

CONTACT POINT

Isobornyl acrylate contained in the insulin patch pump OmniPod as the cause of severe allergic contact dermatitis

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New technologies such as continuous glucose monitoring systems, flash glucose monitoring systems and advanced insulin pumps contribute to a better quality of life and a better health outcome in many patients with diabetes. The most recent advances include a tubing-free insulin infusion system that is attached to the skin with an adhesive. In the United States, the first insulin patch pump, Mylife OmniPod, was made available in 2005, and was introduced to the European market in 2010.

However, some patients have experienced contact dermatitis at the sites where glucose monitoring systems or patch insulin pumps had been fixed. As 1 substance causing allergic contact dermatitis (ACD), isobornyl acrylate (IBOA) was identified in a series of patients from Belgium and Sweden.¹

In contrast to glucose monitoring systems, chemicals in patch pumps inducing ACD have not yet been described. We report here the first case of severe ACD caused by IBOA contained in the insulin patch pump OmniPod.

CASE REPORT

A 10-year-old boy who had suffered from type 1 diabetes from the age of 6 years started treatment with the glucose monitoring system Freestyle Libre in May 2016. Usually, the sensor was attached to the upper arm, and was left there for 14 days; no other external preparations had been used. In July 2016, before formally requesting reimbursement of the costs of the insulin patch pump OmniPod from his health insurance, the patient tested this device for 3 days without any problems. In November 2016, the boy, for the first time, complained about an itch underneath his Freestyle Libre sensor; the itching

progressively worsened, and an erythematous and vesicular rash developed (Figure 1), forcing the patient to remove the sensor after 2 days. Following treatment with topical corticosteroids, the skin symptoms subsided after a few days. A new sensor was then attached to the other upper arm. Within 24 hours, severe itching and ACD recurred. Meanwhile, however, the use of the OmniPod system had been formally approved by the boy's health insurance. One day after the start of OmniPod use, the patient developed similar skin lesions underneath the insulin patch pump (Figure 2).

Patch tests were performed with allergens from the baseline series and from a plastics and glues series, according to the recommendations of the German Contact Allergy Group (Deutsche Kontaktallergie Gruppe; <http://dkg.ivdk.org/>). The latter test series included several acrylates.

The test substances were applied on the patient's back by the use of Finn Chambers (Smart Practice, Phoenix, Arizona) on Scanpor tape (BARD/Angiomed, Karlsruhe, Germany), and were fixed with Fixomull stretch (BSN, Hamburg, Germany). The cutaneous reactions were evaluated upon removal (after 2 days of application) and on day (D) 3. Reactions were classified according to German Contact Dermatitis Research Group criteria. All tests gave negative results. The manufacturers (Abbott, Chicago, Illinois and Ypsomed, Burgdorf, Switzerland respectively) were approached to provide information on potential contact allergens in the Freestyle Libre and OmniPod devices. Because of a confidentiality agreement, we were not allowed to share this information in detail. However, it became clear that, owing to structural differences, it was unlikely that the patch test substances already applied would show contact sensitization to the acrylates contained in medical devices. According to the manufacturer of



FIGURE 1 Allergic contact dermatitis caused by Freestyle Libre

the OmniPod device, there should be no additional layer between the adhesive and the patch pump, as the plastic box is fixed to the adhesive by a heating process. In the case of the Freestyle Libre device, 2 adhesives, that is, (1) the adhesive that attaches the sensor to the skin, and (2) the layer of glue that fixes the sensor to the adhesive layer, were kindly provided by the adhesive manufacturer supplying Abbott. Again, however, patch testing with these 2 adhesives used for the Freestyle Libre device and the 1 adhesive used for the OmniPod device gave negative results.



FIGURE 2 Allergic contact dermatitis caused by OmniPod

Subsequently, we used IBOA 0.1% pet. kindly provided by the authors who were the first to identify IBOA as a relevant contact allergen in glucose monitoring systems.¹ IBOA elicited a strong (++) reaction on D3. We hypothesized that the allergen was not part of the adhesive, but was possibly contained in another part of the OmniPod device, supported by the observation that ACD was most prominent in the centre, where the needle is fixed.

Consequently, after removal of the patch (Fixomull stretch), samples from only the bottom side of the insulin pump (OmniPod) in contact with the skin were immersed in 6 mL of water [liquid chromatography (LC)-mass spectrometry (MS) Grade, ROTISOLV; Roth, Karlsruhe, Germany] or in 6 mL of methanol [gas chromatography (GC) Ultra Grade, RATISOLV $\geq 99.9\%$; Roth]. After 3 days of incubation in the dark at room temperature, the samples were analysed by GC-MS. Only the water eluate has to be extracted once with ethyl acetate (1:1 vol/vol) (LC-MS grade, ROTISOLVE $>99.9\%$; Roth) before the GC-MS analysis.

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 of each eluate was injected in splitless mode (splitless time, 1 minute; split flow rate, 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 GC oven was initially heated isothermally at 50°C for 2 minutes, the temperature was then increased to 280°C (25°C/min), and this temperature was maintained for 5 minutes. 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 those of the reference standard IBOA (Merck, Darmstadt, Germany). The quantity of IBOA was calculated by correlating its characteristic mass peak area with the corresponding precompiled calibration curve. In the water eluates of the insulin pump (skin contact side), and in the water and methanol eluates of the Fixomull patches, no IBOA could be detected. In the methanol eluate of the insulin pump (skin contact side), however, we found 10 $\mu\text{g/mL}$ IBOA. This corresponds to a dose/area of $\sim 0.53 \mu\text{g/cm}^2$ (immersed surface area).

In parallel, our patient was provided with a Stomahesive from ConvaTec (Munich, Germany), which was placed between the skin and the sensor, thereby preventing potential allergens from penetrating into the skin, and enabling our patient to continue using the Freestyle Libre device. The system was fixed on the upper arm, and a sweatband was worn. Furthermore, insulin therapy was switched to conventional injection. Throughout the following weeks, no further relapses of ACD occurred.

DISCUSSION

Contact dermatitis resulting from the use of glucose monitoring systems and patch insulin pumps represents an increasing health issue. The long duration of skin exposure, such as 2 weeks for some devices, may lead to irritant contact dermatitis. Until 2017, only a few cases of ACD caused by components of diabetes control devices had been reported.² In 1995, a first publication described 2 young women suffering from ACD caused by the glue used in 2 different insulin pumps. The authors found that 1 of the culprit allergens was IBOA.³ Recently, it was shown that ACD caused by glucose monitoring systems can also be related to cyanoacrylates.⁴ In this particular case, ethyl cyanoacrylate was shown to be a component of the thin layer of glue fixing the sensor to the adhesive. The number of reports describing allergic reactions to devices is increasing; in addition to the long wearing period, the sensitizing potency of some compounds used for the production of medical devices may be important.

Our patient suffered from ACD caused by a glucose monitoring system, which probably induced sensitization, and later also from ACD caused by a patch insulin pump. Contact allergy to IBOA was confirmed by patch testing, and the presence of IBOA in the insulin pump was confirmed by GC-MS. IBOA was contained only in the plastic box of the OmniPod device; however, it appeared to have migrated into the adhesive part of the device, eventually leading to contact with the skin.

The use of a Stomahesive plate or other hydrocolloid-based and/or silicone-based plates underneath the sensor may help patients to tolerate the glucose monitoring systems. However, such protective skin barriers make wearing the glucose monitoring systems less comfortable. Before the sensor is placed onto these plates, their centres have to be perforated so that the sensor filament can reach the skin. However, this work-around sometimes prevents correct placing of the sensor filament in the skin. Occlusion and additional costs for the plates are other critical points.

Our finding supports observations of the Belgian group, which identified IBOA in the glucose sensor itself.¹ Furthermore, our findings are very well in line with patient reports indicating that the strongest skin symptoms occur directly in the area where the plastic boxes of the sensor and the pump contact the skin. Hitherto, IBOA has not been regarded as a potent allergen; this is most probably related to the limited amount of exposure to this substance. So far, only a few case reports have linked occupational ACD to IBOA, the ACD being caused by an uncured ultraviolet ink and an acrylate coating.⁵ If patients with diabetes type 1 and type 2 are increasingly exposed to new IBOA-containing medical devices, however, the frequency of IBOA-induced contact dermatitis is expected to increase.

Unfortunately, the product documentation of the medical devices does not contain sufficient information on potential allergic hazards, and the producer did not prove helpful. We feel that there is a clear need for legislation obliging manufacturers to disclose the potential health risks of medical products. Following the principle of producer

responsibility, manufacturers should remove hazardous substances from medical devices. The IBOA case may be compared with cyanoacrylate. Recently, a manufacturer of a cyanoacrylate-containing device (Dexcom) used for glucose measurement changed the construction of the sensor set⁶ after a cyanoacrylate had been identified as the cause of ACD. The sensor is now fixed to the adhesive part of the device by a thermic technique, thereby avoiding further use of cyanoacrylate. A corresponding approach is required replacing IBOA. Our finding that the plastic box of the OmniPod device contains IBOA leads us to recommend strongly that manufacturers should eliminate this allergen from this device, as well as from the Freestyle Libre system. It is not yet known whether IBOA is present in other medical devices for blood glucose measurement, such as the Enlite sensor by Medtronic or the Dexcom G sensor by Nintamed. As we have seen skin reactions to the Enlite patch pump system, IBOA may also be contained in this system.

IBOA should be produced as a standardized patch test substance and tested in patients with ACD secondary to wearing a patch pump system.

Conflict of interest

The authors declare no potential conflict of interests.

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