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WILEY CONTACT DERMATITIS

REVIEW

Allergic contact dermatitis caused by medical devices for diabetes patients: A review

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Allergic contact dermatitis caused by medical devices for diabetes patients has been increasingly described in the literature in the last few years. This article reviews the cases of allergic contact dermatitis caused by insulin pumps and glucose sensors reported since the 1970s, the culprit allergen(s), the results of patch tests and/or chromatographic analysis, and preventive measures.

KEYWORDS

acrylate, allergic contact dermatitis, continuous glucose monitoring, cyanoacrylate, diabetes, insulin pump, isobornyl acrylate, medical devices

1 | INTRODUCTION

The incidence of diabetes continues to increase in Europe, as shown in 2015 by an 5% increase for type 1 diabetes mellitus (T1DM) and an 8.8% increase for type 2 diabetes mellitus.[1] Early diagnosis and regular follow-up of patients with T1DM is essential to avoid complications, such as hypoglycaemia and diabetic ketoacidosis. New technologies for diabetics have been introduced over the years, such as insulin pumps, and flash glucose monitoring (FGM) and continuous glucose monitoring (CGM) systems. These medical devices were designed for diabetics to improve diagnosis, follow-up, monitoring, and treatment. The insulin pump allows continuous subcutaneous administration of insulin. FGM and CGM systems replace the self-monitoring of blood glucose levels, and provide a flash or continuous measurement, respectively, of interstitial glucose. Since their introduction, however, several unwanted events have been reported, such as infections attributable to subcutaneous catheter insertion, irritation after repeated applications, detachment of the sensor or transmitter during sports or upon water contact, and allergic contact dermatitis (ACD).[2] This review focuses on the different culprit contact allergens associated with medical devices for diabetics that have previously been identified and described in the literature. A major risk factor promoting ACD is the longer insertion time of these cutaneous devices.[3] Table 1 summarizes all cases of ACD provoked by medical devices for diabetics reported in the literature.

2 | INSULIN PUMPS

Since the mid-1970s, insulin pumps have been used to continuously deliver insulin, mainly to T1DM patients. They consist of a needle that is inserted into the skin and fixed on it with an adhesive patch, connected to a pump by a plastic butterfly or cannula. Several ACD cases caused by the infusion needle, plastic butterfly or cannula have been reported. According to Binder et al, 11% of patients receiving continuous subcutaneous insulin infusion were affected by eczema,[4] although no further information was provided concerning patch test or other results. In 1985, Boom et al described the first 2 ACD cases caused by the infusion set of the insulin pump Actrapid (Novo Nordisk, Bagsvaerd, Denmark), connected to an autosyringe, and fixed on the skin with Tegaderm (3M, St Paul, Minnesota). Both patients showed positive patch test reactions to epoxy resin,[5] which is used to fix the plastic tube to the needle. In 1995, Busschots et al reported 2 further ACD cases caused by 3 different infusion sets: Cliniset (Pharmaplast, Vaerloese, Denmark), Disetronic (Disetronic Medical Systems, Burgdorf, Switzerland), and CliniSoft (Pharmaplast). Patch testing showed positive reactions to phenoxypoly(ethyleneoxy) ethylacrylate (PEEA), isobornyl acrylate (IBOA), β-carboxyethyl acrylate, and 1-benzoyl-cyclohexanol, that is, molecules contained in the ultraviolet-cured glue used to fix the needle into the plastic of the set.[6] In 2001, the presence of PEEA in the infusion set[7] was confirmed by means of gas chromatographic analysis,[7] with similar ACD cases being described later.[8] The different allergens detected by patch testing are shown in Table 1.

TABLE 1 Allergic contact dermatitis related to medical devices for diabetics: cases reported in the literature

Authors	Number of patients described	Medical device for diabetics	Positive patch tests	Allergen(s) identified in the device[a,b]	Alternative proposed
Boom et al (1985)	2	Actrapid autosyringe infusion set	ER *p-tert*-Butylphenol formaldehyde Fragrance mix	ER[b]	Impermeable piece of plaster
Busschots et al (1995)	2	Cliniset Disetronic	PEEA IBOA BCA Benzoylcyclohexanol Cliniset infusion set Disetronic infusion set CliniSoft infusion set	PEEA[b] IBOA[b] BCA[b] Benzoylcyclohexanol[b]	Pureline basic (plastic melted around the needle)
van den Hove et al (1996)	1	Cliniset CliniSoft	MMA BDA EMA HEMA TGDMA TGDA HPMA EGDMA TEGDMA PTA Oligotriacrylate 480		Pureline basic (plastic melted around the needle)
Saccabusi et al (2011)	1	Set per microinfusione	Ni MA EA BA IA MMA EMA BMA BDA HEMA Set per microinfusion catheter	3-Methyl-2-buten-1-ol[a] γ-Butyrolactone[a] Dimethyl adipate[a]	
Schwensen et al (2016)	1	Platinum G4	ECA		
Peeters et al (2017)	2	Platinum G4	ECA HEA HEMA EGDMA Adhesive part platinum G4	ECA[a]	
Aschenbeck et al (2017)	1	Platinum G4	EMA ECA HEMA DGDA Colophonium Abietic acid Pine tar Adhesive part platinum G4	Cyanoacrylate[b]	
Oppel et al (2018)	1	OmniPod FreeStyle Libre	IBOA	IBOA[a]	Stomahesive plate or silicone-based plates underneath the sensor
Herman et al (2017)	15	FreeStyle Libre	EA HPA IBOA Abitol RE Hydroquinone Adhesive part Freestyle Libre	IBOA[a]	
Kamann et al (2018)	3	FreeStyle Libre	IBOA		
Raison-Peyron et al (2018)	4	OmniPod	EA HEA HEMA IBOA Acetone extract OmniPod patch	IBOA[a]	

TABLE 1 (Continued)

Authors	Number of patients described	Medical device for diabetics	Positive patch tests	Allergen(s) identified in the device[a,b]	Alternative proposed
Passanisi et al (2018)	2	Enlite sensor OmniPod	Colophonium	Colophonium[b]	

Abbreviations: BA, butyl acrylate; BCA, β-carboxyethyl acrylate; BDA, butanediol diacrylate; BMA, butyl methacrylate; EA, ethyl acrylate; ECA, ethyl cyanoacrylate; EMA, ethyl methacrylate; EGDMA, ethyleneglycol dimethacrylate; DGDA, diethylene glycol diacrylate; ER, epoxy resin; HEA, hydroxyethyl acrylate; HEMA, hydroxyethyl methacrylate; HPA, hydroxypropyl acrylate; HPMA, hydroxypropyl methacrylate; IA, isobutyl acrylate; IBOA, isobornyl acrylate; MA, methyl acrylate; MMA, methyl methacrylate; Ni, nickel; PEEA, phenoxypoly(ethylenoxy) ethylacrylate; PTA, pentaerythitol triacrylate; RE, resin epoxy; TEGDMA, tertaethyleneglycol dimethacrylate; TGDA, triethyleneglycol diacrylate; TGDMA, triethyleneglycol dimethacrylate.
[a] Confirmed by chromatographic analysis.
[b] Confirmed by manufacturers.

In 2001, Saccabusi et al described a case of ACD, located on the abdomen, which was provoked by the Set per micro infusione insulin pump (Pharmaplast). Several acrylates were shown to be positive upon patch testing, as shown in Table 1. Gas chromatographic analysis was performed, and showed the presence of methyl methacrylate, which is considered to be the main allergen in this setting.[9] Nickel may also be involved in ACD caused by insulin pumps, with 2 cases having been reported.[10,11] Spectrometer and electron microscope analyses confirmed that nickel, present in the needle device, was the culprit. In such cases, a Teflon system could be applied as an alternative.

In 2018, 4 cases of ACD caused by a newer insulin pump, OmniPod (Insulet, Billerica, Massachusetts), were described; this pump is able to deliver the exact insulin dose according to glucose levels. IBOA was identified as the culprit sensitizer, and its presence was confirmed by gas chromatography (GC)-mass spectrometry (MS). This acrylate is probably used to join the different parts of the plastic, rather than as a skin adhesive.[12] Oppel et al[13] detected IBOA only in the sensor's plastic part, with possible IBOA migration into the adhesive. Two other ACD cases caused by newer insulin pump (OmniPod and Enlite; Medtronic, Minneapolis, Minnesota) devices associated with a glucose sensor were recently described; patch tests showed positive reactions to colophonium.[14]

Skin intolerance reactions to plastic material contained in insulin pumps have often been considered to represent simple irritation,[15] with possible ACD being overlooked, thus emphasizing the need for patch testing.

3 | GLUCOSE SENSORS

The glucose sensor is the part of the FGM and CGM systems that measures the interstitial glucose levels. Both systems replace self-monitoring of blood glucose levels by finger pricking. The catheters are inserted under the skin, and kept on the skin with an adhesive patch, with glucose values then being sent to the transmitter. The FGM and CGM systems provide, respectively, flash and continuous measurement of interstitial glucose levels.[16]

3.1 | Flash glucose monitoring

Freestyle Libre (Abbott Diabetes Care, Witney, UK) is the only FGM system that is currently in use in Europe, with the advantage of not requiring any calibration following release onto the market. It is generally fixed on the skin for a 2-week period.

In 2016, Bolinder et al described cutaneous side-effects, such as erythema, itching, and rash, in patients wearing this particular device. Pain, bleeding, oedema and induration were similarly observed, probably because of the insertion of the sensor catheter into the skin.[17] In a study that was focused on these subjects' follow-up, 49% showed erythema when wearing the sensor.[18] Several authors initially considered this to be a simple irritant reaction.[19] In 2017, however, a multicentre study involving 15 patients suffering from dermatitis caused by FreeStyle Libre confirmed the reaction to be ACD.[20] Patch tests indicated that IBOA was the potential culprit allergen; its presence was confirmed by GC-MS analysis of both the sensor's plastic part and the transmitter. This was suggested by a previous analysis performed by Kamann et al.[21] These authors patch tested, in patients presenting a skin reaction to Freestyle Libre, the original adhesive obtained from the manufacturer, consisting of 3 different adhesives superimposed upon each other. Three patients experienced a positive reaction with IBOA, but no reaction with the 3 adhesive pieces, suggesting that IBOA was present in the sensor's plastic part, and had migrated towards the skin.

3.2 | Continuous glucose monitoring

Several CGM devices are currently available in Europe. They are applied on different parts of the body (ie, arm or abdomen) and remain fixed for durations varying from 7 to 10 days, depending on the model. One major disadvantage of these devices is that they require several calibrations during the day.

In 2007, Jadviscokova et al reported that 18% of the 22 patients wearing GCM devices proved to be hypersensitive to them.[22] This figure was, however, based merely on information received from the patients during follow-up, with no patch tests being performed.

In 2016, Schwensen et al described the first ACD case caused by CGM Platinum G4 Dexcom (Dexcom, San Diego, California) in a 2-year-old girl, with a reaction to ethyl cyanoacrylate being the only positive patch test reaction observed. The allergen's presence in the glue of the sensor pod was confirmed by the manufacturer,[23] as well as by Peeters et al, who carried out CG-MS analysis, with 2 sensitized adult patients being detected.[24] In 2017, Aschenbeck et al[25] reported a further case. Intolerance reactions to this CGM device led the device manufacturer to reformulate the adhesive composition in August 2016, omitting ethyl cyanoacrylate.[25] Currently, this transmitter is fixed to the adhesive patch by a heatstaking process, namely a thermal

technique.[26] Oppel et al have advised various medical device manufacturers to apply this process in order to avoid using acrylates, with the associated ACD risk.[13]

4 | PREVENTIVE MEASURES

In certain cases, applying a thin hydrocolloid dressing (with an opening for the needle) between the skin and the adhesive part of the sensor has effectively allowed the sensors to be better tolerated.[2,13] However, if skin sensitization has been shown, future contact with the relevant allergen(s) must be avoided. Patch testing with all molecules contained in the insulin pumps or glucose sensors is essential. In most cases, their exact composition is unknown, and information from the respective manufacturers is generally missing or incomplete. This also hampers counselling of the sensitized patients about possible alternatives. It is therefore necessary to perform chemical analyses in order to confirm the presence or the absence of (an) allergen(s) that gave a positive patch test reaction. These analyses are expensive and time-consuming, and cooperation with interested chemical laboratories is a necessity. Evidently, the implementation of complete labelling of medical devices by European legislation is paramount.

Moreover, all unwanted events observed with these medical devices should be reported to the pharmacovigilance unit, and public authorities should be alerted. Indeed, these ACD cases are not isolated, but constitute a worldwide problem. The European database (European Databank on Medical Devices [EUDAMED]), from which relevant information could be retrieved, is unfortunately not accessible to the public.[27]

5 | CONCLUSION

The market introduction of the insulin pump, along with the FGM and CGM systems, has significantly improved diabetic patient self-management and reduced potential complications such as hypoglycaemia and ketoacidosis. Owing to ACD caused by acrylates contained in these devices, and to the difficulties in identifying the culprit allergens, a number of patients need to, once again, measure blood glucose levels by finger pricking.

From a public health point of view, the control of the contact allergy epidemic and, specifically, the reduction of its impact are a challenge. Manufacturers should be motivated to search for less sensitizing materials, in addition to being obliged to disclose the complete chemical composition of all medical device parts.

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