N,N-dimethylacrylamide - a new sensitizer in the FreeStyle Libre glucose sensor

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Background

Isobornyl acrylate (IBOA) has recently been identified as one sensitizer in the FreeStyle Libre glucose sensor. Analyses by gas chromatography-mass spectrometry (GC-MS) have indicated the presence of N,N-dimethylacrylamide (DMAA) in the sensor.

Material and methods

Seven patients were referred for patch testing after developing skin reactions when using FreeStyle Libre. All patients were patch-tested with IBOA and DMAA. Two patients were tested with adhesive patches which had been removed from the sensors "as is" and two patients were tested with acetone extracts of materials from the sensor. The extracts were analysed by GC-MS.

Results

Six patients reacted to both IBOA and DMAA and one patient reacted only to DMAA. Positive reactions were also observed in both patients tested with the adhesive patch. One patient reacted to both an extract of the adhesive patch and an extract of the sensor itself. When analysed by GC-MS, IBOA was found in both extracts and DMAA was found in the extract of the sensor.

Conclusion

Both IBOA and DMAA may be present in adhesives used in medical devices such as glucose sensors or insulin pumps and should be patch-tested when suspected contact allergic reactions to these products are investigated.

1. Introduction

Isobornyl acrylate (IBOA) has recently been identified as a cause of allergic contact dermatitis in diabetics using FreeStyle Libre (Abbott Diabetes Care, Witney, Oxfordshire, UK), a flash glucose sensor applied with an adhesive onto the skin for up to 14 days (1). The chemical investigations leading to the identification of IBOA was carried out at the Department of Occupational and Environmental Dermatology in Malmö, Sweden. Further analyses by gas chromatography-mass spectrometry (GC-MS) have indicated the presence of N,N-dimethylacrylamide (DMAA, CAS no. 2680-03-7) (Fig 1) in the FreeStyle Libre sensor. Therefore we have patch-tested this substance in patients with suspected allergic contact dermatitis caused by glucose sensors and/or insulin pumps. In this report we present seven patients with a history of skin reactions to FreeStyle Libre, who were diagnosed with contact allergy to DMAA. Six of them were also allergic to IBOA.

2. Patients and methods

2.1 Patients

Case 1: An 11-year-old girl with a one-year history of type 1 diabetes who had used the FreeStyle Libre glucose sensor for two months when she developed a dermatitis at the application site. Using the sensor at different places did not reduce the problems. Her dermatitis healed after she ceased using the FreeStyle Libre sensor. Instead she started using the Dexcom G4 Platinum glucose sensor (Dexcom, San Diego, California) without any skin problems. At examination a sharply demarcated hyperpigmentation was seen at a site of previous FreeStyle Libre application without any ongoing dermatitis.

Case 2: A 28-year-old woman with type 1 diabetes for 16 years was referred because of skin problems from FreeStyle Libre. She had used this device for 2.5 years and already after 4 months she started to experience irritation underneath the patch. For alleviation, she tried to use a hydrocolloid plaster, in which she made a tiny hole for the needle, to be put between the skin and the adhesive patch on the sensor. Four months prior to presentation at the department, her skin problems underneath the patch grew worse with oozing eczematous lesions. Therefore, she ceased using the FreeStyle Libre a month before presentation so that upon examination no eczema was seen. Her history also comprised the use of sculptured acrylic nails for 4 months with pruritus of the neck the day after re-sculpturing the nails.

Case 3: A 6-year-old girl with type 1 diabetes was referred due to dermatitis at the application site of FreeStyle Libre. She had used this glucose sensor for 2 years, and her skin symptoms started after 6 months. Since then, she was treated intermittently with a topical class III corticosteroid (mometasone furoate).

Case 4: An 11-year-old non-atopic girl with type 1 diabetes diagnosed in 2016 was referred due to dermatitis at the application site for FreeStyle Libre. Since 2017 she was using the insulin pump OmniPod (Insulet Corporation, Billerica, Massachusetts), and the glucose sensor FreeStyle Libre. Both were applied alternatively on the upper arms. She changed the application site of the insulin pump every 3 days, while the sensor was changed every 14 days. After 6 months of therapy she developed itching and eczematous skin lesions corresponding to the application area of FreeStyle Libre. A hydrocortisone butyrate cream led to resolution of eczema that, however, recurred with further applications of the glucose

sensor. At the time of the patch test investigation she started to use a hydrocolloid plaster underneath the glucose sensor. The patient continued the use of OmniPod insulin pump in spite of its content of IBOA (2), since she had never experienced any skin reactions in connection to the insulin pump, probably due to the short application time of the device to the skin.

Case 5: An 11-year-old girl with no previous skin disease or allergy suffered from diabetes for two years. After using FreeStyle Libre for one year she developed a skin reaction situated distinctly under the sensor. She had no skin problems from the adhesive of the infusion sets for insulin delivery that she used. She stopped using FreeStyle Libre and the school nurse applied a topical corticosteroid. After some time she completely discontinued use of the device owing to intense itching and recurring eczema regardless of where on the outer aspect of the upper arm she attached the sensor. At presentation she had ceased using the sensor but still had dryness and scaling on the outer aspects of the upper arms.

Case 6: A 52-year-old woman suffering from type 1 diabetes had used FreeStyle Libre for two years. After two months of use, she developed an annular eczematous dermatitis at the glucose sensor site on her arm. She tried to use a thin hydrocolloid dressing between the skin and the sensor without any beneficial effect. Since then, she has used self-monitoring of blood glycaemia and her diabetes has again became unstable. She had never been exposed to sculptured acrylic nails.

Case 7: A 66-year-old man suffering from type 1 diabetes had used FreeStyle Libre for one year. After one month of use, he developed annular eczematous dermatitis at the glucose

sensor application site of his arm. Henceforth, he applied an adhesive barrier wipe (Skin-Tac wipe, Torbot group, Warwick, New York) between the skin and the sensor, which made it possible for him to continue using the FreeStyle Libre sensor.

2.2 Patch testing

Cases 1–5 were evaluated at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, and cases 6-7 were evaluated at the Department of Dermatology of the Cliniques universitaires Saint-Luc in Brussels. All commercial patch test preparations were from Chemotechnique Diagnostics (Vellinge, Sweden) in Malmö and/or Trolab (Hermal, Reinbek, Germany) in Brussels. Patch testing was performed with 8 mm Finn Chambers AQUA (SmartPractice, Phoenix, Arizona) in Case 1 and 4 and with 8 mm Finn Chambers (SmartPractice) attached to Scanpor tape (Norgesplaster, Vennesla, Norway) in cases 2 and 3. Case 5-7 was tested with IQ Ultra chambers (Chemotechnique Diagnostics). The tests were occluded on the back for 48 hours. Reading of the tests was performed on day (D)3 and D7 in cases 1-5 and on D2 and D4 in cases 6 and 7. The tests were read and scored according to the ICDRG and ESCD criteria (3, 4)

In Malmö all patients were tested with an in-house glucose sensor series containing IBOA 0.1% and 0.01% pet. and DMAA 0.1% pet. (both from Sigma-Aldrich, Steinheim, Germany) as well as a number of substances indicated from GC-MS analyses to be present in the FreeStyle Libre sensor, including antioxidants for plastic materials such as BHT and *p-tert*-butylphenol. Cases 1, 2 and 4 were also tested with the Swedish baseline series. The constituents of sesquiterpene lactone mix (SLM), i.e. alantolactone, costunolide, and dehydrocostus lactone (all from Sigma-Aldrich) were each tested at a concentration of 0.1%

(w/v) in ethanol in cases 1, 4, and 5. In Brussels cases 6 and 7 were tested with IBOA 0.1% pet. and with DMAA 0.01% and 0.1% pet. (both from Sigma-Aldrich,) and with the European baseline series, meth(acrylates), plants and plastics/glues series. Both cases were also tested with alantolactone, costunolide, dehydrocostus lactone (all from Sigma-Aldrich, each tested 0.1% pet.), and with a piece of the adhesive patch from the sensor.

Case 1 was additionally patch-tested with 2-ethyl cyanoacrylate and with acetone ultrasonic bath extracts (5) made from (i) the adhesive patch from FreeStyle Libre sensor, (ii) the Freestyle Libre sensor (with the patch removed), and (iii) a Dexcom G4 Platinum sensor. Each extract was concentrated to a volume of 1 mL with a rotary evaporator before being used for patch testing. Two months later, supplementary patch testing with DMAA at 0.032% (w/v), 0.010%, 0.0032%, 0.0010%, and 0.00032%, all in acetone, using IQ Ultra chambers was performed. Case 2 was additionally tested to an extended baseline series and an acrylate series containing 2-ethyl cyanoacrylate, and on D3 additional patch-testing was performed with acrylamide 0.1% (w/v) pet. and N-methylolacrylamide 0.1% (w/v) pet. (both from Sigma-Aldrich). Case 3 was initially patch tested with the Swedish baseline series and the glucose sensor series using 8 mm Finn Chambers AQUA. Due to numerous patch test reactions repeated testing with the glucose sensor series, SLM 0.1% pet., and extracts of Finn Chambers AQUA and adhesives agents was performed 6 months later using 8 mm Finn Chambers attached to Scanpor tape. On D3 additional testing was performed with DMAA 0.032% and 0.010% pet. Only the results from the second test occasion testing is reported here. Case 4 was additionally patch tested with separate acetone extracts of the FreeStyle Libre sensor and patch. The extracts were prepared as described above. Case 5 was additionally patch tested with acetone extracts of Enlite glucose sensor, Enlite overtape and Sure-T Paradigm infusion set (all from Medtronic Minimed, Northridge, California) and also

with Skin-Prep wipes and Remove adhesive remover (both from Smith & Nephew, Fort Worth, Texas) tested "as is". Twenty dermatitis patients served as controls and they were patch tested with DMAA 0.032% (w/w) and 0.010% (w/w) pet.

2.3 Chemical investigations

The extracts of the FreeStyle Libre patch and unit tested in case 1 were each evaporated to a volume of approximately 100 μ L and were then analyzed by gas chromatography-mass spectrometry (GCMS) (1). The National Institute of Standards and Technology (Gaithersburg, Maryland) library of mass spectra was used for identification of substances. Dilutions of IBOA and DMAA in acetone were used as reference standards.

3. Results

3.1 Patch tests

The patch test results are summarized in table 1. Regarding case 1, Ppositive reactions were observed on D3 for IBOA, DMAA, SLM, costunolide, and both FreeStyle Libre extracts (sensor and patch)-, At supplementary testing with a dilution series of DMAA, a +-reaction was noted for DMAA 0.032% in acetone, but lower test concentrations were negative. In case 2, positive reactions were noted for *Myroxylon pereirae*, IBOA, and DMAA. The tests with acrylamide and N-methylolacrylamide were negative.

Case 3 showed positive reactions for DMAA 0.10 and 0.032%pet, and a doubtful reaction was observed for 0.010% DMAA. Tests for IBOA and sesquiterpene lactones were negative. The results regarding the Finn Chambers AQUA extracts are reported elsewhere. Case 4 reacted positively to DMAA, IBOA and alantolactone. Case 5 reacted to IBOA, DMAA, hydroxyethyl acrylate, and costunolide. She had a doubtful reaction with redness and

infiltration in the margins of the test preparation of the extract of the Enlite glucose sensor. All other tests with products brought by the patient were negative. Case 6 tested positively to IBOA, DMAA, *Myroxylon pereirae*, compositae mix, SLM, alantolactone, costunolide, hydroquinone, resorcinol monobenzoate, and the adhesive patch form FreeStyle Libre. Case 7 tested positive to IBOA, DMMA, and the adhesive patch from FreeStyle Libre.

No reactions were observed for the DMAA preparations patch tested in 20 controls.

3.2 Chemical investigations

In the GC-MS analyses IBOA was found both in the extract of the patch ($\approx 6 \ \mu g/cm^2$) and the sensor ($\approx 6 \ \mu g/cm^2$). DMAA was found in the extract of the sensor ($\approx 2 \ \mu g/cm^2$) but was not found in the patch ($< 0.5 \ \mu g/cm^2$). The presence of DMAA was indicated from the library spectra and further confirmed by comparison of retention time and mass spectra of a DMAA reference and also by spiking the FreeStyle Libre extract with DMAA (Online supplemental Figs. 2 and 3).

4. Discussion

Medical devices for insulin infusion and monitoring of blood glucose levels, which are attached to the skin with an adhesive for up to 14 days, have been reported to cause severe contact allergic reactions in diabetics. IBOA has been identified as a sensitizer in both FreeStyle Libre (1) and the OmniPod insulin pump (2). Furthermore, there are reports on contact allergic reactions to 2-ethyl cyanoacrylate in the Dexcom G4 Platinum glucose sensor (6-8), but the manufacturer has since abandoned the use of the adhesive containing 2-ethyl cyanoacrylate (9).

This report highlights DMAA as an additional sensitizer in FreeStyle Libre. Both DMAA and IBOA are used as monomeric diluents in UV curing adhesives (10). We have tried to obtain information on the adhesives used in FreeStyle Libre from the manufacturer but have failed. However, IBOA and DMAA frequently appear to be present together in high concentrations in medical grade UV-curing adhesives. One example is an adhesive from Loctite which contains 25-50% IBOA and 20-40% DMAA (11). It is likely that IBOA and DMAA found in the extract of the FreeStyle Libre sensor originate from an adhesive used to join the top and bottom part of the plastic cover of the sensor. According to the manufacturer of the adhesive patch, no IBOA is used in the adhesive in contact with the skin or in the adhesive used to fix the patch to the sensor (12). However, in our analyses we found IBOA also in the extract of the adhesive patch. Although the presence of DMAA could not be demonstrated in extract of the patch, it is possible that also small amounts of DMAA migrate from the sensor to the adhesive patch.

To the best of our knowledge there is only one previous report of contact allergy to DMAA. This case was a worker at a factory assembling surgical needles who reacted to a medical device adhesive used at the factory. When patch-tested, positive reactions to DMAA and tetrahydrofurfuryl acrylate, which both were ingredients of the adhesive, were observed (13). Contact allergy to acrylamide, N,N'-methylenebisacrylamide, and N-methylolacrylamide has been reported in printers handling photopolymerizing printing plates (14). Contact allergy to acrylamide has also been described in a "batch-mixer" employed at a plastics factory (15). Acrylamide (16-18), and piperazine acrylamide (19) have been reported as sensitizers in laboratory workers handling polyacrylamide electrophoresis gels. Contact allergy to N-(2ethylamino)ethyl acrylamide and N,N'-methylenebisacrylamide has been reported in laboratory technicians producing microspheres for embolization of human cardiovascular or neurosurgical procedures (20). Case 2 was patch-tested with both acrylamide and Nmethylolacrylamide but no reactions to these compounds were observed.

Although we have identified two sensitizers in FreeStyle Libre, we cannot rule out the possibility of other sensitizers in the sensor. However, we observed no reactions to other substances indicated by our chemical analyses to be present in the FreeStyle Libre sensor. Case 6 reacted to hydroquinone and resorcinol monobenzoate, but these substances were not observed in the analyses of the extracts. A high share of positive reactions to SLM has previously been described in patients reacting to IBOA (1). We found positive reactions to SLM and/or its constituents in 4 of the 7 patients presented here. The reason for this overrepresentation of simultaneous reactions is yet to be explained and will be discussed in a separate paper.

Our cases have presumably been sensitized to DMAA present in an adhesive used in the FreeStyle Libre sensor. Six of them were also sensitized to IBOA which is also found in the sensor. The high degree of concomitant reactions to DMAA and IBOA is likely explained by a simultaneous exposure to these substances when using the FreeStyle Libre sensor. Due to structural differences cross-reactions between IBOA and DMAA seem unlikely. As both IBOA and DMAA are ingredients of adhesives used for medical devices, they should be patch-tested when investigating suspected contact allergic reactions to medical devices such as glucose sensors and insulin pumps.

References

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	Test preparation	Case no.						
		1	2	3	4	5	6	7
	FreeStyle Libre patch "as is"	NT	NT	NT	NT	NT	++	+
	FreeStyle Libre patch acetone extract	+	NT	NT	-	NT	NT	NT
	FreeStyle Libre sensor acetone extract	++	NT	NT	-	NT	NT	NT
	DMAA 0.1% pet.	++	+++	++	+	+	++	++
	DMAA 0.032% pet.	+*	NT	+	NT	NT	NT	NT
	DMAA 0.01% pet.	_*	NT	?+	NT	NT	++	++
	IBOA 0.1% pet.	++	+++	-	+	+	++	++
	IBOA 0.01% pet.	+	+++	-	-	-	NT	NT
して	Baseline series	SLM +	MP ++	NT	-	NT	MP + SLM ++ CM +	-
	Sesquiterpene lactones							
	Alantolactone 0.1% ethanol	-	NT	NT	+	-	++**	_**
	Costunolide 0.1% ethanol	+	NT	NT	-	+	+**	_**
	Dehydrocostus lactone 0.1% ethanol	-	NT	NT	-	-	_**	_**
	Acrylate series	NT	-	NT	NT	NT	-	-
						hydroxy	hydrog	-
	Other positive substances	ox. limone ne +	-	-		ethyl acrylate +	uinone + resorci nol monob	

Table 1. Summary of patch test reactions in 7 patients positive to N,N-dimethylacrylamide (DMAA). The strongest reaction on either day (D) 3 or 7 (case 1-5) or D2 or D4 (case 6-7) is given in the table.

*vehicle: acetone **vehicle: petrolatum NT, not tested CM, compositae mix MP, Myroxylon pereirae SLM, sesquiterpene lactone mix



Figure 1. Molecular structure of N,N-dimethylacrylamide