

The role of acrylic acid impurity as a sensitizing component in electrocardiogram electrodes

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Summary

Background. Allergic contact dermatitis caused by (meth)acrylates is well known, both in occupational and in non-occupational settings. Contact hypersensitivity to electrocardiogram (ECG) electrodes containing (meth)acrylates is rarely reported.

Objective. To report the first case of contact dermatitis caused by acrylic acid impurity in ECG electrodes.

Materials and methods. Patch tests were performed with separate components of electrodes and some (meth)acrylates. This was followed by high-performance liquid chromatography of electrode hydrogel.

Results. The patient was contact-allergic to electrode hydrogel but not to its separate constituents. Positive reactions were observed to 2-hydroxyethyl methacrylate (2-HEMA), 2-hydroxypropyl methacrylate (2-HPMA) and ethyleneglycol dimethacrylate (EGDMA). Subsequent analysis showed that the electrode hydrogel contained acrylic acid as an impurity. The latter was subsequently patch tested, with a positive result.

Conclusion. The sensitization resulting from direct contact with ECG electrodes was caused by acrylic acid, present as an impurity in ECG electrodes. Positive reactions to 2-HEMA, 2-HPMA and EGDMA are considered to be cross-reactions.

Key words: acrylates; acrylic acid; allergic contact dermatitis; ECG electrodes; high-performance liquid chromatography; hydrogel; methacrylates; patch test.

Poly-acrylates are thermoplastic polymers obtained from unsaturated monomers such as acrylic acid and its ester derivatives (1). Methacrylates are poly-acrylates in which a methyl group is attached to the α -carbon atom, instead

of a hydrogen atom. Since the 1950s, these polymers have been used in many occupational and non-occupational fields (2). They are widely used in the medical (dental prostheses, temporary bridges and filling, orthopaedic prostheses and cements, contact lenses, and materials for histology), industrial (printing inks, lacquers, paints, glues and adhesives for engineering, electric and electronic applications, plastics, leather, textiles, and floor waxes) and cosmetic (acrylic nails and powder fillers in face creams) fields (3). As widely reported in the literature, (meth)acrylate monomers frequently cause allergic contact dermatitis (ACD), both in occupational (4, 5) and in non-occupational (6, 7) settings.

Four cases of ACD induced by disposable electrocardiogram (ECG) electrodes containing acrylates have been

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reported in the literature (8–11). In these reports, the diagnoses were based on positive patch test reactions to the hydrogel part 'as is', even if its precise acrylate composition or the relevance of positive patch tests for some (meth)acrylates was not identified.

In this study, we found monomeric acrylic acid (2-propenoic acid) as an impurity in the electrode hydrogel, and identified it as the culprit allergen of ACD. Moreover, we discuss the relevance of concomitant patch test reactions to (meth)acrylates.

Materials and Methods

Case history

A 64-year-old non-atopic man was referred to us with multiple, itchy, eczematous patches on the anterior aspect of his chest (Fig. 1), corresponding to the sites of contact with disposable pre-gelled F2060® electrodes (Fiab SpA, Vicchio, Florence, Italy) used for Holter ECG monitoring. The device was applied 24 hr before the patient presented to us. The eruption consisted of vesicles, with intense erythema and swelling, which resolved in 2 weeks with the use of systemic and topical corticosteroids. The patient's past medical history included chronic ischaemic heart disease since 2010; after that, he had undergone Holter ECG monitoring every 3 months. He had not had any dental or orthopaedic implants.

One month after the resolution of skin lesions, patch tests were performed with the Società Italiana di Dermatologia Allergologica, Professionale e Ambientale (SIDAPA) baseline series and the individual components of F2060® ECG electrodes: the central metal part, the central hydrogel part, and the outer annular adhesive and non-adhesive sides of the foam (Table 1). The allergens (FIRMA Diagent, Florence, Italy) were tested on the upper back with Haye's Test Chambers (Haye's Service B.V., Alphen aan den Rijn, The Netherlands) on Soffix™ tape (Artsana, Grandate, Italy), and removed after 2 days. The readings (20 min, D2, D4, and D7) were performed according to International Contact Dermatitis Research Group criteria. Patch testing showed a positive reaction to nickel sulfate (+) and strong positive reactions to the hydrogel part of the electrode (+++) and adhesive foam (++). There were no other additional positive reactions at D7. To exclude the presence of nickel sulfate impurity in the hydrogel part, this was patch tested in 20 nickel-positive subjects, with negative results.

The technical data sheet from the manufacturer of the F2060® electrodes was requested. The manufacturer informed us that the metal part contained nickel-free stainless steel, and that the non-adhesive and adhesive



Fig. 1. Multiple eczematous plaques at contact sites with electrocardiogram monitoring electrodes.

Table 1. Patch tests results (SIDAPA standard series and individual parts of the disposable electrocardiogram electrode according to the manufacturer)

Patch test	D2	D4
SIDAPA standard series		
Nickel sulfate (5%)	+	+
F2060® electrode		
Metal part*	–	–
Non-adhesive side of foam*	–	–
Adhesive side of foam*	++	++
Hydrogel part*	+++	+++
Poly-acrylic acid (0.1%, 1%, 2%)†	–	–
Glycerol*	–	–
Potassium chloride*	–	–

*As is.

†In pet.

sides of the foam were, respectively, made of a polyethylene plastic holder and of poly-acrylate derivatives. The hydrogel part was made of water, glycerol, potassium chloride, and poly-acrylic acid (poly 2-propenoic acid).

Poly-acrylic acid (0.1%, 1% and 2% pet.), glycerol and potassium chloride were subsequently patch tested, with negative results (Table 1). In addition, the acrylate and the dental series were tested: positive reactions to 2-hydroxyethyl methacrylate (2-HEMA) (+++), 2-hydroxypropyl methacrylate (2-HPMA) (+++) and ethyleneglycol dimethacrylate (EGDMA) (++) were

Table 2. Patch test results for (meth)acrylates of the dental and acrylate series

Patch test	D2	D4
Ethyleneglycol dimethacrylate (2%)*	++	++
2-Hydroxyethyl methacrylate (5%)*	+++	+++
2-Hydroxypropyl methacrylate (2%)*	+++	+++
2,2-Bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane (2%)*	–	–
<i>N,N</i> -dimethylaminoethyl methacrylate (0.2%)*	–	–
1,6-Hexanediol diacrylate (0.1%)*	–	–
Methyl methacrylate (5%)*	–	–
Tetraethyleneglycol dimethacrylate (2%)*	–	–
Tetrahydrofurfuryl methacrylate (2%)*	–	–
Triethyleneglycol dimethacrylate (2%)*	–	–
Urethane dimethacrylate (2%)*	–	–
Acrylic acid (2.0%) [†]	+++	+++
Acrylic acid (1.0%) [†]	+++	+++
Acrylic acid (0.1%) [†]	+++	+++
Acrylic acid (0.01%) [†]	++	++
Acrylic acid (0.001%) [†]	–	–

* All in pet.

[†] All in saline solution.

observed (Table 2). In view of the positive reaction to the hydrogel part and the absence of reactions to its separate constituents, we analysed the hydrogel part with high-performance liquid chromatography (HPLC) to determine the possible presence of residual monomers of acrylic acid or related compounds.

Chemical analysis

HPLC was performed with a chromatographic system composed of a 600 Waters Apparatus with a quaternary pump and a 2487 Photodiode Array detector (Waters, Milford, MA, USA) (12).

The separation was performed in isocratic mode at a flow rate of 1.8 ml/min at room temperature on a separation (250 × 4 mm², 3 μm) Prontosil 200-3-C30 Chromatography column (Bischoff, Leonberg, Germany). The ultraviolet (UV)–visible absorbance was recorded over the 200–800-nm range. The extraction solution was a 0.01% aqueous solution of orthophosphoric acid. The electrode hydrogels and some drops of pure acrylic acid (the latter was used as reference) were dissolved in 5 ml of the extraction solution and stirred overnight. The samples were then centrifuged at 2000 *g* for 15 min, and the upper layer was injected into the chromatographic system. The mobile phase was 30/70 0.01% orthophosphoric acid aqueous solution/AcCN.

Results

The normalized chromatograms obtained at 220 nm for the pure acrylic acid and for the analysed hydrogel are shown in Fig. 2a. The chromatogram of the allergenic electrode hydrogel shows a peak with the same retention time as that observed for the pure acrylic acid, together with other peaks that indicate the presence of the other components of the hydrogel.

Normalized absorption spectra associated with the above chromatograms, obtained for pure acrylic acid and for the analysed hydrogel at the retention time of the main component, are shown in Fig. 2b. There is a close similarity between the acrylic acid and allergenic hydrogel absorption spectra, supporting the hypothesis of the presence of monomeric acrylic acid in the allergenic hydrogel.

In view of the results of chemical analysis, our patient was patch tested with acrylic acid (0.1%, 1.0% and 2% in saline solution) (Table 2). Positive reactions at D2 and D4 were found (Fig. 3). Acrylic acid tested at the

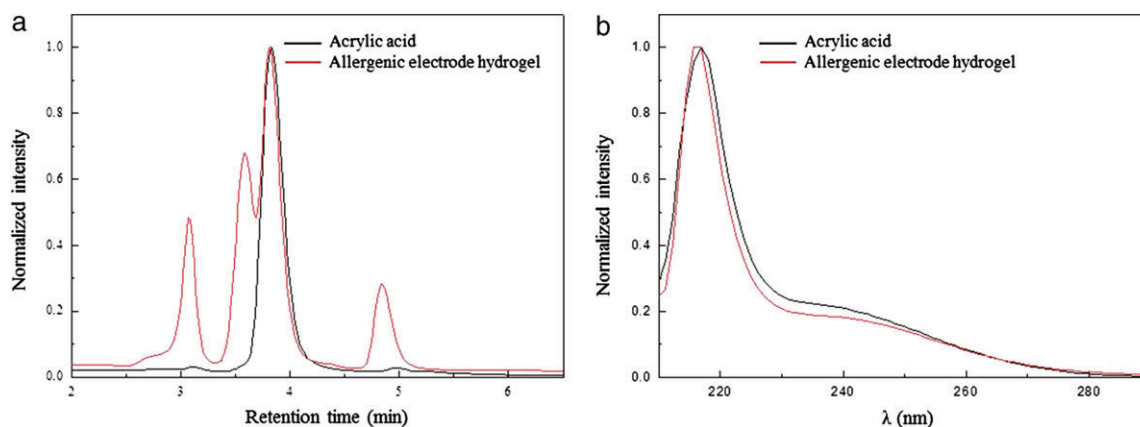


Fig. 2. (a) Normalized chromatograms for pure acrylic acid and for the analysed hydrogels at 230 nm. (b) Normalized absorption spectra associated with chromatograms obtained for pure acrylic acid and for the analysed hydrogels at the same retention time.

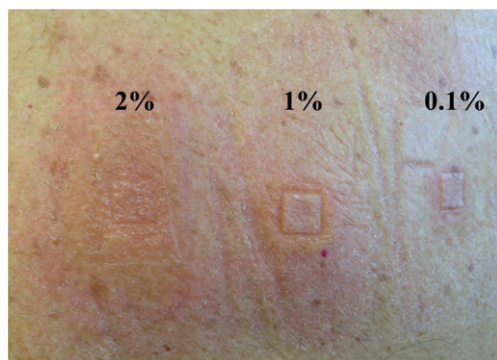


Fig. 3. Positive patch test reactions to acrylic acid (2%, 1% and 0.1% in saline solution).

same concentrations in 20 healthy subjects gave negative results. Subsequently, our patient was patch tested with acrylic acid at lower concentrations (0.01% and 0.001%). The lowest concentration of acrylic acid giving a positive patch test reaction was 0.01% (no positive reaction was observed at 0.001%). Moreover, the concentration of acrylic acid in the gel was estimated on the basis of HPLC calibration with pure acrylic acid dissolved in water. Five experiments to extract acrylic acid in the gel with different volumes of water were carried out. We found $(1.5 \pm 0.1) \times 10^{-3}$ ml of acrylic acid in the hydrogel, corresponding to a concentration of 0.5% (vol/vol).

Discussion

The characteristic moiety of (meth)acrylic acid structures is, from a chemical point of view, the carbonyl group (in the form of free acid or an alkyl ester) bound to a vinyl group, which is immediately adjacent (α - β position). Such a structure, which is common to many known allergens, is strongly polarized. The oxygen atom takes a part of the electron cloud from the adjacent carbon atom; this causes accumulation of negative charges around the oxygen and of positive charges around the carbon atom bound to it. This structure is very reactive, as it can easily react with proteins and other molecules to produce addition products. Moreover, the space geometry of substituents can favour or depress the electronic polarization or shield the electron cloud (13).

There are many reports of ACD caused by ECG monitoring electrodes in the literature, and the aetiological roles of many allergens have been reported: propylene glycol, *p*-*tert*-butylphenol formaldehyde resin, Euxyl® K400, tragacanth gum, pine oil and *p*-chloro-*m*-xylenol contained in electrode hydrogel; colophonium derivatives in the adhesive part; and nickel in the metal part (14–18). From 2001 to the present, four case reports of

ACD caused by ECG electrode dots have been published (8–11). In these, (meth)acrylate monomers were identified as the responsible allergens, and diagnoses were determined on the basis of a positive patch test reaction to the hydrogel part. Positive reactions to the adhesive foam have been attributed to hydrogel contamination by reactive monomers, as in our patient (Table 3).

In our study, we showed the presence of monomer acrylic acid impurity by HPLC. As in many other chemical reactions, polymerization reactions do not use 100% of the monomers, and residual traces of unreacted monomers could dissolve inside the polymer matrix in the electrode hydrogel. Monomers may be strong allergens, even if their residual amount is probably very low. In our opinion, ACD caused by the hydrogel is attributable to acrylic acid. Its concentration in hydrogel (0.5%) is far higher than the lowest concentration giving a positive patch test reaction (0.01%).

The other HPLC peaks represent the accompanying ingredients of the gel formulation. The UV spectrum shows that the accompanying substances do not have strong absorption in the UV region, and therefore do not show unsaturation levels comparable to that of acrylic acid. We believe that these accompanying substances do not have any allergenic potential.

The allergenic potential of acrylic acid and its derivatives results from a carbon–carbon double bond conjugated with the carbonyl group (called the α - β unsaturated carbonyl). Poly-acrylic acid is a non-reactive substance because all of the carbon–carbon double bonds have been opened and transformed into simple carbon–carbon bonds during the polymerization reaction (1). Moreover, as poly-acrylic acid has a very high molecular weight and shows a saturated chemical structure, it should not be an allergen.

The skin lesions started 24 hr after exposure to the electrodes, suggesting pre-existing contact allergy to acrylates resulting from previous multiple use of Holter ECGs.

Concerning the positive (2-HEMA, 2-HPMA, and EGDMA) and negative reactions to other (meth)acrylate monomers observed in our patient, it is evident that different geometrical configurations of molecules determine (i) their ease of diffusion into the skin and (ii) the allergenic potential of different structures, related to the activation or inactivation of the polarized form of molecules (19). All of the non-reactive (meth)acrylates observed in our patient have very high molecular weights and have less polarized configurations than the three positive ones. This shows that the acrylic structure is necessary for there to be a high probability of allergenic potential, but the strength of this reactivity may be depressed or enhanced by the interference of the surrounding, more

Table 3. Electrode hydrogel composition and positive patch test reactions to acrylates and methacrylates in the 4 reported cases of allergic contact dermatitis caused by electrocardiogram electrodes

Year	Sex/age (years)	Electrode hydrogel composition	Methacrylate/acrylate positive patch test reactions
2001 (8)	Female/53	Glycerol, polyethylene glycol, potassium chloride, tylose, benzoic acid, Euxyl™ K400, and acrylic acid derivatives	Hydroxyethyl acrylate, urethane diacrylate aliphatic, butanediol diacrylate
2013 (9)	Female/51	Several acrylates, including methacrylates and iso-octyl acrylate, a polyether polymer, sodium chloride, and potassium chloride	Tetraethyleneglycol dimethacrylate, 1,4-butanediol dimethacrylate
2013 (10)	Female/64	Acrylates	Methyl methacrylate, triethyleneglycol dimethacrylate, ethyleneglycol dimethacrylate
2014 (11)	Female/28	Acrylates	Butyl acrylate, ethyleneglycol dimethacrylate, 2-hydroxyethyl methacrylate

or less bulky, substituents in the molecular structure (4, 20). Taking into account all of these factors, the positive reactions observed with 2-HEMA, 2-HPMA and EGDMA are considered to be cross-reactions. Indeed, the observed differences in the behaviour of acrylic acid and its several esters show that the structure of the esterified alcoholic group (or the free OH⁻ group, when the pure acids are involved) can influence the polarization level of the carbonyl group, consequently modifying the reactivity of the whole α - β unsaturated carbonyl structure. In our experience, positive reactions occur when the alkyl substituent bears a hydroxyl group or the free acid, which

has a very polar hydroxyl group. Once more, this shows that, in allergenic structures, the electronic configuration together with the geometry of the molecules and preferential molecular configurations can affect the reactivity of potentially similar haptens.

In conclusion, the presence of (meth)acrylic monomer acid impurities in poly-(meth)acrylates has not been adequately investigated until now, as the analytical search for impurities is difficult and expensive. The identification of monomer reactive impurities represents an important step in detection of the culprit allergen responsible for allergic reactions to acrylates.

References

- Geukens S, Goossens A. Occupational contact allergy to (meth)acrylates. *Contact Dermatitis* 2001; **44**: 153–159.
- Ramos L, Cabral R, Gonalo M. Allergic contact dermatitis caused by acrylates and methacrylates – a 7-year study. *Contact Dermatitis* 2014; **71**: 102–107.
- Sasseville D. Acrylates in contact dermatitis. *Dermatitis* 2012; **23**: 6–16.
- Aalto-Korte K, Henriks-Eckerman M L, Kuuliala O, Jolanki R. Occupational methacrylate and acrylate allergy cross reactions and possible screening allergens. *Contact Dermatitis* 2010; **63**: 301–312.
- Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Methacrylate and acrylate allergy in dental personnel. *Contact Dermatitis* 2007; **57**: 324–330.
- Haughton A M, Belsito D V. Acrylate allergy induced by acrylic nails resulting in prosthesis failure. *J Am Acad Dermatol* 2008; **59** (Suppl. 5): S123–S124.
- Cravo M, Cardoso J C, Gonalo M, Figueiredo A. Allergic contact dermatitis from photobonded acrylic gel nails: a review of four cases. *Contact Dermatitis* 2008; **59**: 250–251.
- Jelen G. Acrylate, a hidden allergen of electrocardiogram electrodes. *Contact Dermatitis* 2001; **45**: 315–316.
- Lyons G, Nixon R. Allergic contact dermatitis to methacrylates in ECG electrode dots. *Australas J Dermatol* 2013; **54**: 39–40.
- Nuñez-Acevedo B, Gonzlez-Fernndez M T, Juangorena M M, Vidal C. Multifunctional acrylates as possible sensitizers in electrocardiogram electrode allergy. *Ann Allergy Asthma Immunol* 2013; **111**: 77–78.
- Ozkaya E, Kaviak Bozkurt P. Allergic contact dermatitis caused by self-adhesive electrocardiography electrodes: a rare case with concomitant roles of nickel and acrylates. *Contact Dermatitis* 2014; **70**: 121–123.
- Jamshidi A, Ahmad Khan Beigi F, Kabiri K, Zohuriaan-Mehr M J. Optimized HPLC determination of residual monomer in hygienic SAP hydrogels. *Polym Test* 2005; **24**: 825–828.
- Angelini G, Rigano L, Foti C et al. Occupational sensitization to epoxy resin and reactive diluents in marble workers. *Contact Dermatitis* 1996; **35**: 11–16.
- Uter W, Schwanitz H J. Contact dermatitis from propylene glycol in ECG electrode gel. *Contact Dermatitis* 1996; **34**: 230–231.
- Oestmann E, Philipp S, Zuberbier T, Worm M. Colophony-induced contact dermatitis due to ECG electrodes in an infant. *Contact Dermatitis* 2007; **56**: 177–178.
- Avenel-Audran M, Goossens A, Zimerson E, Bruze M. Contact dermatitis from electrocardiograph-monitoring electrodes: role of p-tert-butylphenolformaldehyde resin. *Contact Dermatitis* 2003; **48**: 108–111.
- Ralph J, Coskey M D. Contact dermatitis caused by ECG electrode jelly (gum). *Arch Dermatol* 1977; **113**: 839–840.
- Fisher A A. Dermatologic hazards of electrocardiography. *Cutis* 1977; **20**: 687–695.
- Rustemeyer T, De Groot J, Von Blomberg B M E et al. Cross-reactivity patterns of contact-sensitizing methacrylates. *Toxicol Appl Pharmacol* 1998; **148**: 83–90.
- Dupuis G, Benezra C. *Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach*. New York, Marcel Dekker Inc., 1982; pp. 79–81.