

ORIGINAL ARTICLE

Allergic contact dermatitis caused by isobornyl acrylate in OmniPod, an innovative tubeless insulin pump

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Email: n-raison@chu-montpellier**Background:** The frequency of allergic contact dermatitis caused by (meth)acrylates is increasing worldwide, and isobornyl acrylate (IBOA) has been identified as a culprit sensitizer in FreeStyle Libre, a medical device used by diabetic patients.**Objectives:** To report on 4 patients sensitized to IBOA contained in OmniPod, a new, tubeless insulin pump, and to describe the clinical and chemical analytical work-up.**Method:** Four patients with eczematous skin eruptions after using OmniPod, including 2 with previous adverse skin reactions to FreeStyle Libre, were patch tested with a baseline series and additional (meth)acrylates, including IBOA in several concentrations and/or vehicles. Gas chromatography-mass spectrometry (GC-MS) was used to identify the presence of IBOA in OmniPod.**Results:** All patients were shown to be sensitized to IBOA. GC-MS identified IBOA in OmniPod, with the highest concentrations being found in the unit itself and not in the adhesive patch.**Conclusions:** The OmniPod tubeless insulin pump is another source of IBOA, and its use may lead to primary sensitization to this acrylate, or may provoke elicitation of allergic contact dermatitis in previously sensitized patients. Our cases highlight the need to obtain satisfactory cooperation from pharmaceutical companies involved in the manufacture of these widely used medical devices.

KEYWORDS

adhesive, allergic contact dermatitis, case report, CAS no. 5888-33-5, diabetes mellitus, gas chromatography-mass spectrometry, insulin pump, isobornyl acrylate, OmniPod, medical device

1 | INTRODUCTION

We report 4 cases of allergic contact dermatitis caused by OmniPod (Insulet Corporation, Billerica, Massachusetts), a new and innovative tubeless insulin pump that was recently launched to improve the quality of care of patients with diabetes mellitus (Figure 1). Patch tests with isobornyl acrylate (IBOA) (CAS no. 5888-33-5) gave positive reactions in all 4 patients, and chemical analyses identified this particular acrylate in the device.

2 | PATIENTS AND METHODS

2.1 | Patients

2.1.1 | Case 1

A 67-year-old woman with diabetes mellitus type 1 diagnosed 12 years previously presented with itchy, red and vesicular plaques and secondary desquamation at the application sites of an OmniPod insulin pump, 4 months after she had started using this system. She

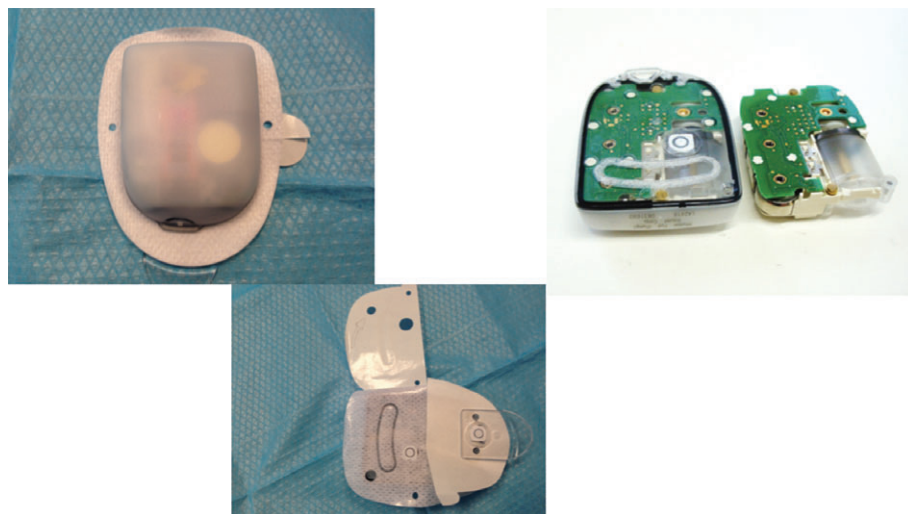


FIGURE 1 OmniPod system. Upper left: a new OmniPod device: the pod and the adhesive. Middle: the adhesive. Upper right: 2 OmniPod systems without the adhesive: left one, with the plastic cover; right one, with the plastic cover removed

continued using the device for another 10 months while trying to alleviate the symptoms by putting a hydrocolloid dressing between the adhesive part of the pod and her skin. However, the skin eruption persisted and had to be regularly treated with topical corticosteroids.

The patient was patch tested on the back with allergens from the European baseline series and a plastics and glues series (Chemotechnique, Vellinge, Sweden), with IQ Ultra Chambers (Chemotechnique). Patch testing was also performed with an in-house (meth)acrylate series, consisting of 13 (meth)acrylates (all from Chemotechnique; Table 1). These were supplemented with IBOA, provided by O. Aerts (Antwerp, Belgium), patch tested at 0.01%, 0.05% and 0.1% pet.; additionally, a small piece of the adhesive from the OmniPod device was patch tested "as is". All patch tests were occluded for 2 days with Oper tape (Iberhospitex, Innovative Health Technologies, Barcelona, Spain) and read on day (D) 2 and D3. The patient was instructed to observe the patch tested area until D7, and to contact the department if any new reactions appeared.

TABLE 1 In-house (meth)acrylate series (from Chemotechnique) (cases 1-3); all haptens in petrolatum

(Meth)acrylate	Test concentration (%)
Methyl methacrylate	2
Triethylene glycol dimethacrylate	2
Urethane dimethacrylate	2
Ethylene glycol dimethacrylate	2
Bisphenol A glycidyl methacrylate	2
2-Hydroxyethyl methacrylate	2
Bisphenol A dimethacrylate	2
Butyl methacrylate	2
2-Ethylhexyl acrylate	0.1
Ethyl acrylate	0.1
2-Hydroxyethyl acrylate	0.1
1,6-Hexanediol diacrylate	0.1
Ethyl cyanoacrylate	10

2.1.2 | Case 2

A 48-year-old woman with type 1 diabetes mellitus diagnosed 10 years previously was referred for localized, pruritic dermatitis at the application sites of an OmniPod insulin pump that she had used for 2 years; skin problems started after she had used the pump for 1 year (Figure 2). In spite of the use of a hydrocolloid dressing between the adhesive of the pod and the skin, eczema persisted, requiring the intermittent application of topical corticosteroids. Interestingly, this patient later also showed eczematous skin reactions to the FreeStyle Libre glucose sensor, which she had previously tolerated, having used this device only on an irregular basis. The patient later reported that, a few years previously, she had applied long-lasting nail polish without observing any reaction. Patch tests were performed as in case 1.

2.1.3 | Case 3

A 16-year-old girl, with type 1 diabetes mellitus diagnosed 1 year previously, consulted with localized, pruritic and erythematous dermatitis at the application sites of an OmniPod insulin pump that she had used for 2 months. This dermatitis occurred after the first use of this system. The patient's history showed that, as in case 2, this patient had experienced contact dermatitis caused by the FreeStyle Libre glucose sensor, after using it for 6 months, leading to discontinuation of its use. Patch tests were performed as in cases 1 and 2.

2.1.4 | Case 4

A 34-year-old woman was referred with an itchy rash at the application site of her OmniPod pump. She was diagnosed with diabetes mellitus 11 years previously, but had no previous history of dermatitis. She had started to use the FreeStyle Libre glucose sensor in April 2015, and the OmniPod pump in August 2015. In October 2015, she developed an itchy rash at the site of the FreeStyle Libre sensor, and she switched to a Dexcom G4 Platinum glucose sensor (Dexcom, San Diego, CA, USA), which she tolerated. However, in spring 2016 she developed an itchy rash at the site of the OmniPod application site. She tried to alleviate the dermatitis with topical corticosteroids and the use of adhesive tape under the device. On examination, dermatitis corresponding to the application areas of the insulin pump was



FIGURE 2 Localized contact dermatitis caused by the adhesive of the OmniPod insulin management system

documented. Patch tests were applied on the back with 8-mm Finn Chambers (Smart Practice, Phoenix, Arizona), and fixation with Scanpor tape (Norgesplaster, Vennesla, Norway). Patch test preparations were supplied by Chemotechnique. Patch tests, applied for 2 days

TABLE 2 Patch test results

	Case 1	Case 2	Case 3	Case 4
IBOA 0.1%	+	++ (Figure 2)	+	++
IBOA 0.05%	+	++	+	+ (0.032% Ac.)
IBOA 0.01%	-	?	-	?
Other positive tests (D3 or D4 unless otherwise stated)	<i>Myroxylon pereirae</i> +	<i>Myroxylon pereirae</i> + 2-HEA 0.1% pet. ++ EA 0.1% pet. + (D7) 2-HEMA 2% pet. ++ (D7)		Nickel sulfate 5% pet. + Ac. extract of the OmniPod patch +
Patch test with a small piece of the OmniPod adhesive	-	-	- (FreeStyle Libre adhesive also negative)	- (FreeStyle Libre adhesive also negative)

and read on D3 and D7, were performed with the Swedish baseline series, the department's extended baseline series, and an acrylate series. Additionally, the patient was tested with the adhesive patch from the OmniPod pump "as is", and with an ultrasonic bath extract of the patch in acetone.¹ Later, this patient was additionally tested with the adhesive patch from FreeStyle Libre "as is", with an ultrasonic bath extract of the latter in acetone, and with a dilution series of IBOA in acetone ranging from 0.1% (wt/vol) to 0.00000032% (wt/vol).

Because of the severity of the dermatitis, the OmniPod insulin pump eventually had to be replaced with another brand (Animas Vibe pump; Animas Corporation, West Chester, Pennsylvania), after which the dermatitis resolved.

2.2 | Chemical analyses

Extracts made from different parts of OmniPod units were analysed with gas chromatography-mass spectrometry.² Dilutions of IBOA in acetone were used as reference standards. Separate extracts were made from adhesive patches from OmniPod and from the OmniPod units (with the patches removed), retrieved from case 3. The different parts were extracted in acetone for 20 to 24 hours. The extracts were then filtered and evaporated to a final volume of 100 μ L before being analysed. Additionally, an extract of the adhesive patch tested in case 4 was analysed, and an extract was also made from the OmniPod unit (from which the patch was removed), as described above. Another OmniPod unit from the same batch was dismantled, and parts from the plastic cover and parts from the inside were extracted and analysed separately.

3 | RESULTS

3.1 | Patch test results

All relevant patch test results are summarized in Table 2. All patients reacted to IBOA 0.1% and 0.05% pet. (Figure 3); 1 of them (case 4) reacted down to 0.032% in acetone. The lowest concentration in pet. (0.01%) gave negative results in 2 patients, and doubtful reactions in another 2 subjects. In case 2, concomitant reactions to other acrylates were observed, that is, to 2-hydroxyethylacrylate (2-HEA), ethyl acrylate (EA), and 2-hydroxyethylmethacrylate (2-HEMA), the last

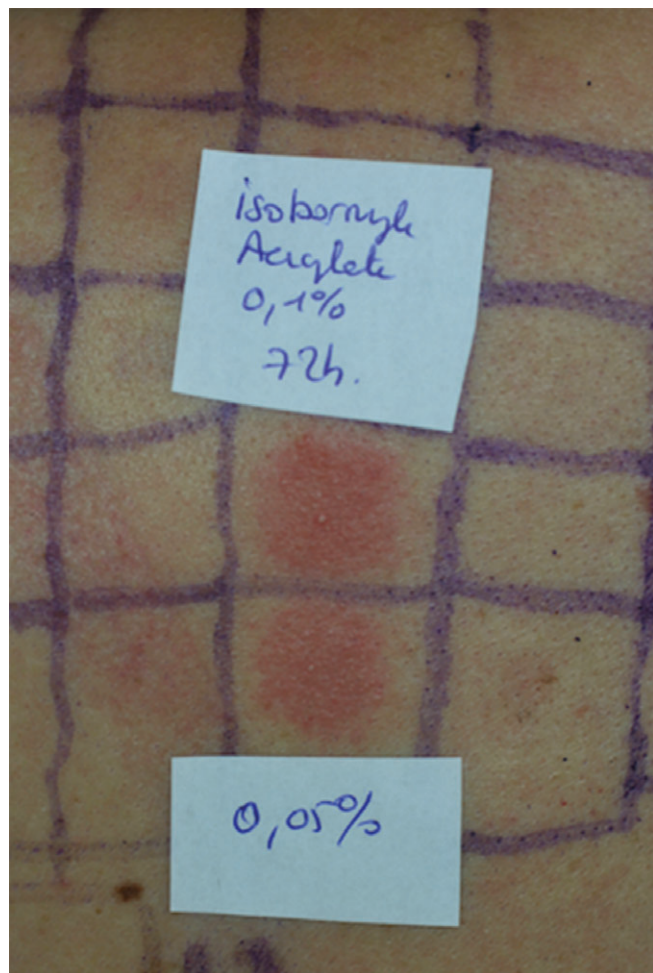


FIGURE 3 Positive patch test reactions to isobornyl acrylate 0.05% and 0.1% pet. on day 3 (case 2)

2 of these only giving a positive reaction at the late reading (D7). Surprisingly, in all cases, a patch test with a small piece of the adhesive of OmniPod remained negative, whereas case 4 showed a positive patch test reaction to an acetone extract of this adhesive patch.

3.2 | Chemical analyses

In the analyses of 2 OmniPod devices (1 used and 1 unused) from case 3, possible traces of IBOA were seen in the patch from the unused OmniPod, but not in the patch from the used one. However, higher amounts of IBOA were found in both OmniPod units (with the patches removed). The concentrations of IBOA in these extracts correspond to total amounts of approximately 5 μg in the used unit and 40 μg in the unused unit. In the extract of the adhesive patch from case 4, small amounts of IBOA, corresponding to a total of ~ 5 μg in the patch, were observed. The concentration of IBOA in the extract from the OmniPod unit (from which the patch was removed) corresponded to a total amount of 190 μg in the unit. The analysis of the dismantled OmniPod showed the presence of IBOA only in parts from the inside of the unit, containing electronics, the delivery pump, and the connection between the pump and the cannula.

4 | DISCUSSION AND CONCLUSION

The OmniPod Insulin Management System is an “all-in-one” insulin pump consisting of a “pod” and a Personal Diabetes Manager (PDM). The pod contains the insulin reservoir and cannula, which can be worn on the skin like an infusion set for up to 3 days. The PDM is tubelessly connected to it, and acts as a distant remote control to calculate the exact dose of insulin needed. It is also used to calculate the blood glucose level by analysing a test strip with blood obtained by classic skin finger pricks. The device is not only more accurate but also more discrete than other, older insulin pump systems, because of its innovative, tubeless design. Patients can wear the pod at all times, even without clothing, and it is waterproof. However, given that the OmniPod is a fully integrated system, a strong adhesive, the exact components of which have not been disclosed, is necessary to keep the pod attached to the skin.

Allergic contact dermatitis caused by OmniPod insulin pumps has not been previously reported, and contact allergy caused by insulin pump infusion sets is generally considered to be rare. In most cases, the adhesive part of the system has been identified as the culprit. Acrylates have often been incriminated, especially the monomer 2-phenoxyethyl acrylate (CAS no. 48145-04-6) and its oligomers.^{3,4} Epoxy resin has also been reported as a culprit sensitizer.⁵ One case report described a patient who reacted to several (meth)acrylates, but the authors could not obtain samples of the glue components to complete the work-up, as is unfortunately often the case.⁶

In 1995, contact allergy to IBOA was reported in 2 young women who developed eczema and abscesses around the injection sites of their insulin pumps.³ They showed contact-allergic reactions to components of the adhesive glue and to plastic scrapings from the infusion set. Furthermore, they had positive patch test reactions to phenoxypoly (ethyleneoxy) ethyl acrylate 0.1%, β -carboxyethyl acrylate 0.1%, 1-benzoylcyclohexanol 1%, and IBOA 0.1%, all in pet. The last of these was shown to be a culprit allergen present in the ultraviolet (UV)-cured adhesive, and that had subsequently diffused into the plastic parts of the infusion set.

Recently, Herman et al reported on 15 Belgian and Swedish patients who suffered from severe allergic contact dermatitis caused by FreeStyle Libre, a newly introduced flash glucose meter. In all but 1 of their patients, IBOA could be shown to be the culprit allergen.² Meanwhile, the number of patients suffering from allergic contact dermatitis caused by this specific glucose meter is clearly increasing. In fact, 1 of the 4 patients presented here (case 2) had later also reacted to the FreeStyle Libre device. She most likely became sensitized to IBOA present in OmniPod, and, subsequently, when she was exposed to IBOA in FreeStyle Libre, allergic contact dermatitis relapsed. In contrast, cases 3 and 4 had first reacted to FreeStyle Libre, and most likely became sensitized to IBOA by this system.

In all 4 cases it is, once again, regrettable that the manufacturers of OmniPod and FreeStyle Libre, used by so many patients worldwide, refuse to give any information about the exact composition of the adhesives or other materials contained in these medical devices, despite our repeated requests.

IBOA is mostly known as a photopolymerizable monomer that is used in various industrial products, such as UV-cured inks and adhesives. Occupational contact dermatitis caused by this acrylate has been observed in an industrial process operator.⁷ However, the authors of this particular publication concluded that it was not relevant to add IBOA to a (meth)acrylate test series, because aimed testing of IBOA 0.1% pet. in 14 patients with (meth)acrylate contact allergy in an occupational setting had shown no other cases of IBOA sensitization.

In our case 2, concomitant reactions were observed to 2-HEA, 2-HEMA, and EA, although no other acrylates could be identified in the chemical analyses. Concomitant reactions to IBOA and other (meth)acrylates have only rarely been reported.² The patient told us that she had never been exposed to acrylates from artificial nails or occupational exposure, but that she had used, a few years ago, long-lasting nail gel polish. Therefore, we could not exclude the possibility that she had been sensitized to these acrylates via this route. None of our 4 patients had a previous history of allergic contact dermatitis caused by other glues or adhesives, except for cases 3 and 4, who had previously developed allergic contact dermatitis caused by FreeStyle Libre adhesive, accounting for their initial sensitization to IBOA. Conversely, in cases 1 and 2, the onset of the OmniPod-related skin symptoms after several months of use of this particular device strongly suggests that primary sensitization to IBOA was induced because of its presence in OmniPod.

No positive patch test reactions were seen to pieces of the adhesive of the OmniPod tested "as is". It is likely that the amount of IBOA present in the small pieces used for patch testing was too small to elicit a positive reaction. This is further supported by case 4, in whom the use of an ultrasonic bath extract of the adhesive probably resulted in a sufficient amount of IBOA to elicit a positive patch test reaction. Furthermore, the chemical investigations showed that, in fact, most IBOA originates from parts of the pod other than the adhesive, which may also explain why the patients showed skin reactions while using the whole OmniPod device, but did not react to a patch test containing only the adhesive part of the system. This is very reminiscent of what was observed with the FreeStyle Libre device²: the adhesive patch itself was most likely not the major source of IBOA, but it was suspected that the acrylate was released from a glue used to internally join the top and bottom parts of the sensor.

In conclusion, we report another important source of sensitization to, and elicitation of allergic contact dermatitis caused by, IBOA present

in OmniPod, another new medical device used by many diabetic patients. Complementing the recent case series from Herman et al, who showed that the most appropriate patch test concentration of IBOA was 0.1% pet., our cases add to the evidence that the addition of IBOA 0.1% pet. to a (meth)acrylate series is warranted, as it may well be an overlooked allergen contained in these and similar medical devices. We also underline that this study was possible thanks to collaborative work between different departments in different countries.

Conflict of interest

The authors declare no potential conflict of interests.

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