Two decades of occupational (meth)acrylate patch test results and focus on isobornyl acrylate

Wietske A. Christoffers, Pieter-Jan Coenraads and Marie-Louise A. Schuttelaar

Department of Dermatology, University of Groningen, University Medical Centre Groningen, 9700 RB Groningen, The Netherlands

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Summary

Background. Acrylates constitute an important cause of occupational contact dermatitis. Isobornyl acrylate sensitization has been reported in only 2 cases. We encountered an industrial process operator with occupational contact dermatitis caused by isobornyl acrylate.

Objectives. (i) To investigate whether it is relevant to add isobornyl acrylate to the (meth)acrylate test series. (ii) To report patients with (meth)acrylate contact allergy at an occupational dermatology clinic.

Patients/materials/methods. Our patch test database was screened for positive reactions to (meth)acrylates between 1993 and 2012. A selected group of 14 patients was tested with an isobornyl acrylate dilution series: 0.3%, 0.1%, 0.033%, and 0.01%. Readings were performed on D2, D3, and D7.

Results. One hundred and fifty-one patients were tested with our (meth)acrylate series; 24 had positive reactions. Most positive reactions were to 2-hydroxypropyl acrylate, 2-hydroxyethyl acrylate, 2-hydroxypropyl methacrylate, and diethyleneglycol diacrylate. Hypothetical screening with 2-hydroxypropyl acrylate, ethyleneglycol dimethacrylate, ethoxylated bisphenol A glycol dimethacrylate and trimethylol propane triacrylate identified 91.7% of the 24 patients. No positive reactions were observed in 14 acrylate-positive patients tested with the isobornyl acrylate dilution series. The 0.3% isobornyl acrylate concentration induced irritant reactions in 3 patients.

Conclusions. We report a rare case of allergic contact dermatitis caused by isobornyl acrylate. However, this study provides insufficient support for isobornyl acrylate to be added to a (meth)acrylate series.

Key words: acrylate; allergic contact dermatitis; isobornyl acrylate; occupational.
patch testing with components of the glues and the plastic scrapings from their infusion set, including positive reactions to phenoxypoly(ethyleneoxy)ethylacrylate 0.1%, β-carboxyethyl acrylate 0.1%, 1-benzoylcyclohexanol 1%, and isobornyl acrylate 0.1%. The latter turned out to be one of the culprit allergens that had been used in the UV-cured adhesive and had diffused into the plastic of the infusion set. To the best of our knowledge, this is the only report of isobornyl acrylate contact allergy. Other studies failed to demonstrate isobornyl acrylate sensitization, even after prolonged exposure at high doses (3, 5, 6).

Case Report
A 47-year-old atopic man was referred to our centre because of therapy-resistant hand eczema. He had been working as a process operator in a factory producing glass fibres for over 20 years. His work involved painting glass fibres with UV-cured paint, printing the glass fibres, covering them with an acrylate coating, and cleaning the machines. His skin problems cleared during holidays, and relapsed when he returned to work.

The patient was patch tested with the European baseline series and 12 department-specific additions, the cosmetic series, and our (meth)acrylate series containing 29 commercially available (meth)acrylates (Chemotechnique Diagnostics, Vellinge, Sweden; Table 1). The patch tests were applied on the upper back for 48 hr under occlusion with van der Bend® square chambers (Van der Bend BV, Brielle, The Netherlands) and Fixomull® Stretch (BSN Medical, Hamburg, Germany). The tests were read on D3 and D7 according to the guidelines of the International Contact Dermatitis Research Group (ICDRG). There were no positive reactions to the extended European baseline series and the cosmetic series. The patient showed 1+ and 2+ positive patch test reactions to 11 different (meth)acrylates (Table 1). However, all of the acrylates turned out to be currently clinically irrelevant, because they were not present in the substances that the patient worked with at that moment. Nonetheless, an acrylate was suspected to be the causative allergen, given the nature of his present occupation. A workplace visit showed that isobornyl acrylate was a component of the glass fibre coatings [Desolite™ (DSM Desotech, Heerlen, The Netherlands) and Bufferlite™ DU-2002 (DSM Desotech)] and UV-cured ink (Herkula-Ultracoat™ OF 813; Krefeld, Germany) with which he came into contact during the production process. Thus, isobornyl acrylate was suspected as a relevant allergen. A patch test with isobornyl acrylate 0.1% pet. (Sigma Aldrich, Zwijndrecht, The Netherlands; in-house preparation) under 48 hr of occlusion resulted in a 2+ positive reaction on D3 and D7 (Fig. 2).

This case of isobornyl acrylate contact allergy and the concomitant various positive reactions to other clinically irrelevant acrylates led to the investigation into potentially missed isobornyl acrylate sensitizations in other patients. The question is whether contact allergy to isobornyl acrylate is rare or just underdiagnosed, and whether isobornyl acrylate should be added to (meth)acrylate patch test series. Therefore, we screened our database for patients with allergic reactions to (meth)acrylates, and patch tested a selected group with a dilution series of isobornyl acrylate, in order to detect any missed sensitization and potential cross-reactivity. In addition, the results of almost 20 years of patch testing with the (meth)acrylate patch test series are presented.

Materials and Methods
Database study
The (meth)acrylate series with 29 different (meth) acrylates has been used for patch testing at our dermatology department since 1993. The patch test database was screened for the patients tested with the (meth)acrylate series since 1993.

Our (meth)acrylate series consists of 29 different (meth)acrylates (Table 1) supplied by Chemotechnique Diagnostics. The types of acrylate in the series have not been changed over the last 19 years. However, the
Table 1. Patch test results between January 1993 and July 2012 according to the International Contact Dermatitis Research Group (ICDRG) guidelines

<table>
<thead>
<tr>
<th>Acrylate</th>
<th>Patient number</th>
<th>Total number of positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl acrylate 0.1%</td>
<td>1st</td>
<td>7</td>
</tr>
<tr>
<td>Butyl acrylate 0.1%*</td>
<td>2nd</td>
<td>10</td>
</tr>
<tr>
<td>2-Ethylhexyl acrylate 0.1%*</td>
<td>3rd</td>
<td>1</td>
</tr>
<tr>
<td>2-Hydroxyethyl acrylate 0.1%*</td>
<td>4th</td>
<td>1</td>
</tr>
<tr>
<td>2-Hydroxypropyl acrylate 0.1%*</td>
<td>5th</td>
<td>12</td>
</tr>
<tr>
<td>Methyl methacrylate 2%</td>
<td>6th</td>
<td>5</td>
</tr>
<tr>
<td>Ethyl methacrylate 2%</td>
<td>7th</td>
<td>6</td>
</tr>
<tr>
<td>2-Hydroxyethyl methacrylate 2%</td>
<td>8th</td>
<td>8</td>
</tr>
<tr>
<td>2-Hydroxypropyl methacrylate 2%</td>
<td>9th</td>
<td>11</td>
</tr>
<tr>
<td>Ethylenglycol dimethacrylate 2%</td>
<td>10th</td>
<td>10</td>
</tr>
<tr>
<td>Triethylene glycol dimethacrylate 2%</td>
<td>11th</td>
<td>6</td>
</tr>
<tr>
<td>1,4-Butanediol dimethacrylate 2%</td>
<td>12th</td>
<td>6</td>
</tr>
<tr>
<td>Urethane dimethacrylate 2%</td>
<td>13th</td>
<td>4</td>
</tr>
<tr>
<td>Bis-EMA 1%</td>
<td>14th</td>
<td>3</td>
</tr>
<tr>
<td>Bis-MA 2%</td>
<td>15th</td>
<td>1</td>
</tr>
<tr>
<td>Bis-GMA 2%</td>
<td>16th</td>
<td></td>
</tr>
<tr>
<td>1,4-Butanediol diacrylate 0.1%</td>
<td>17th</td>
<td>8</td>
</tr>
<tr>
<td>1,6-Hexanodiacrylate 0.1%</td>
<td>18th</td>
<td>5</td>
</tr>
<tr>
<td>Diethylene glycol diacrylate 0.1%</td>
<td>19th</td>
<td>11</td>
</tr>
<tr>
<td>Tripropylene glycol diacrylate 0.1%</td>
<td>20th</td>
<td>2</td>
</tr>
<tr>
<td>Trimethylolpropane triacrylate 0.1%</td>
<td>21st</td>
<td>3</td>
</tr>
<tr>
<td>Pentaerythritol triacrylate 0.1%</td>
<td>22nd</td>
<td>1</td>
</tr>
<tr>
<td>Oligotriacrylate 0.1%</td>
<td>23rd</td>
<td></td>
</tr>
<tr>
<td>Epoxy acrylate 0.5%</td>
<td>24th</td>
<td>3</td>
</tr>
<tr>
<td>Urethane diacrylate (aliphatic) 0.1%</td>
<td>25th</td>
<td>0</td>
</tr>
<tr>
<td>Urethane diacrylate (aromatic) 0.05%</td>
<td>26th</td>
<td>1</td>
</tr>
<tr>
<td>Triethylene glycol diacrylate 0.1%</td>
<td>27th</td>
<td>9</td>
</tr>
<tr>
<td>N,N-Methylene bisacrylamide 1%</td>
<td>28th</td>
<td>1</td>
</tr>
<tr>
<td>Total number of positive reactions</td>
<td>148</td>
<td></td>
</tr>
</tbody>
</table>

Bis-EMA, ethoxylated bisphenol A glycol dimethacrylate; Bis-GMA, bisphenol A glycylid methacrylate; Bis-MA, 2,2-bis[4-(methacryloxy)phenyl]propane.

*The concentrations of butyl acrylate, 2-hydroxyethyl acrylate and 2-hydroxypropyl acrylate were 0.5% in patients 1–3 and were reduced to 0.1% in patients 4–24.

*subject included in the isobornyl acrylate sub-study.

bsubject not included in the isobornyl acrylate sub-study.

index patient with a positive patch test reaction to isobornyl acrylate.

Patch test results of the (meth)acrylate series containing 29 different acrylates in pet. are given. Tests were read on D2 and D3, according to the guidelines of the ICDRG, between January 1993 and October 2008. They were also read on D3 and D7 between November 2008 and July 2012, in order to register late reactions.

Besides the patch test results and concomitant reactions, patient characteristics were registered according to the MOAHLFA index (7). The clinical relevance and the possible exposure to acrylates were assessed by means of a detailed history, including occupational history and potential exposure to acrylates. When contact with an acrylate-containing product was suspected, Material Safety Data Sheets (MSDSs) were studied to confirm a causative relationship. In some cases, a workplace visit was also undertaken.

The clinical relevance was labelled as ‘certain’ when the patient developed an itching dermatitis after exposure to at least one product containing acrylates (according...
to the product label or MSDS). The clinical relevance was labelled as 'probable' when a patient had developed an itching dermatitis after exposure to one or more products probably containing acrylates, but a specific product had not been identified as the cause of the clinical reaction. The clinical relevance was labelled as 'possible' when a patient developed an itching dermatitis after the use of various products with or without acrylates, and materials other than acrylates may have been the cause of dermatitis in the patient. Finally, the clinical relevance was labelled as 'unlikely' when a patient had no contact at all with products containing acrylates as far as was established (8, 9).

Isobornyl acrylate sub-study

Patients with a previously demonstrated acrylate sensitization were selected from our patch test database and approached by letter. The inclusion criterion was: at least one positive reaction to a (meth)acrylate diagnosed between January 2000 and July 2012. Patients using oral prednisone and pregnant women were excluded.

The included subjects were patch tested with an isobornyl acrylate dilution series of 0.3%, 0.1%, 0.033% and 0.01% pet. The patch test consisted of van der Bend® square chambers (Van der Bend BV, Brielle, The Netherlands) filled with 20 mg of isobornyl acrylate (CAS no. 5888-33-5; purity 91.8%) in pet., and fixed with Fixomull® Stretch (BSN Medical, Hamburg, Germany). The isobornyl acrylate was supplied by Sigma Aldrich (Amsterdam, The Netherlands), and dilutions were prepared in-house by our pharmacy. The patch test syrings were stored in a refrigerator (7°C) and freshly prepared every 4 weeks. The patch tests were prepared immediately prior to application, and applied on the upper back for 48 hr under occlusion. The results were read on D2, D3 and D7 according to the ICDRG guidelines.

The study was approved by the Medical Ethics Committee of the University Medical Centre Groningen.

Results

Database results

A total of 151 patients were tested with the (meth)acrylate series at the dermatology department between January 1993 and July 2012. Twenty-four (15.9%) of these 151 patients had a positive reaction to at least one acrylate (Table 1). Most of the positive reactions were caused by 2-HPA 0.1% pet. (12/148), 2-HEA 0.1% pet. (12/148), 2-hydroxypropyl methacrylate (2-HPMA) 2% pet. (11/148), and diethyleneglycol diacrylate (DEGDA) 0.1% pet. (11/148), whereas no positive reactions to urethane diacrylate (aliphatic) 0.1% pet. were encountered. We noted 7 irritant reactions to various acrylates, and only 10 doubtful reactions were registered.

A minority (n = 8, 33.3%) of the patients were males, and half of them (n = 13, 54.2%) were older than 40 years, with a mean age of 42.7 years (range 25–65 years). Only 4 (16.7%) patients suffered from atopic dermatitis. The MOAHLFA index was M33.3, O87.5, A54.2, H87.5, L0.0, F12.5, A16.7. The duration of their dermatitis ranged from 1 month to 2.5 years (mean 6 months). The duration of exposure to acrylates varied from 2 days to 20 years, but was unknown in several cases. The final diagnosis was ‘allergic contact dermatitis’ in almost all of the patients (95.8%); in 1 patient, the diagnosis was hyperkeratotic hand eczema, possibly occupationally related.

Twenty-one (87.5%) of the 24 sensitized patients had a risk of occupational exposure, and 14 cases (66.7%) were labelled as certainly occupation-related. Of the remaining occupational cases, 6 cases (28.6%) were labelled as probably occupation-related, and 1 case (4.8%) was labelled as possibly occupation-related. Among the occupationally exposed patients were nail stylists (n = 8), assembly line workers (n = 4), printers (n = 3), laboratory technicians (n = 2), dental technicians (n = 2), a painter (n = 1), and a dairy farmer (n = 1) who used a two-component hoof glue. All of the occupational cases presented with fingertip dermatitis or hand eczema, except for 1 patient who developed facial eczema in addition to the existing atopic dermatitis after starting training as a nail stylist. In 2 cases, there was secondary spread, and 1 patient suffered from angioedema.

Three (12.5%) of our 24 patients with (meth)acrylate contact allergy were considered to have been sensitized in a non-occupational manner. In 1 case, the patient suffered from stomatitis caused by new dentures (relevance: labelled as ‘certain’), whereas another case might have been caused by the use of artificial nails (relevance: labelled as ‘possible’). The third case developed erythema and oedema on her face after using an acrylate coating for her boat (relevance: labelled as ‘certain’). The symptoms resolved in all 3 cases after avoidance of the acrylate-containing products.

Isobornyl acrylate sub-study

Fourteen of the 24 potential subjects were included in the isobornyl acrylate sub-study (Fig. 3). There were various reasons for non-inclusion: 3 subjects were excluded because they used immunosuppressive drugs, 2 subjects declined because they had previously developed intense
itching after patch testing, and 5 subjects either did not respond or were untraceable.

The MOAHLFA index of the 14 included subjects was M: 28.6, O: 85.7, A: 50.0, H: 85.7, L: 0, F: 14.3, A: 14.2. The majority of the included subjects (n = 12, 85.7%) had a known occupational risk. Among the occupationally exposed subjects were nail stylists (n = 6), printers (n = 2), assembly line workers (n = 1), laboratory technicians (n = 1), dental technicians (n = 1), and a dairy farmer (n = 1) who used a two-component hoof glue. Two (14.3%) of the 14 cases were sensitized in a non-occupational manner.

The 14 included subjects were patch tested with the dilution series of isobornyl acrylate: 0.3%, 0.1%, 0.033% and 0.01% (Table 2). None of them developed a positive patch test reaction to the isobornyl acrylate. However, isobornyl acrylate 0.3% provoked an irritant reaction in 3 (21.4%) of the subjects. Five healthy controls were also patch tested with the isobornyl acrylate dilution series. None of them showed any irritant reactions or signs of sensitization.

Discussion

Acrylate contact allergy

Acrylates are considered to constitute an uncommon, although important, cause of contact allergy in general dermatology practices. The prevalence, based on screening series added to the baseline, varies between 1.0% and 1.6% (10, 11). In our study, 24 of the 151 (15.9%) patients patch tested with the (meth)acrylate series in the last 19 years reacted positively to at least one acrylate. This difference may be explained by the selected population. At our department, (meth)acrylates are not routinely tested, but are only tested if the physician has a strong suspicion of acrylate contact allergy (12). Moreover, a substantial amount of data was derived from our Expert Centre for Eczematous and Occupational Dermatoses, whereby most of the patients were occupationally exposed. This is in line with a previous study by Kanerva et al. (13) who reported positive reactions in 48 out of 275 (17.5%) patients with a history of occupational exposure to (meth)acrylates.

Between January 1993 and January 2002, we tested 32 patients with the (meth)acrylate series, and only 3 (9.4%) of them developed a positive reaction. Between 2002 and 2011, a total of 104 patients were tested, and 15 (14.4%) of them had positive reactions. The (meth)acrylate series was patch tested in 16 patients during the last year, and 6 (37.5%) of them have had positive reactions so far. This increase may be explained by the more frequent use of (meth)acrylates (14). Another plausible explanation is the selection of our patients who are eligible for patch testing. In addition, the patch test procedure has been improved over the years. Handling of the acrylate allergens was improved by storing them in a refrigerator and preparing them only minutes before application, to prevent evaporation and thus optimize the patch test concentration. Another improvement was the reading of the results on D7, to pre-empt late reactions. Eight of the 88 positive reactions were exclusively identified on D7; however, all of these patients had reacted to other acrylates on D3. However, for an accurate and complete diagnosis, an additional D7 reading is recommended.

Most positive reactions in our (meth)acrylate series were elicited by 2-HPA, 2-HEA, 2-HPMA, and DEGDA. In a comprehensive overview, Kanerva et al. (13) found a similar ranking, with 2-HEA (16/132), 2-HPMA...
(29/242) and 2-HPA (14/132) in the top four. DEGDA (13/243) was ranked 10th, but this acrylate caused more positive reactions (23/66) in the more recent overview by Aalto-Korte et al. (3), who tested 541 patients and found that 75 of them reacted to at least one acrylate. We did not observe positive reactions to urethane diacrylate (aliphatic) (alUDA), which is known to be a rare sensitizer. Even so, positive reactions to alUDA have been reported, especially in association with artificial nails (2, 15, 16), warranting inclusion of this allergen in the (meth)acrylate series.

Screening for (meth)acrylates is of real interest. Inclusion of a few acrylates in the baseline series as a screening tool for acrylate contact allergy has been proposed. A hypothetical series of four acrylates [2-HPA, ethylene glycol dimethacrylate (EGDMA), ethoxylated bisphenol A glycol dimethacrylate and trimethylolpropane triacrylate] would have identified 92% of our patients.

Goon et al. (17) composed two different acrylate mixes, one with triethylene glycol diacrylate (TREGDA) 0.1%, 2-hydroxyethyl methacrylate (2-HEMA) 1.0%, and EGDMA 1.0%, and another with TREGDA 0.1% and 2-HEMA 2.0%, to screen for acrylate sensitization in the baseline series. Screening with the individual components of these mixes would have identified fewer than half of our patients, respectively 11 (45.8%) and 10 (41.7%), although we did not investigate 2-HEMA at 2.0%, but only at 1.0%.

Goon et al. (1, 2) tested 1632 patients, and 48 had positive results to one or more (meth)acrylates. They composed a hypothetical screening series containing 2-HEMA, EGDMA, TREGDA, 2-HPMA, bisphenol A glycidyl methacrylate, and 1,4-butanediol diacrylate (BUDA) or 1.6-hexanediol diacrylate (HDDA), which would have identified all of their past patients (dental, industrial, and nail) with suspected (meth)acrylate contact allergy. However, in our cohort, 17 (70.8%) of our 24 patients would have been identified with this series, irrespective of whether BUDA or HDDA was used.

Aalto-Korte et al. (3) produced a hypothetical screening series with four allergens (EGDMA, DEGDA, 2-HPMA, and pentaerythritol triacrylate) that identified 92.4% (61/66) of their occupationally exposed patients, whereas it identified only 17 (70.8%) of our 24 patients.

Owing to this discrepancy and the fact that a substantial number of our patients would have been missed, we prefer to use a supplementary series containing 29 (meth)acrylate allergens in addition to the baseline series in patients.

**Isobornyl acrylate contact allergy**

An additional case of contact allergy caused by isobornyl acrylate is reported in this study. In this occupational case, the sensitizers were uncured UV ink and acrylate coating. With avoidance of these products, the skin problems of the industrial process operator resolved. To date, 1 year later, he is working at another department in the same factory without any complaints.

Sensitization to isobornyl acrylate is uncommon. Our study did not show any new cases of isobornyl acrylate sensitization besides the index patient. Together with the study by Busschots et al. (4), this means that only 3 cases of isobornyl acrylate sensitization have been identified to date.

Unfortunately, our index patient was only patch tested with the 0.1% concentration, and declined further patch testing. Otherwise, he would have been tested with the dilution series to ascertain the lowest concentration able to elicit a positive reaction to isobornyl acrylate (18). A concentration of 0.1% is the preferred patch test concentration for acrylates, because of the irritant potency and the risk of active sensitization (19, 20). However, acrylates are known for their volatility, and recent studies have shown a poor correlation between the measured (lower) and the stated (higher) concentrations of acrylate patch test concentrations (21, 22). In addition, a woman suspected of having occupationally related contact allergy provoked by an adhesive containing 61% isobornyl acrylate did not react to an isobornyl acrylate patch test (6). Moreover, various workers exposed to acrylates showed no reaction to isobornyl acrylate 0.1% (3, 5, 23). This, together with the lack of evidence of sensitization to 0.1% in other studies, compelled us to include a higher concentration of 0.3%. However, the concentration of 0.3% turned out to be too high, and caused irritant reactions in 3 patients. These reactions consisted of ‘shiny skin’ in 2 patients and irritant papules on the corners of the patch test chambers in the remaining subject. Although the index patient was only patch tested with 0.1% isobornyl acrylate, he did develop a 2+ positive reaction, which is in line with the patients reported by Busschots et al. (4), who developed 2+ and 3+ positive patch test reactions at a concentration of 0.1%, making it a legitimate concentration for showing sensitization.

Acrylates, which are chemically more similar to isobornyl acrylate, were expected to cross-react with isobornyl acrylate. Given the fact that none of the included subjects showed any reaction to isobornyl acrylate, no valid conclusions can be drawn regarding the cross-reactivity of isobornyl acrylate with other (meth)acrylates in vivo. Furthermore, cross-reactivity of (meth)acrylates with isobornyl acrylate seems to be less plausible, because
cross-reaction was not observed in this study and has not been reported in the literature.

Conclusion

We have described an additional rare case of allergic contact dermatitis caused by isobornyl acrylate.

Cross-reactivity between isobornyl acrylate and other acrylates could not be shown in a selected group of previously sensitized patients. The ideal patch test concentration for isobornyl acrylate seems to be 0.1%.

This study and the current literature provide insufficient support for isobornyl acrylate to be routinely used in the (meth)acrylate patch test series at our department. Isobornyl acrylate contact allergy seems to be rare. However, this allergen should be considered as a potential sensitizer in individual cases.

References