyle glucose sensor were sensitized to *N,N*-dimethylacrylamide, 6 of whom also to IBOA, the presence of which was also confirmed in the device. Both IBOA and *N,N*-dimethylacrylamide seem to be frequently present together in high concentrations in medical grade UV-cured adhesives, such as Loctites.³⁶

Interestingly, more than half of IBOA-sensitized individuals also show positive patch tests reactions to the sesquiterpene lactone mix 0.1% in pet., as present in the European baseline series, and/or to its individual components.² Notably positive reactions to alantolactone (0.1% pet.), and to a lesser extent to costunolide and/or dehydrocostus lactone, have been observed (Figs. 3–5). Occasionally, patients also



Figure 2. Severe ACD caused by the IBOA-containing FreeStyle Libre glucose sensor; in this patient, spontaneous detachment of the sensor frequently occurred.



Figure 3. Positive patch test reactions, on D4, to (from top to bottom): IBOA 0.1% pet., 0.05% pet., and 0.01% pet.

react to the compositae mix II (2.5% pet.), whereas concomitant reactions to parthenolide (0.1% pet.) and α -methylene- γ -butyrolactone (0.01% pet.) are only very rarely observed. Although still not fully excluded, chemical analyses by means of GC-MS could not demonstrate the presence of sesquiterpene lactones in the FreeStyle Libre sensor or in patch test materials containing IBOA. Conversely, IBOA could not be demonstrated in any of the sesquiterpene lactone patch test materials. Moreover, the manufacturer of the FreeStyle sensor has recently also denied the presence of these compounds in the device.²⁴ This makes concomitant sensitization, through concomitant exposure, rather unlikely. Although IBOA and the 3 previously mentioned lactones share the same chemical reactive function, that is, a carbonyl group (C=O), their spatial structure is completely different, hence not likely to activate the same T-cell receptor, thus also making cross-reactivity rather unlikely. Nevertheless, a further evaluation of potential cross-reactivity is currently under investigation by A.H. (UCL, Brussels). Possible hypotheses for the frequently observed concomitant reactions to IBOA and sesquiterpene lactone mix may still concern (a) a common precursor molecule, such as camphene, or (b) (non)enzymatic reactions, for example, auto-oxidation on air exposure, that might modify the chemical structure of IBOA, resulting in the formation of a new substance able to cross-react with sesquiterpene lactones.² With regard to the former, it



Figure 4. Positive patch test reactions, on D4, to the sesquiterpene lactone mix 0.1% pet. in the same patient as Figure 3.

should be stressed that IBOA patch test preparations, made from raw materials obtained through chemical suppliers, are not 100% pure but may contain impurities, such as camphene residues. The latter have been found in sesquiterpene lactone-containing plants, as well as in UV-cured adhesives (up to 1%) used in medical devices (ie, Loctites).²

An Italian case report demonstrated that adhesives of diabetes devices, such as the IBOA-containing Omnipod insulin pump, but also the Enlite glucose sensor, might contain colophonium (rosin), although not verified through chemical analyses.³⁸ This has not been demonstrated for the IBOA-containing FreeStyle glucose sensor, for which the manufacturer has recently also denied its presence.²⁴ Nevertheless, with regard to the latter, concomitant reactions to colophonium, or its derivatives abitol and abietic acid, have occasionally been observed. In this regard, it should be mentioned that some patients, to achieve an improved adhesion of their diabetes devices to the skin, may use supplemental adhesives (eg, Skin-Tac wipes; Torbot group,

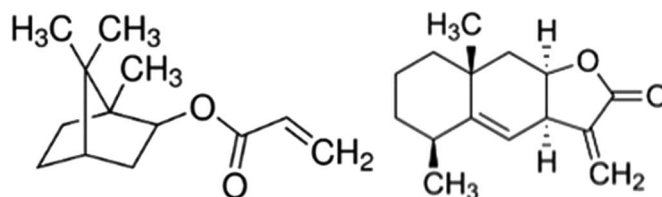


Figure 5. Isobornyl acrylate (IBOA) (left) and the frequently coreacting alantolactone (right).

Warwick, NY), which contain “rosin” (synonym colophonium). This might ultimately cause separate, concomitant sensitization to this omnipresent contact allergen (personal observation by O.A.).

Positive patch test reactions to metals, preservatives, and especially fragrances, as well as to many other substances, have also often been observed in IBOA-sensitized patients, although most of these lack relevance with regard to the IBOA-containing devices. Nevertheless, some patients seem to be polysensitized. Finally, no concomitant reactions have been observed to ethyl cyanoacrylate.

Management of Allergic Contact Dermatitis From IBOA-Containing Medical Devices

Simply relocating the culprit device is of no help in cases of ACD. Only complete avoidance of, or at least a substantial decrease in exposure to, a culprit sensitizer is necessary to avoid progressive worsening and relapsing dermatitis. Many patients, however, do not want to give up on the use of the IBOA-containing medical devices that markedly increased their quality of life. Therefore, many solutions are tried,³⁹ ranging from film-forming agents (eg, Cavilon No Sting Barrier Film; 3M, Saint Paul, MN), over corticosteroid nebulizers (eg, mometasone-containing nasal sprays), to physical barriers (eg, hydrocolloid dressings: Compeed, Stomahesive), or combinations thereof.^{24,37,40} Many of these solutions have been derived from experiences in the management of ACD in stoma patients. Finnish researchers, for example, specifically reported that Eakin Surround (TG Eakin Limited, Comber, United Kingdom) offered the best protection in their series.²⁴ These tools, being medical devices themselves, might indeed offer some alleviation of the symptoms; however, many patients still experience dermatitis to some extent; moreover, these devices may be impractical to use and be expensive. In the previously mentioned Finnish study, not a single patient was able to continue the use of the culprit sensor without some kind of barrier method, but even then, the dermatitis still did not resolve completely.²⁴ Particularly with regard to the frequently advised film-forming agents, the Antwerp department showed that in most cases these barrier sprays, although claimed to prevent ACD and even contact dermatitis syndrome,³⁷ do not offer adequate protection. Of 16 patients who tried the latter solution, only 5 experienced limited and transient improvement of the dermatitis, and eventually only 2 patients, of whom one deemed to experience ICD rather than ACD, were satisfied with this solution.²⁸ Sometimes, barrier methods have also been shown to be sources of (additional) ICD or ACD. For example, Cavilon contains an acrylate terpolymer of which the actual acrylate components remain unidentified; many adhesives are based on—again largely unknown—(meth)acrylates; and hydrocolloid dressings may contain colophonium-derived allergens.^{1,41} The use of barrier methods might also hamper the proper functioning of the glucose sensors and related devices. In this regard, the Medicines & Healthcare Products Regulatory Agency in the United Kingdom has even advised against the use of such barrier materials.⁴² Overall, many patients still have to give up on the use of their IBOA-containing devices and try another device on a “trial-and-error” basis. However,

simply switching from, for example, one glucose sensor to another, does not always heal the eczema either.²⁴ The presence of IBOA, or a cross-reacting substance, or a concomitantly present allergen to which the patient has been sensitized, may all be possible explanations. For example, Oppel et al¹⁵ showed that patients experiencing ACD from FreeStyle may tolerate Dexcom glucose sensors, shown by GC-MS to be free from IBOA. However, Hyry et al²⁴ found that one of their patients who tried this solution still had mild remaining dermatitis. Overall, vigilance is required as some alternatives may contain potentially the same or cross-reactive acrylate sensitizers. For example, many patients, who react to the IBOA-containing FreeStyle device, have also shown reactions to Enlite sensors,²⁴ raising the question whether the latter might also contain IBOA.^{43,44} Recently, it was confirmed that IBOA is a contact allergen in the Enlite glucose sensor and likely also in the infusion set Paradigm MiniMed QuickSet.⁴⁵ Curiously, some patients who previously did not tolerate the IBOA-containing FreeStyle Libre and Omnipod devices now seem to tolerate these devices again, possibly related to changes in the manufacture process. However, the exact changes remain unclear, and at present, both older and newer versions of these devices have been put on the market, with no clear possibility to distinguish between both, hence still leaving physicians and patients puzzled (personal observation, A.H.).

What the IBOA Story Teaches Us: Gaps in the Workup of ACD From Medical Devices

To adequately handle cases of ACD from medical devices, the identification of culprit sensitizer(s) is paramount. Only this way a diagnosis can be reached, and safer, allergen-free alternatives can be proposed. When the previously mentioned 2 first cases of ACD from IBOA in diabetes devices were reported, both the manufacturer of the insulin pumps and the supplier of the glue were remarkably cooperative in supplying information and samples of raw materials for patch testing.¹⁰ This contrasts with the obstacles encountered by physicians and patients nowadays: difficulties in obtaining information on chemicals used during the manufacture of medical devices often still hamper the correct workup of numerous patients. Nevertheless, every cloud has a silver lining: recent production changes made by the manufacturer of a popular IBOA-containing glucose sensor²⁷ indicate that occasionally the efforts and results of multidisciplinary collaboration do convince manufacturers to improve their medical devices, ultimately benefitting patients. We can only hope that companies will be inclined to better cooperate with dermatologists in the future; that is, they will supply relevant information, respond to inquiries concerning the manufacture process, and provide samples of (raw) materials for patch testing. Furthermore, well-known sensitizers, if possible, should be avoided, and the use of alternative materials and/or manufacture processes, such as “heat staking,” should be considered, whenever feasible.⁴⁶ Finally, authorities should impose full labeling of medical devices. Indeed, the IBOA story will also convince policymakers to side with patients and physicians when it comes to updating regulations. At present, and most regrettably

also in the forthcoming EU legislation on medical devices, such labeling obligation is still lacking.⁴⁷ In line with this pharmacovigilance, authorities should update and organize their databases and make these publicly accessible, at least to physicians dealing with (cutaneous) adverse effects from medical devices.¹⁹

CONCLUSIONS

Medical devices increasingly contain several types of (meth)acrylates worldwide, which unfortunately are not labeled on the packaging nor in the leaflets and not necessarily contained in commercialized patch test trays. These shortcomings seriously complicate the workup and care of patients experiencing ACD caused by them.⁴⁸ The recent epidemic of ACD from IBOA in diabetes devices, once deemed to be a rarely sensitizing acrylate, is a sad illustration hereof and probably represents only the tip of the iceberg. Isobornyl acrylate has been quite well characterized in terms of patch test modalities, concomitant reactions, and main allergen sources, but its precise cross-reactivity profile as well as further allergen sources remains to be determined. This acrylate truly merits the title of “Allergen of the Year,” as it is exemplary of everything that is currently going wrong in the diagnosis and prevention of ACD from medical devices. The IBOA saga teaches us that a more constructive dialog between manufacturers, dermatologists, and regulatory agencies can be the key to improve the management of ACD from them in the future. However, this would not only require manufacturers to unconditionally lend their cooperation but also require legislators to finally apply regulations on medical devices, including full labeling of their composition.

ACKNOWLEDGMENTS

The authors thank Mrs Patricia Willekens, a dedicated patch test nurse of the Dermatology Department of the University Hospital Antwerp (UZA), Belgium, who, with the rather accidental discovery of isobornyl acrylate (IBOA) sensitization in the first patient, made serendipity provide an eureka moment.

REFERENCES

- Herman A, Aerts O, Baeck M, et al. Allergic contact dermatitis caused by isobornyl acrylate in FreeStyle® Libre, a newly introduced glucose sensor. *Contact Dermatitis* 2017;77(6):367–373.
- Herman A, Mowitz M, Aerts O, et al. Unexpected positive patch test reactions to sesquiterpene lactones in patients sensitized to the glucose sensor FreeStyle Libre. *Contact Dermatitis* 2019;81:354–367.
- Foti C, Romita P, Rigano L, et al. Isobornyl acrylate: an impurity in alkyl glucosides. *Cutan Ocul Toxicol* 2016;35(2):115–119.
- Kerre S, Strobbe T, Naessens T, et al. Alkyl glucosides: newly identified allergens in foam wound dressings. *Contact Dermatitis* 2018;79(3):191–193.
- Material Safety Data Sheet (MSDS) of isobornyl acrylate. Available at: <https://www.sigmaaldrich.com>. Accessed July 4, 2019.
- Kiec-Swierczynska M, Krecisz B, Swierczynska-Machura D, et al. An epidemic of occupational contact dermatitis from an acrylic glue. *Contact Dermatitis* 2005;52:121–125.
- Kanerva L, Jolanki R, Leino T, et al. Occupational allergic contact dermatitis from 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate in a modified acrylic structural adhesive. *Contact Dermatitis* 1995;33:84–89.
- Christoffers WA, Coenraads PJ, Schuttelaar ML. Two decades of occupational (meth)acrylate patch test results and focus on isobornyl acrylate. *Contact Dermatitis* 2013;69(2):86–92.
- Aalto-Korte K, Alanko K, Kuuliala O, et al. Occupational methacrylate and acrylate allergy from glues. *Contact Dermatitis* 2008;58:340–346.
- Busschots AM, Meuleman V, Poesen N, et al. Contact allergy to components of glue in insulin pump infusion sets. *Contact Dermatitis* 1995;33:205–206.
- Saccabusi S, Boatto G, Asproni B, et al. Sensitization to methyl methacrylate in the plastic catheter of an insulin pump infusion set. *Contact Dermatitis* 2001;45(1):47–48.
- Jolanki R, Kanerva L, Estlander T, et al. Allergic contact dermatitis from phenoxyethoxy ethylacrylates in optical fiber coating, and glue in an insulin pump set. *Contact Dermatitis* 2001;45(1):36–37.
- van den Hove J, Jacobs MC, Tennstedt D, et al. Allergic contact dermatitis from acrylates in insulin pump infusion sets. *Contact Dermatitis* 1996;35(2):108.
- Herman A, de Montjoye L, Tromme I, et al. Allergic contact dermatitis caused by medical devices for diabetes patients: a review. *Contact Dermatitis* 2018;79(6):331–335.
- Oppel E, Kamann S, Reichl FX, et al. The Dexcom glucose monitoring system—an isobornyl acrylate-free alternative for diabetic patients. *Contact Dermatitis* 2019;81(1):32–36.
- Brahimi N, Potier L, Mohammedi K. Cutaneous adverse events related to FreeStyle Libre device. *Lancet* 2017;389:1396–1397.
- Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Cutaneous adverse events related to FreeStyle Libre device – authors’ reply. *Lancet* 2017;389(10077):1396–1397.
- Kamann S, Aerts O, Heinemann L. Further evidence of severe allergic contact dermatitis from isobornyl acrylate while using a continuous glucose monitoring system. *J Diabetes Sci Technol* 2018;12(3):630–633.
- Heinemann L, Kamann S. Adhesives used for diabetes medical devices: a neglected risk with serious consequences? *J Diabetes Sci Technol* 2016;10(6):1211–1215.
- Schwensen JF, Friis UF, Zachariae C, et al. Sensitization to cyanoacrylates caused by prolonged exposure to a glucose sensor set in a diabetic child. *Contact Dermatitis* 2016;74(2):124–125.
- Peeters C, Herman A, Goossens A, et al. Allergic contact dermatitis caused by 2-ethyl cyanoacrylate contained in glucose sensor sets in two diabetic adults. *Contact Dermatitis* 2017;77(6):426–429.
- Aschenbeck KA, Hylwa SA. A diabetic’s allergy: ethyl cyanoacrylate in glucose sensor adhesive. *Dermatitis* 2017;28(4):289–291.
- Corazza M, Scuderi V, Musmeci D, et al. Allergic contact dermatitis caused by isobornyl acrylate in a young diabetic patient using a continuous glucose monitoring system (FreeStyle Libre). *Contact Dermatitis* 2018;79(5):320–321.
- Hyry HSI, Liippo JP, Virtanen HM. Allergic contact dermatitis caused by glucose sensors in type 1 diabetes patients. *Contact Dermatitis* 2019;81:161–166.
- Mine Y, Urakami T, Matsuura D. Allergic contact dermatitis caused by isobornyl acrylate when using the FreeStyle Libre. *J Diabetes Invest* 2019;10(5):1382–1384.
- Jauregui I, Sanchez J, Segurolo A, et al. Allergic contact dermatitis by isobornyl acrylate in glucose monitoring devices: report of two cases. *Contact Dermatitis* 2019;81(3):219–220.
- Available at: <https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Mise-a-disposition-de-dispositifs-FreeStyle-Libre-avec-des-captateurs-modifies-Point-d-Information>. Accessed June 25, 2019.
- Pyl J, Dendooven E, Van Eekelen I, et al. Prevalence and prevention of contact dermatitis caused by FreeStyle Libre: a monocentric experience. *Submitted*.

29. Berg AK, Nørgaard K, Thyssen JP, et al. Skin problems associated with insulin pumps and sensors in adults with type 1 diabetes: a cross-sectional study. *Diabetes Technol Ther* 2018;20:475–482.
30. Berg AK, Olsen BS, Thyssen JP, et al. High frequencies of dermatological complications in children using insulin pumps or sensors. *Pediatr Diabetes* 2018;19(4):733–740.
31. Available at: <https://abbott.mediaroom.com/2019-02-21-New-Real-World-Evidence-Analysis-of-Nearly-Half-a-Million-FreeStyle-R-Libre-System-Users-Shows-Higher-Rates-of-Scanning-Improves-Glucose-Control>. Accessed July 20, 2019.
32. Raison-Peyron N, Mowitz M, Bonardel N, et al. Allergic contact dermatitis caused by isobornyl acrylate in OmniPod, an innovative tubeless insulin pump. *Contact Dermatitis* 2018;79(2):76–80.
33. Oppel E, Högg C, Summer B, et al. Isobornyl acrylate contained in the insulin patch pump OmniPod as the cause of severe allergic contact dermatitis. *Contact Dermatitis* 2018;79(3):178–180.
34. Wilkinson M, Gonçalves M, Aerts O, et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis* 2019;80(1):1–4.
35. Herman A, de Montjoye L, Marot L, et al. Induction of leukoderma following allergic contact dermatitis to FreeStyle Libre. *Contact Dermatitis* 2019;81(6):456–458.
36. Mowitz M, Herman A, Baeck M, et al. N,N-dimethylacrylamide—a new sensitizer in the FreeStyle Libre glucose sensor. *Contact Dermatitis* 2019;81(1):27–31.
37. Shinkawa E, Washio K, Tatsuoka S, et al. A case of contact dermatitis caused by isobornyl acrylate in FreeStyle Libre: the usefulness of film-forming agents. *Contact Dermatitis* 2019;81(1):56–57.
38. Passanisi S, Lombardo F, Barbalace A, et al. Allergic contact dermatitis and diabetes medical devices: 2 clinical cases. *Contact Dermatitis* 2018;79(2):115–117.
39. Messer LH, Berget C, Beatson C, et al. Preserving skin integrity with chronic device use in diabetes. *Diabetes Technol Ther* 2018;20(S2):S254–S264.
40. Kamann S, Oppel E. Hydrocolloid blister plaster decreases allergic contact dermatitis caused by FreeStyle Libre and isobornyl acrylate. *Contact Dermatitis* 2019;81(5):380–381.
41. Cressey BD, Belum VR, Scheinman P, et al. Stoma care products represent a common and previously underreported source of peristomal contact dermatitis. *Contact Dermatitis* 2017;76(1):27–33.
42. Medical Device Alert No. MDA/2019/003 of the Medicines & Healthcare products Regulatory Agency, 2019. Available at: https://assets.publishing.service.gov.uk/media/5c4f35e1ed915d7d51fd5a35/MDA-2019-003_Final13.pdf. Accessed June 25, 2019.
43. Mowitz M, Fornander L, Hosseiny S, et al. Patch testing with isobornyl acrylate in 16 Swedish patients with contact dermatitis from glucose sensors and/or insulin pumps. *Acta Derm Venereol* 2019;99(13):1286–1287.
44. Kamann S, Oppel E, Liu F, et al. Evaluation of isobornyl acrylate content in medical devices for diabetes treatment. *Diabetes Technol Ther* 2019;21:533–537.
45. Herman A, Baeck M, de Montjoye L, et al. Allergic contact dermatitis caused by isobornyl acrylate in the Enlite glucose sensor and the Paradigm MiniMed Quick-Set insulin infusion set. *Contact Dermatitis* 2019;81(6):432–437.
46. Gisin V, Chan A, Welsh JB. Manufacturing process changes and reduced skin irritations of an adhesive patch used for continuous glucose monitoring devices. *J Diabetes Sci Technol* 2018;12(3):725–726.
47. Herman A, Goossens A. The need to disclose the composition of medical devices at the European level. *Contact Dermatitis* 2019;81(3):159–160.
48. Aerts O, Herman A, Bruze M, et al. FreeStyle Libre: contact irritation versus contact allergy. *Lancet* 2017;390(10103):1644.