



ORIGINAL ARTICLE

The Dexcom glucose monitoring system—An isobornyl acrylate-free alternative for diabetic patients

Eva Oppel¹ | Stefanie Kamann² | Franz-Xaver Reichl^{3,4} | Christof Högg^{3,4}

¹Department of Dermatology and Allergy, University Hospital, LMU Munich, Munich, Germany

²Department of Allergy, Dermatology Feldafing, Feldafing, Germany

³Department of Conservative Dentistry and Periodontology, University Hospital, LMU Munich, Munich, Germany

⁴Walther Straub Institute of Pharmacology and Toxicology, Faculty of Medicine, LMU Munich, Munich, Germany

Correspondence

Dr Stefanie Kamann, Dermatologie Feldafing, Seewiesstrasse, 82340 Feldafing, Germany.

Email: stefanie.kamann@gmx.de

Background: Glucose monitoring systems, for example, Freestyle Libre (Abott) and Dexcom (Nintamed), are increasingly being used instead of conventional blood sugar measurement. However, many patients have experienced adverse skin reactions such as severe allergic contact dermatitis (ACD). Finally, in August 2017, the culprit allergen in Freestyle Libre, isobornyl acrylate (IBOA), was identified.

Objectives: After patients have developed ACD, it is recommended that they no longer use their glucose monitoring systems. Thus, it is important to find an alternative IBOA-free device.

Patients and Methods: Five patients presented with ACD caused by Freestyle Libre. Each was patch tested with allergens from the baseline series and from a plastics and glues series, and additionally with IBOA 0.1% pet. Gas chromatography-mass spectrometry (GC/MS) of the Freestyle Libre sensor and the Dexcom sensor was performed. The Dexcom sensor remained on the skin of all patients for at least 2 days.

Results: All patients were sensitized to IBOA. GC/MS showed the presence of IBOA in the Freestyle Libre sensor, whereas the Dexcom sensor was IBOA-free. None of the patients had skin reactions to the Dexcom sensor.

Conclusions: Patients with Freestyle Libre and IBOA allergy may use the Dexcom sensor as an alternative for glucose monitoring.

KEYWORDS

acrylates, allergic contact dermatitis, continuous glucose monitoring systems, Dexcom, flash glucose monitoring system, Freestyle Libre, insulin pump, isobornyl acrylate, patch test

1 | INTRODUCTION

New technologies for glucose monitoring have enabled exciting developments in recent years. Conventional blood glucose measurement often entails painful hardening of the fingertips. Especially at night and when an individual is on the move, it is difficult to use the blood sugar set. This measurement is also just a snapshot of the blood glucose level, without predicting how it might develop in the next hour. Modern glucose measuring systems, in which a small sensor is inserted under the skin to check glucose levels in tissue fluid, have improved the life quality of many diabetes patients. Each sensor stays in place for several days (currently up to 14 days, depending on the device) before it must be replaced. Measurements of tissue fluid just subcutaneously may reflect blood glucose levels with some delay, and

may not be as accurate as measurements of glucose in the blood. Notwithstanding this, trend arrows in the field of view of the scanner or receiver indicate whether a blood glucose level is currently stable, rising, or falling. The patient can thus react immediately by eating, or the delivery of insulin.

Currently, a distinction is made between continuous glucose monitoring (CGM) systems, for example, Dexcom (Dexcom, San Diego, California) (Figure 1) and flash glucose monitoring (FGM) systems, such as Freestyle Libre (Figure 2) (Abbott, Lake Bluff, Illinois). CGM means that tissue glucose monitoring is performed continuously. Via Bluetooth, the values are transmitted to the receiver or to a mobile phone of choice. An (imminent) hypoglycaemia is indicated by a warning sound, which is particularly helpful at night or during sports activities. A CGM system is usually worn on the abdominal skin for,



FIGURE 1 Freestyle Libre



FIGURE 2 Dexcom

currently, up to 10 days. Thereafter, the sensor is removed with plaster, and a new one is attached to a different skin area. CGM systems have been on the market since 2006, and have undergone constant development. Nevertheless, the FGM system Freestyle Libre has improved the life quality of many diabetic patients. When it was launched in Germany at the end of 2015, waiting lists had already existed for months. The sensor is very easy to punch into the skin, and can currently remain for up to 14 days on one site. The glucose values can only be accessed if the patient “flashes”; this means that the associated scanner is held in the immediate vicinity of the sensor.

With the spread of these new technologies, but especially after the introduction of Freestyle Libre, an increasing number of skin reactions have been described.^{1,2} These include, in particular, irritant contact dermatitis and allergic contact dermatitis (ACD) lesions. More than two thirds of Freestyle Libre users are likely to suffer from unspecified skin reactions, as shown in the March 2016 issue of the *Insuliner* magazine.³ These are usually irritations resulting from the long time for which the sensor is worn. Although these skin irritations are very common, they do not occur with every wearing cycle, and may differ in intensity. ACD is less common, but is of great importance. If it occurs under the sensor set, it is so pronounced that the



FIGURE 3 Allergic contact dermatitis caused by Freestyle Libre

system has to be removed after a short time. At the base, redness and blistering appear, usually with a yellowish exudate (Figure 3).

In addition to the long exposure time and individual risk factors such as age, a compromised skin barrier, moisture, and sweating, factors predisposing to the development of contact allergy are, in particular, the amount and allergenic potency of one or more previously unknown allergens. A recent report by Belgian and Swedish dermatologists showed that several of their patients with skin reactions resulting from the use of Freestyle Libre were sensitized to a specific acrylate (isobornyl acrylate [IBOA]).⁴

Patients with ACD have almost no chance of continuing to use Freestyle Libre. Nevertheless, they do not want to abandon their system, and try to insert special plates and plasters beneath their sensor. These improvised constructions are, of course, compromises, and there is a need to find alternative IBOA-free monitoring systems for these patients.

2 | MATERIALS AND METHODS

2.1 | Patients and patch testing

The demographic data, period of onset of the dermatitis, test series and allergens tested, and the patch test results for all five patients are shown in Table 1. All patients suffered from type I diabetes and used Freestyle Libre on the upper arm. All developed ACD caused by Freestyle Libre (Figure 3). Patch tests were performed with allergens from the baseline series and from the plastics and glues series, according to the recommendations of the German Contact Allergy Group (Deutsche Kontaktallergie Gruppe; <http://dkg.ivdk.org/>). Moreover, a small sample of IBOA 0.1% pet. was tested, which was kindly provided by the authors who first described IBOA sensitization in patients reacting to Freestyle Libre.¹ Following occlusion for 2 days, all patch test reactions were read, according to guidelines, on day (D) 2 and D3, and sometimes also later. In parallel, our patients were provided with a Dexcom CGM sensor G5, which they fixed on their skin for 2 days.

TABLE 1 Demographic data (patient, age, and sex), period of onset of allergic contact dermatitis (ACD) after the first use of Freestyle Libre (first ACD onset), patch test series (baseline and glue series) and specific allergens tested (isobornyl acrylate [IBOA] 0.1% pet. and Dexcom) of five patients with type 1 diabetes showing ACD caused by Freestyle Libre

Patient	Age (y)	Sex	First ACD onset	Baseline	Glue series	IBOA 0.1%	Dexcom
1	11	M	5 mo	Negative	Negative	D3: ++	Negative
2	27	M	7 mo	Negative	Negative	D3: ++	Negative
3	40	M	8 mo	Negative	Negative	D3: ++	Negative
4	28	F	1 y	Ni D3: ++	HEA D3: +	D3: +++	Negative
5	54	M	5 mo	Negative	Negative	D3: ++	Negative

Abbreviations: D3, day 3; F, female; HEA, hydroxyethyl acrylate; M, male; Ni, nickel.

2.2 | Laboratory methods

The adhesives from three Dexcom sensors (LOT 5236840) (n = 3) and three Freestyle Libre sensors (Abbott, Wiesbaden, Germany; LOT0M00004H8HW) (n = 3) were removed. The Dexcom sensors and transmitter (Dexcom, S/N 6K71W) and Freestyle Libre sensors were transferred into individual weighing bottles with NS stopper (45 mL, 60 × 30 mm; neoLab, Heidelberg, Germany). Six millilitres of water (liquid chromatography-mass spectrometry [LC-MS] Grade, ROTISOLV; Roth, Karlsruhe, Germany) or 6 mL of methanol (GC Ultra Grade, RATISOLV ≥ 99.9%; Roth) was added in order to immerse the bottom side (dermal contact side) in a solvent level of ~2 mm. As an internal standard, caffeine (CF) solution (0.01 mg/mL) (high-performance liquid chromatography ≥ 99.0%; Sigma-Aldrich, St Louis, Missouri) was added. After 3 days of incubation in the dark at room temperature, the samples were analysed with gas chromatography-mass spectrometry (GC/MS).

Corresponding removed adhesives of the Dexcom sensors (n = 3) and of the Freestyle Libre sensors (n = 3) were incubated in brown glass vials (1 mL; Macherey-Nagel, Düren, Germany) in 1 mL of water or in 1 mL of methanol at room temperature, and were analysed with GC/MS after 3 days. As an internal standard, CF solution (0.01 mg/mL) was added. In the case of Freestyle Libre, two different adhesives, which were provided by the supplier Adhesive Research (Glen Rock, Pennsylvania), were tested. One adhesive fixes the sensor onto the skin, and the second is the thin-layer glue that fixes the sensor to the skin adhesive.

The water eluate was previously extracted once with ethyl acetate (LC-MS Grade, ROTISOLV ≥ 99.9%; Roth) (1:1 vol/vol). To optimize layer separation, the samples were centrifuged for 10 minutes.⁵

The analysis of the eluates was performed on a Finnigan Trace GC ultra gas chromatograph connected to a DSQ mass spectrometer (Thermo Electron, Dreieich, Germany). A J&W VF-5 ms capillary column (length, 30 m; inner diameter, 0.25 mm; coating, 0.25 µm; Agilent, Böblingen, Germany) was used as the capillary column for gas chromatographic separation. Helium 5.0 was used as the carrier gas, at a constant flow rate of 1 mL/min. The temperature of the transfer line was 250°C. For sample analysis, 1 µL was injected in splitless mode (splitless time, 1 minute; split flow, 50 mL/min). For capillary transfer, the programmable temperature vaporizing inlet was heated from 30°C to 320°C (14.5°C/s), and finally held for 5 minutes at this temperature. The gas chromatography oven was initially heated isothermally at 50°C for 2 minutes; the temperature was then increased to 280°C (25°C/min), and the oven was held for 5 minutes at this

temperature. The mass spectrometer was operated in electron impact mode at 70 eV (ion source temperature: 240°C). Samples were recorded in full scan mode (m/z 50-600). Identification of IBOA was achieved by comparing the mass spectra and retention time with the reference IBOA standard (Merck, Darmstadt, Germany). For the reference IBOA standard, a calibration was performed (limit of quantification [LOQ] water, 0.20 µg/mL; LOQ MeOH, 0.10 µg/mL). The quantity of identified IBOA was calculated by correlating its characteristic mass peak area with the corresponding precompiled calibration curve (CF internal standard).

3 | RESULTS

Patient characteristics and patch test results are shown in Table 1. All patients had allergic reactions to Freestyle Libre. None reacted to Dexcom sensors. All patients patch tested with IBOA 0.1% pet. (n = 5) showed positive reactions (Figure 4A,B). Positive patch test reactions to allergens from additional patch test series were sometimes also observed, but rarely. For example, one patient had a positive reaction to hydroxyethyl acrylate.

In the water eluates of Dexcom sensors and transmitter, Freestyle Libre, and all corresponding adhesives, no IBOA (<LOQ) could be detected. In the methanol eluates of Dexcom sensors, the Dexcom transmitter, and the corresponding Dexcom adhesives, no IBOA (<LOQ) could be detected. In the methanol eluates of Freestyle Libre sensors, a maximum of 8.12 µg/mL could be detected. This corresponds to a dose/area of ~0.75 µg/cm² per mL (immersed surface area). In both types of adhesive (the skin adhesive and the thin-layer glue between sensor and skin adhesive), no IBOA (<LOQ) could be detected.

4 | DISCUSSION

The literature contains only a few reports of skin allergies to diabetes devices until 2016. Discussions with diabetologists and articles on numerous diabetes internet forums of affected patients show that skin reactions only become apparent some months after the introduction of Freestyle Libre. In 1995, two diabetic patients were described who had reacted to adhesives in the infusion set of their insuline pump. Interestingly, IBOA was one of the components contained in the ultraviolet (UV)-cured glue used to fix the needle into the plastic stand.⁶

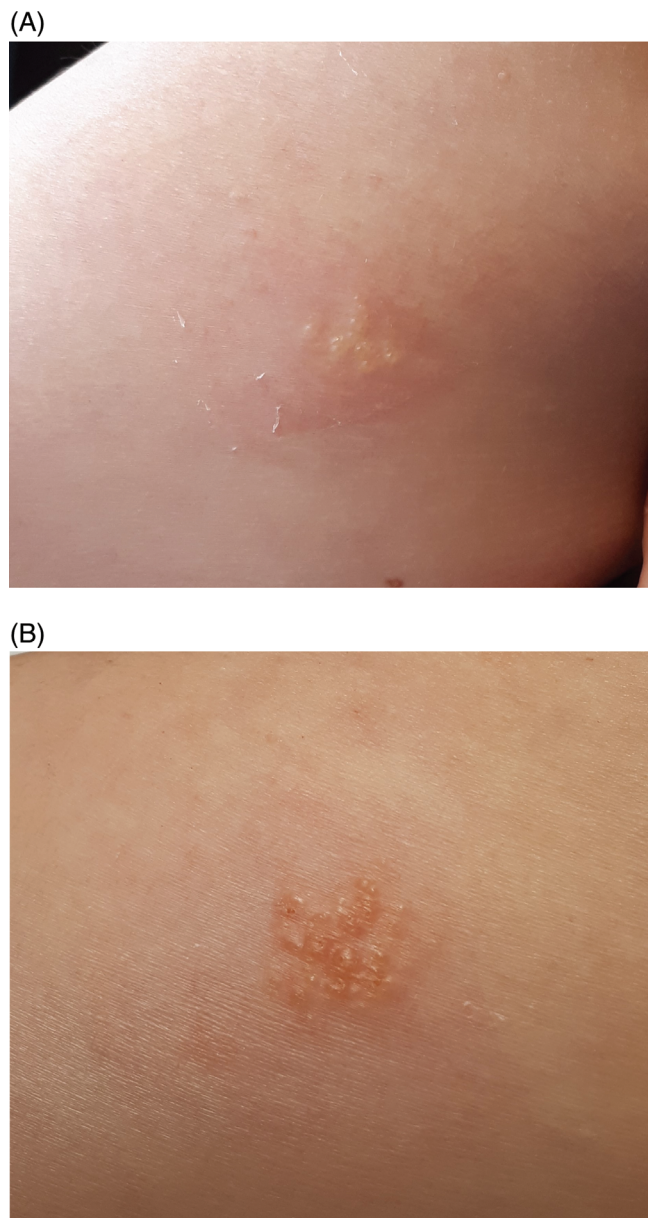


FIGURE 4 (A), Positive patch test reaction (+) to isobornyl acrylate (IBOA) on day 2. (B), Positive (crescendo) patch test reaction (++) to IBOA on day 3

In 2016, the case of a child who developed ACD caused by Dexcom set G4 was published.⁷ In the patch test, a positive reaction to ethyl cyanoacrylate, which was included in the intermediate layer of the kit, was found. Two adults with ACD caused by 2-ethyl cyanoacrylate contained in glucose sensor set G4 were also described.⁸ The company responded quickly by attaching the sensor to the dermal patch by use of a thermic ultrasound technique, thus avoiding an intermediate adhesive layer.⁹ Our patients were provided with the heat-staked G5 sensor.

The triggering allergen in Freestyle Libre remained elusive for many months. Finally, a European group succeeded in detecting the culprit allergen of Freestyle Libre in the middle of 2017.⁵ By the use of GC/MS, the acrylate IBOA could be found in the sensor set, and the patch test with IBOA 0.1% pet. gave positive reactions in 12 of 13 patients.⁵ In the present study, we tested IBOA 0.1% pet., which

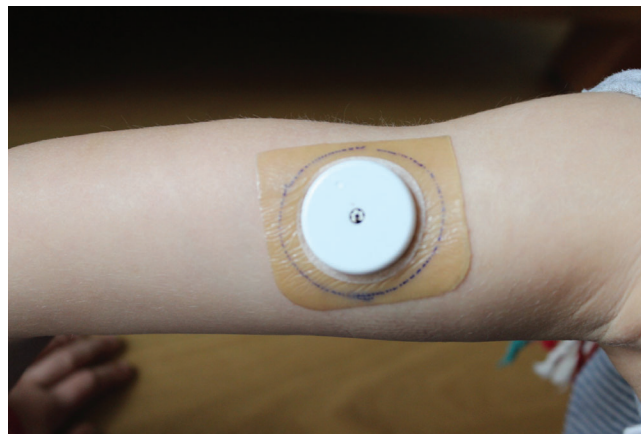


FIGURE 5 Stomahesive plate underneath a Freestyle Libre sensor

had been kindly been provided by these authors, to diagnose a boy with Freestyle Libre allergy. Positive reactions after 48 and 72 hours were seen.¹⁰ In the meantime, IBOA has also been detected by the use of gas chromatography in the patch pump Omnipod, which is a pump that sticks directly onto the skin and has no catheter system such as those in conventional insulin pumps.^{11,12}

It is therefore clear that IBOA is present in the Freestyle Libre sensor and the patch pump Omnipod, whereas the adhesives that were supplied to us by Adhesive Research (Freestyle Libre) and BSN, Hamburg, Germany) (Omnipod) are free from IBOA. That means that IBOA must somehow be dissolved from the sensor and the pump and diffuse into the adhesive part of the devices, thereby coming into contact with the skin.

Otherwise, IBOA is used particularly in the automobile industry for UV and weather protection.¹³ In material safety data sheets, it is classified as an irritant for the skin and eyes. In August 2013, Christoffers et al carried out a study with various acrylates, and concluded that IBOA does not have to be included in patch tests.¹⁴ Now, however, the situation has changed, because, with Freestyle Libre and the patch pump Omnipod, a continuously increasing number of diabetics are being exposed to IBOA. Furthermore, especially in Freestyle Libre, the amount of IBOA seems to be relevant. At present, it can not be estimated how many patients suffer from ACD following IBOA sensitization. ACD typically occurs months, or even years, later. Recent studies from Denmark found skin reactions in patients using diabetic devices to be very common. However, they did not distinguish between ACD and skin irritation, or between CGM and FGM.²

Patients with IBOA allergy try to alleviate their condition by wearing their Freestyle Libre sensors with a plate or thicker plaster beneath their systems. Hydrocolloid plates such as Compeed or stomaplates such as Stomahesive (Figure 5) underneath their sensors may help them to tolerate the glucose monitoring systems for a while. However, such protective skin barriers reduce the comfort of the glucose monitoring systems. Before the sensor is placed onto these plates, they have to be perforated with a small hole so that the sensor filament can reach the skin. However, sometimes this arrangement does not work very well, because the sensor filament cannot be correctly placed into the skin. Also, small skin reactions may occur at the site of filament placement. The occlusive milieu and additional costs for the

plates are also critical. Nevertheless, patients accept these disadvantages so that they can continue to use their Freestyle Libre systems, but most of them look for an alternative.

With the intention of finding an alternative for the affected patients, we examined the CGM system Dexcom for IBOA, and performed patch testing in patients with Freestyle Libre and IBOA allergy. All five patients tolerated Dexcom very well; three of them had already switched to this system 4 months previously, with no further skin reactions. At the end of 2018, an extended-wear Dexcom sensor needing less calibration, called G6, appeared. Dexcom R&D confirms “that the G5 and G6 sensor pod share the same patch material, patch adhesive, patch connection to sensor pod method, sensor pod materials, and the transmitter materials are the same.” Two of three patients have already been using the new G6 for ~2 months, and have not yet shown any allergic skin reactions. However, in view of the fact that that may be a long lag time until sensitization occurs, further surveillance should address possible ACD caused by G6 sensors.

In conclusion, IBOA seems to be a major allergen in diabetes devices, and should be avoided by sensitized patients. Therefore, manufacturers should avoid using IBOA in diabetes devices. In the case of Freestyle Libre, the sensor itself, and not the adhesives, contains IBOA. Dexcom provides a safe alternative in patients who have used Freestyle Libre and have acquired IBOA contact allergy. However, we must be aware of the fact that acrylates other than IBOA are used in adhesives, and that plastic and glue materials in different sensors may cause ACD. For example, in the present study, one patient also had a positive patch test reaction to hydroxyethyl acrylate. Another important aspect is that, in the case of Freestyle Libre, ACD usually occurs after several months in most patients. Thus, follow-up of our patients using G5 and G6 is needed.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

ORCID

Eva Oppel  <https://orcid.org/0000-0002-8412-2667>

Stefanie Kamann  <https://orcid.org/0000-0002-5486-1055>

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