

Continuous glucose monitoring systems give contact dermatitis in children and adults despite efforts of providing less “allergy- prone” devices Investigation and advice hampered by insufficient material for optimized patch test investigations

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Abstract

Background: Medical devices are increasingly being reported to cause contact allergic dermatitis reactions.

Objective: Review of patients with diabetes type I referred for suspected allergic contact dermatitis to insulin pump or glucose sensor systems. **Method:** We have reviewed 11 referred diabetes mellitus patients investigated for allergic contact dermatitis reactions to medical devices and specifically Dexcom G6®. Extracts from the medical devices were analysed.

Results: The majority of patients was children, the majority had relevant allergies and particularly allergy to isobornyl acrylate which was also found in the glucose sensor system Dexcom G6®.

Conclusions: The following case reports bring in focus the fact that patients sensitized through use of one medical device and being advised the use of another, or find another product for a while useful, are not by necessity free from future episodes of allergic contact dermatitis. The case reports emphasize the need for collaboration since it is impossible for even well-equipped laboratories to properly investigate the medical devices when information on the substances used in production is not uniform and complete and material to investigate are scarce. The importance of adequate patch test series and testing with own material and furthermore the importance to re-analyse medical devices and re-analyse test data are emphasized.

Introduction

In recent years, several cases of allergic contact dermatitis (ACD) to glucose sensors and insulin pumps have been reported. Isobornyl acrylate (IBOA) and *N,N*-dimethylacrylamide (DMAA) have been identified as major culprit allergens (1-5). However, also other allergens have been reported such as ethyl cyanoacrylate and colophony (6,7). The medical devices such as continuous glucose monitoring (CGM) systems, flash glucose monitoring (FGM) systems and insulin pumps have improved glucose control in diabetes type I patients (8,9). In Sweden it has become increasingly common to use insulin pumps and glucose sensors for diabetes type I patients, this being particularly the case in children. It is estimated that 7000-8000 children and youths in Sweden have diabetes type I. According to the national guidelines for treatment (10) all children with diabetes mellitus type I should be provided with either CGM or FGM. The rationale for use in children is to improve and simplify glucose control for the majority but also to provide equal care. Normalized glucose values already from the beginning of the disease tend to follow the child until adulthood (11,12) and are thus of utter importance.

However, adverse skin reactions at the site of application are reported by more than one third of adult users (13). It has been found that skin reactions constitute one of the main causes of treatment discontinuation (14-16). Also children have been found to have skin reactions (17) to insulin pumps and CGM/FGMs. In one study (18) more than 60% of patients using insulin pumps reported current dermatological complications and more than 45% of those using CGM/FGM. In another study (19) where children with dermatological complications were patch tested 8% were found contact allergic to acrylates or resins.

In this report we have reviewed patients, of whom the majority was children, that were referred in the period January 2019 – March 2020. The patients had in common that they had used, or had been advised to use, Dexcom G6®, CGM system (Dexcom, Inc., San Diego, California) a medical device prescribed to diabetes patients in Sweden. Previously, Dexcom sensors have been known to cause contact allergy to ethyl cyanoacrylate (7). The monitoring system has been recommended as it has been found not to contain IBOA (20-22).

In the department patients from southern Sweden are referred and we investigate patients with all sorts of medical devices. In 2017 a dedicated medical device patch test series was

developed in the Department of Occupational and Environmental Dermatology (16). As modifications of the series have been made repeatedly, the number and concentrations of test substances are not exactly the same in all the patients reported here.

Material and Method

Patients

In total, during the period investigated, 8 type 1 diabetes patients with adverse skin reactions suggestive of ACD at the sensor application site were investigated in the Department of Occupational and Environmental Dermatology in Malmö. Three additional patients being referred due to previous problems with medical devices are reported., They were using or were to start using Dexcom G6® but did not primarily experience problems with this medical device. Of these, one patient had developed ACD problems from Dexcom G6® at follow up. Demographic data are shown in table 2.

Patch test preparations

All patients were patch tested with the Swedish baseline patch test series including sesquiterpene lactone mix (SLM) 0.1% in petrolatum (pet.) and additionally 14-25 selected allergens from our medical device patch test series (table 1), individually chosen with knowledge of previous exposures with regard to medical devices. IBOA was generally tested in pet. at a concentration of 0.1% w/w and 0.3% w/w respectively. Chemotechnique Diagnostics (Vellinge, Sweden) provided the patch test preparations unless otherwise stated. All other test preparations were prepared at the Department of Occupational and Environmental Dermatology in Malmö, Sweden. 7 patients were patch tested for the adhesive as is. Apart from the defined substances 7 of the patients were patch tested with ultrasonic bath extracts of materials from the Dexcom G6®. The materials were extracted (sonicated) in ~20 ml acetone for 5 minutes and were then concentrated to a volume of 0.5 ml. In addition, 3 patients were tested with extracts prepared for chemical investigations described below.

Patch testing

The Finn chamber aqua® technique (SmartPractice, Phoenix, Arizona, USA) was used. 20 mg of the petrolatum test preparations were applied on the chambers and 15 µl of liquid preparations. The tests were occluded on the back for 2 days. Reading of the tests was performed on day (D) 3 and D7. The tests were read and scored according to the ICDRG and ESCD criteria (23,24) and with additional gradings according to Hindsén et al. (25).

Chemical investigations

Extracts made from materials from three different sensors were analysed. For the first sensor (LOT no 5251276) separate extracts were prepared from i) the adhesive patch and ii) the sensor (including the plastic support). The materials were cut into small pieces and were then extracted in 5 ml acetone at room temperature for 72 h. Thereafter the extracts were concentrated to a final volume of 0.2 ml using a rotary evaporator. These concentrated extracts were used for patch testing in case 2, 7, and 9. When analysed by gas chromatography-mass spectrometry (GC-MS) the extracts were first diluted 10 times and filtered.

From two other sensors, one unused (LOT 5256750) and one used by a patient (LOT no unknown), separate extracts were made from i) the adhesive patch, ii) the sensor, and iii) the plastic support. The materials were cut into small pieces and were then extracted in acetone at room temperature for 72 h. The volumes used were 2 ml for the extracts of the adhesive patches and sensors and 5 ml for the extracts of the plastic support. The extracts were filtered and analysed undiluted. In addition, a 1 ml aliquot of one of the extracts of the plastic support was concentrated 10 times and analysed.

The extracts were analysed by gas chromatography-mass spectrometry (26). Dilutions of IBOA in acetone were used as reference standards. The detection limit for IBOA was 0.01 µg/ml.

Results

Of the 11 patients 8 were children, mean age (range) 8 years (5-14), and 3 adults, mean age: 38 years. 8 had a history of atopy and 3 of atopic dermatitis. The patients had been exposed to different medical devices and different brands, in general >3 different types had been tried at referral, and mean time of medical device usage was 2.25 years, with the range a few months to a few years. 6 patients reported previous use of Freestyle Libre® (Abbott Diabetes Care, Witney, UK) and 7 use of the insulin pump Omnipod® (Insulet Corporation, Billerica, Massachusetts). All but one reported use of other medical devices in the form of FGM/ CGM or pump. 3 of the patients were referred for problems related to other insulin pumps or FGM/CGM. In the patients referred for Dexcom G6®-associated problems, it was difficult to

get exact information on how long they had used the device prior to the start of the dermatitis. Patch test results are summarized in table 2.

Of the extracts, 1 patient reacted both to the extract of the sensor and the extract of the adhesive patch. There were 2 doubtful reactions, one to the extract of adhesive and one to the adhesive as such. 6 patients were contact allergic to IBOA, 1 patient reacted with a doubtful reaction. Of the 8 patients patch tested also with IBOA 0.3%, 2 (25%) reacted only to this concentration. Furthermore, one contact allergy to IBOA 0.3% was only detected on the D7 reading. No late appearing reactions for IBOA was found.

Positive patch test reactions to SLM were observed in 4 patients, and one doubtful reaction. In the SLM-allergic patients 2 positive reactions were noticed to alantolactone, 2 to costunolide and 1 to dehydrocostus lactone. There were in all 3 positive reactions to colophony (1 at 20% and 2 at 60%) and 1 doubtful reaction.

Chemical analysis

IBOA was detected in all of the three analysed sensors. The extracts made from the adhesive patches contained IBOA in concentrations corresponding to 0.1 – 0.7 µg/patch. In the extracts of the sensors 0.8 – 1.3 µg IBOA was found. No IBOA could be detected in the extracts of the plastic support. Figures 1 and 2 show chromatograms of a sensor extract and an IBOA reference sample, and mass spectra of the IBOA peak in the extract and in the IBOA reference sample.

Discussion

ACD generally disappears as exposure to the culprit allergen ceases. However, contact allergy remains throughout life with the risk of elicitation of ACD if exposed to the allergen again. Given the fact that the medical device is in close contact to the skin for prolonged periods of time it is not surprising that contact allergy is a differential diagnosis when skin problems occur under the medical device. Although medical devices offer many potential benefits for a majority of users, recent studies have highlighted the risk of skin problem in general with prolonged exposure on the skin and furthermore, a risk of an associated ACD (4,13,15).

The diagnosis of ACD to medical devices of this sort has been hampered by the difficulty in getting adequate information on what the medical devices are made of, information on how to patch test and the possibility to get correct patch test material. Furthermore, in order to analyse possible allergens of the product adequate material (ie devices) is needed, laboratory equipment with the possibility to perform e.g. GC-MS analyses and experienced personnel to evaluate results have to be present. The patients becoming allergic also risk becoming sensitive to possible cross reacting substances. In patients sensitized to IBOA after using FreeStyle Libre®, there is an overrepresentation of contact allergy to the SLM in the baseline patch test series (1,27). So far, this association has not been possible to explain. Can the allergen be avoided, the dose or the time the material is in continuous contact with the same skin area be sufficiently reduced the individual will not experience dermatitis and can thus continue to use the product. The problem is that the composition of the medical device is not declared and it is often difficult to retrieve information. In 2017, two new regulations for medical devices were adopted in the European Union, in order to ensure better protection of public health and patient safety; medical devices (Regulation EU 2017/745) (28) and in vitro diagnostic medical devices (Regulation EU 2017/746)(29). However, though an improvement, the regulations risk giving inadequate help to those with allergic contact dermatitis. For the users, but also the prescribers, i.e. the medical professionals, it is important and urgent to obtain more transparency regarding the composition of medical devices. A clear disclosure of the components of the device that has induced the reaction would facilitate patch testing in order to diagnose, or exclude a possible allergic contact dermatitis. Today patients with skin problems due to medical devices are often inadequately investigated and a diagnosis is delayed or even not given. When the culprit allergen is found today it is furthermore difficult to help the patient in an adequate way as other medical devices do not have information on composition either.

All the patients investigated were referred due to possible ACD from medical devices. The history of the patients was similar, they had all but one (patient no 9) used other insulin pumps or glucose sensors prior to starting to use Dexcom G6®. Some of them had experienced problems almost immediately and sometimes after a couple of months.

Both the Dexcom G5® and the Dexcom G6® sensors have previously been reported to be free from IBOA (20,21). However, our analyses have shown the presence of small amounts of IBOA in both the adhesive patches removed from the sensors as well as in the sensors themselves. There are several different possible explanations to the differences between our

results and those previously published: Different solvents used for the extractions (acetone versus methanol), different extraction procedures (extraction of whole sensor cut into small pieces versus immersing the dermal contact side in ~2 mm solvent), and different sensitivities of the instruments used. Differences between sensor batches might also be a possible explanation.

Both in the case of FreeStyle Libre® (1) and Omnipod® (2) IBOA is thought to originate from UV-curing acrylate containing adhesives used in other parts of the devices which then migrates to the adhesive patch. Also in the case of Dexcom G6® this is a possible scenario, but as we have not had access to adhesive patches which have not been mounted on sensors, it is hard to draw conclusions from our results. The applicator holding the sensor before it is applied to the skin could also be a possible source of IBOA

The amounts of IBOA in the adhesive patches were 0.1 – 0.7 µg/patch which corresponds to a surface concentration of 0.005 – 0.03 µg/cm². In analyses of adhesive patches from Freestyle Libre® the surface concentrations of IBOA between 0.2 and 6 µg /cm² have been reported (1,5). As a comparison, the surface concentration of IBOA in a 0.1% pet. preparation tested in an 8 mm Finn Chambers AQUA is 40 µg/cm². Three patients showed strong (++ or +++) positive reactions to 0.01% IBOA in pet (4 µg/cm²).

It is therefore not unlikely that the low IBOA amounts found in the sensors could elicit ACD in sensitized individuals. Actually, in our patients all who tested positively to IBOA had previously used other IBOA-containing devices (all had used FreeStyle Libre® and in 3 cases also Omnipod®). This could explain both the fact that the patients reacted to the lower concentration found in the Dexcom G6® and often in close relationship to starting up use of the device, ie there was an elicitation due to previous sensitization. Only one patient with +++ reactions to both 0.1% and 0.01% IBOA tested positively to the extracts of the sensor and adhesive patch. Possibly, the IBOA exposure when patch testing with extracts or adhesive patches *as is* with a 48 h occlusion time is too low to elicit a positive reaction in most individuals. However, they may react when using the sensor as the exposure time is significantly longer, up to 10 days. It is possible that more patients would have reacted to the extracts if we would have had access to more sensors and were able to prepare stronger extracts. We had but one patient (no:9) who had only been exposed to Dexcom G6. In this patient we could not confirm a contact allergy to IBOA, and the extract of adhesive showed a doubtful reaction. A contact allergy to hydroabietyl alcohol was confirmed and the patient

also had doubtful reactions to colophony. The pattern of reactivity regarding IBOA and SLM is however interesting to note and the fact that the patient had not been exposed to IBOA in the device for more than 3 months and presumably at the lower concentration detected, which most likely explain why no contact allergy to IBOA was detected neither contact allergy to SLM. On the other hand, among the 6 IBOA-allergic patients simultaneous contact allergy to SLM was identified in 4 (65%) (Table 1) (1, 27) Interestingly, in those 2 patients requiring IBOA at 0.3% for the allergy diagnosis, no contact allergy to SLM was detected..

Of course also other allergens may be involved. Interestingly, 4 patients were positive to colophony and/or hydroabietyl alcohol. Similar to IBOA, a higher concentration of colophony than the one present in the baseline patch test series may be required to establish contact allergy . Only one patient of 11 (no:6) tested positively to colophony at 20% (found in the baseline patch test series) while 2/7 (28%) tested positively to the concentration at 60% (30). This being a retrospective study we had no opportunity to patch test all patients at 60%, and so it is unknown if more would have tested positive. Such a pattern of reactivity might have indicated a possibility of a colophony-related culprit contact allergen in Dexcom G6.

Different colphony derivatives may be used as tackifiers in pressure-sensitive acrylate-based adhesives (26,31). The GC-MS analyses indicated the presence of methyldehydroabietate in the extract of the adhesive patches, which in turn indicate the presence of colophony. This, however, needs to be further investigated. Whether the fact that there may be several possible contact allergens in the medical devices and whether if already sensitized to one allergen for example through use of a previous device will increase, not only the risk of getting ACD, even if the allergen content is lowered in a new device, but also possibly the risk of becoming sensitized to another allergen will need to be evaluated. It should also be noted that, however a small number of patients with 8/11 children all but one (87%) had more than one contact allergy. In 3 patients more than 4 contact allergies were found. This can be compared to a retrospective study in Denmark showing a prevalence of at least one positive reaction to the European baseline patch test series of about 25% (32). The patients in our study were patch tested with the Swedish baseline series but also with aimed testing resulting in the special pattern with an overrepresentation of resin-based and SLM-related allergens is interesting when comparing with the results of the referred study. 7 of 8 children had contact allergies relevant to their exposure to medical devices.

These case reports emphasize the need for a careful evaluation on how to perform extracts in order to be able to identify possible allergens. It furthermore indicates the need for

collaboration between the company producing the medical devices and the clinician investigating a possible ACD in a patient with medical device. With access to sufficient device material the possibility to improve the extracts used increases and thus the chance of actually finding a culprit allergen through patch testing. When the patch testing of an extract gives a positive reaction followed by negative reactions in controls, the extract can be used for separation and identification based on patch testing with thin layer chromatograms (33). The need to patch test accurately is clearly indicated as the allergens in the medical devices, however relevant, may be found in low concentrations. In four patients no relevant contact allergies were found. In three of these IBOA was not patch tested in a concentration of 0.3%. A diagnosis of irritant contact dermatitis is of course possible. When contacted, the parents of one of the patients (no:1), stated that their daughter had been able to use of Dexcom G6 ® and that the skin problems were fluctuating, indicating a possible irritant reaction. When a patient with a suspected ACD reaction to medical devices is investigated there is a need to consider several possible pitfalls in the diagnostic setup (33). Whether all the correct allergens have really been patch tested and in the right dose. If an extract is patch tested was it performed in an optimal way. Then, if the reaction is negative the time the medical device is used in continuous contact with the skin should be taken into account as an allergen may be found in a low, but clinically relevant concentration. The fact that the majority of the patients reviewed is children, where almost all had already used several medical devices, and already had many contact allergies also emphasizes the need for collaboration both between the medical profession, the patient organisations and the companies producing the items since these individuals, will need and want to use medical devices, most probably for the rest of their lives.

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Pat no	Sex	Age (yrs)/ age at DM diagnosis	Atopy/ eczema	Time of use and number of medical devices used (yrs)(no)	DG6 sensor extract	DG6 adhesive as is	DG6 adhesive extract	IBOA 0.3% D3/D7	IBOA 0.1% D3/D7	IBOA 0.01% D3/D7	Colophony 20% /60%	Hydroabietyl alcohol /abietic acid	SLM/alantolactone /costunolide/ dehydrocostus lactone	Other positive substances patch tested
1*	F	6/1	+/+	1 (2)#	NT	NT	NT	NT	-	-	-/NT	-/-	-/-/-/-	Al+++
2	F	12/ 9.5	+/-	2 (4)**	+(+)	NT	+(+)	NT	+++ /NR	+++ /NR	-/NT	NT/NT	+++ /+++ /+++ /-	Amerchol +
3	M	14/4	-/-	2.5(5)**#	-	-	NT	++	++	++	-/NT	NT/NT	++ /++ /-/-	TDM + Tested positive to Freestyle extract
4	M	6/3.5	+/+	1.5 (3)**	-	-	-	+/+(+)	+(+)	(+)	-/+	NT/NT	+/- /+ /+	ECA++
5	M	5/3	+/-	1(4)#	-	-	-	NT	-	-	-/+	-/-	-/- /-/-	Tested positive to Omnipod extract
6*	F	34/32	-/-	3.5 (7)**#	NT	NT	NT	- /++	-	-	+(+)/NT	++/-	-/- /-/-	FMII++, MP++ Hec + OM + Tested positive to Medtrum extract
7	M	7/6	+/-	1 (2)#	-	NT	-	-	-	-	-/-	-/-	-/- /-/-	Tested positive to Omnipod extract
8	F	46/39	+/+	2 (4)**	-	-	-	+ /++	-	-	-/-	NT/NT	-/- /-/-	Oxlin++
9	M	7/7	+/-	0.25 (1)	-	-	(+)	(+)	(+)	-	(+) /(+)	+/-	(+) /- /(+) /(+)	-
10	F	13/8	-/-	1 (2) #	-	(+)	-	-	-	-	-/-	-/-	-/- /-/-	-
11	F	35/26	+/-	9 (4)**#	-	-	-	+++	+++	++	-/-	-/-	+/- /-/-	Ni++ Dgl ++ oxlim+ oxlin +

Table 1. Demographic data and patch test results

Allergens: Al, aluminium chloride hexahydrate; Dgl, decylglucoside; ECA, ethyl cyanoacrylate; FM I, fragrance mix I; FM II, fragrance mix II; Hec, hexylcinnamic aldehyde; IBOA, isobornyl acrylate; MP, Myroxylon pereirae; Ni, nickel; TDM, textile dye mix; OM, oak moss absolute; oxlim, oxidized limonene; oxlin, oxidized linalool; SLM, sesquiterpene lactone mix. Reactivity is marked on day 3 and D7 separately if there is a crescendo reaction. If the reaction is the same or weaker at patch test reading at D7 this is not noted.

F, female, M, male, –, negative; (+), doubtful; + to +++, positive where +(+) refers to a reaction stronger than a + reaction according to the standard criteria (23,24) but not fulfilling the criteria for a ++ reaction () NT not tested, NR: not read. * primarily not referred due to problems with Dexcom G6® ** Previously used FGM system Free style Libre® # previously or presently using insulin pump Omnipod ®

Fig 1. Total ion chromatograms (TIC) and extracted ion chromatograms of m/z 55.0179 of an IBOA reference (1 μ g/ml IBOA in acetone) and an acetone extract of the Dexcom G6 sensor.

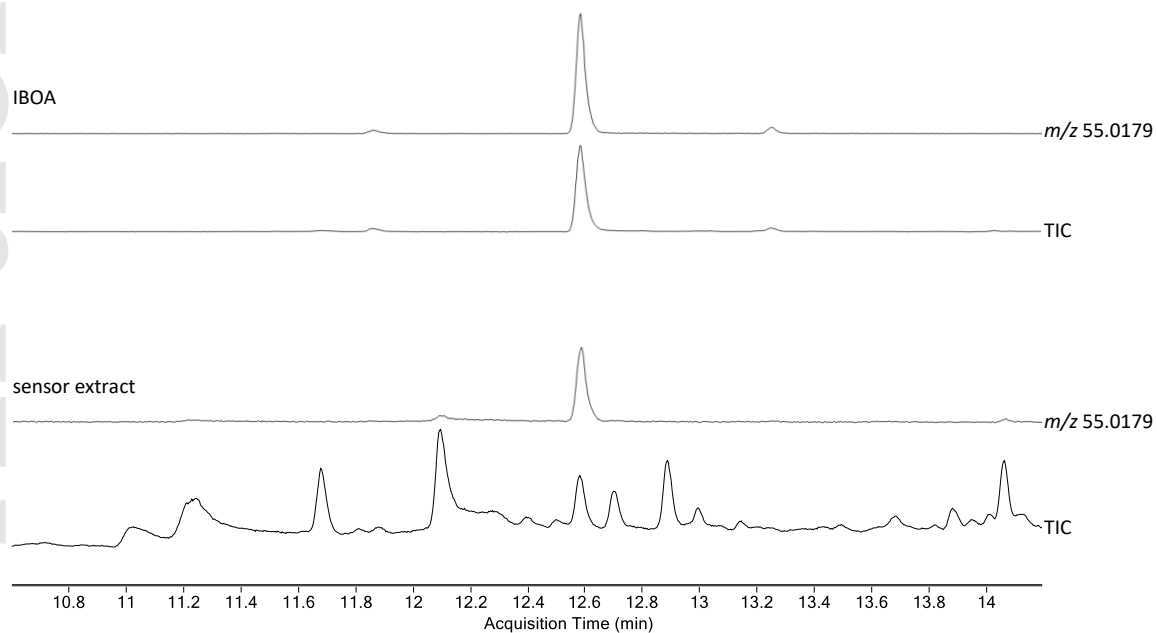


Fig 2. Mass spectra of the IBOA peak in a 1 $\mu\text{g/ml}$ IBOA reference and in a Dexcom G6 sensor extract.

