The development and course of patch test reactions to 2-hydroxyethyl methacrylate and ethyleneglycol dimethacrylate

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Abstract

Methacrylic monomers are used in dental work, why dental personnel, technicians, and patients are at risk of being sensitized. 2-hydroxyethyl methacrylate (2-HEMA) and ethyleneglycol dimethacrylate (EGDMA) are commonly used. Allergic test reactions to them sometimes appear beyond day 7. This study was designed to study the development and course of positive test reactions to 2-HEMA and EGDMA in allergic patients as a mean to elucidate the issue of patch test sensitization. 12 patients with contact allergy to 2-HEMA and EGDMA were retested with dilution series. The clinical course was followed for 1 month.

During the study, 25 positive test reactions to 2-HEMA and 19 to EGDMA were diagnosed. Within the 1st week, 21 were noted for 2-HEMA and 18 for EGDMA. After 10 days, another 2 reactions appeared for 2-HEMA and 1 for EGDMA. All but 1 patient with the latter reactions also had positive reactions within the 1st week. After 1 month 12 reactions for 2-HEMA and 10 for EGDMA remained. Patch test reactions to 2-HEMA and EGDMA are long-lasting. The patch test concentrations of 2.0% for 2-HEMA and EGDMA may be continually used. Positive test reactions emerging after 10 days do not automatically imply active sensitization.

Acrylic and methacrylic monomers are used extensively as restorative materials in the dental profession and in the manufacture of dental prostheses (1-4).Dental personnel (5-8) and technicians (3,9,10) are therefore at risk of being sensitized to these chemicals when working with them prior to hardening. If these monomers are used in dental restorations there is also a risk of sensitization in dental patients, albeit lower than in the professionals (2,11-13). In Sweden, dermatologists investigate cases of suspected contact allergy and allergic contact dermatitis to dental chemicals by patch testing to a dental series composed of substances used in the dental profession and which have shown a sensitizing potential. More than a third of the substances in one such dental series (Chemotechnique Diagnostics, Tygelsjö, Sweden) (14) is (meth)acrylates, well-known sensitizers that are patch tested in internationally recommended concentrations used all over the world, i.e. acrylates at 0.1% w/w in petrolatum and methacrylates at 2.0% w/w in petrolatum. The rationale for lower patch test concentrations for acrylates compared to methacrylates is the higher risk of patch test sensitization and irritancy to the former. Patch test concentrations for (meth)acrylates have to some extent been worked out after a “trial and error” principle, i.e. if a (meth)acrylate has sensitized a number of

patients at patch testing, the patch test concentration has been lowered (15,16). Some acrylics have even been extracted from patch testing series because of its high sensitizing capacity (4,17).

Two dental methacrylates are 2-hydroxyethyl methacrylate (2-HEMA) and ethyleneglycol dimethacrylate (EGDMA). The monofunctional acrylate 2-HEMA is often used in dentin bonding systems because it is hydrophilic and EGDMA, a difunctional methacrylate, is used in dental composite resins and sometimes also in bonding systems. When testing to these (meth)acrylates late positive patch test reactions are not uncommon, i.e. a positive reaction is seen on day (D) 7 at first and sometimes even beyond D7, the latter being suggestive of active patch test sensitization. The possibility of an ordinary but late patch test reaction appearing after D7 has also to be considered, which is often seen when patch testing to gold sodium thiosulfate (18) and sometimes to corticosteroids (19). The present study was therefore designed to study the development and course of positive patch test reactions to 2-HEMA and EGDMA in patients hypersensitive to these methacrylates as a mean to elucidate the issue of patch test sensitization.

Materials and methods

Study design

The study was performed as a multicentre study. The 3 participating clinics were the Department of Occupational and Environmental Dermatology, Malmö University Hospital, Malmö, Sweden, the Department of Medicine, Occupational and Environmental Dermatology, Karolinska Institute and Stockholm Centre for Public Health, Stockholm, Sweden, and the Department of Dermatology, Ryhov Hospital, Jönköping, Sweden. Ethical committee approvals were obtained from the participating clinics and written informed consent was obtained from all participating patients.

Patients

12 patients, 11 females and 1 male (mean age 47 years, range 31-63 years) were recruited, 11 of which had been patch tested to a dental series previously and 1 to a nail acrylics series, and all of which were shown to be allergic to 2-HEMA and EGDMA. There were 7 dental nurses, 2 dentists, 2 individuals with artificial nails, and 1 nurse.

Test substances

2-HEMA (Fluka Chemie AG, Neu-Ulm, Germany) was dissolved in ethanol 99.5% v/v to 2.0% v/v. From this stock solution, further dilutions were prepared with a dilution factor 10 from 0.2% down to 2×10^{-9}%. EGDMA (Chemotechnique Diagnostics, Tygelsjö, Sweden) was dissolved in ethanol 99.5% v/v to 2.0% v/v. From this stock solution, corresponding dilutions to 2-HEMA were made.

Patch testing

Van der Bend® chambers (Brielle, The Netherlands) mounted on Micropore® tape (3M, USA) were used. 20 µl of the test solution was applied to the filter paper of the plastic chamber and the patches were placed on the upper back. Scanpor® tape (Norgesplaster A/S, Vennesla, Norway) was used to secure the strips to the back.

Test evaluation

Test strips were removed from the back after 2 days. The first test reading was performed on D3 and thereafter, readings were repeated on D7, D10, D14, D17, D21, D24, and D28. The evaluation was done according to the International Contact Dermatitis Research Group (ICDRG) criteria (20).

Results

Of the 12 tested patients, 11 reacted (pat. nos. 1-11). All 11 reacted to 2-HEMA whereas 10 reacted to EGDMA.

For 2-HEMA, the first reactions appearing were of an allergic nature for 24 tests and doubtful for 2 tests. Of the initially 2 doubtful reactions, 1 developed into a clear allergic reaction

making the total number of allergic tests 25. Of these 25 allergic reactions 21 had appeared in the 1st week, and during the following 3 days, a further 2 reactions appeared. After 10 days, 2 new allergic reactions came. After 4 weeks, 12 reactions were still present (48%).

For EGDMA, the first reactions appearing were of an allergic nature for 18 tests and doubtful for 4 tests. Of the initially 4 doubtful reactions, 1 developed into a clear allergic reaction making the total number of allergic tests 19. Of these 19 allergic reactions 18 had appeared in the 1st week. During the following 3 days, no new reactions appeared. After 10 days, 1 new allergic reaction came. After 4 weeks, 10 reactions were still present (53%). The patch test reactions on the various reading days are given in Table 1. The earlier a test appeared, the longer it remained and a long duration was also noted for the most intense reactions.

Discussion

To recruit sufficient numbers of patients allergic to 2-HEMA and/or EGDMA a multicentre study was needed. In that situation, the reading and scoring of patch test reactions may be considered a weak point, because the risk of several readers having a difference in experience where the readings of above all the weak and the doubtful patch test reactions may have been different (21). However, the participating dermatologists were all very experienced.

A similar study like the present one has been performed with gold sodium thiosulfate (18). In that study it was pointed out that biased readings cannot be excluded with this study design. One way to overcome this would have been to apply patches randomly on the back and with each patch test concentration tested on randomly chosen days, which means that each patient should have been tested on 10 different days. This would have been both complicated and inconvenient for the patients.

In our experience allergic patch test reactions to (meth)acrylates have a tendency to appear late, i.e. after D3 or D4. Therefore the recommendation to perform 2 patch test readings, i.e. on D3/D4 and on D7, is especially good for (meth)acrylates. Reading patch tests on a second

late occasion, preferably 1 week after patch test application, is recommended by many authors (18) and also by the Swedish Contact Dermatitis Group. Looking at the outcome for the internationally recommended patch test concentrations for 2-HEMA (2.0%), there was no difference for the readings only on D3 compared to the readings on both D3 and D7 in patients nos. 2-11. The only patient that stood out was no. 1, who did not react to 2-HEMA until after D10. For EGDMA 2.0% in pet, 1/10 patients was missed with only a D3 reading, while none of the allergic patients were missed with a reading on both D3 and D7. This is of course not surprising since all the patients had been traced with 2.0% in the first place. However, looking at all positive reactions in the present study, readings on D3 and D7 was shown to miss some reactions, as 4/25 (16%) of the allergic reactions to 2-HEMA and 1/19 (5.3%) of the allergic reactions to EGDMA appeared later than after 1 week.

Active sensitization is the most serious adverse reaction to patch testing. Patch test sensitization is mostly detected by a flare up reaction at the test site at least 10 days after test application (22). On repeat testing the test is already positive on D2-4. Even without an evident flare-up reaction, active patch test sensitization may be revealed when retesting patients after an interval. In such an event, a positive reaction to a substance that has tested negatively previously is more likely to represent patch test sensitization than a sensitization that may have taken place after environmental exposure to an allergen (23). It may also represent an increased level of reactivity, but if patch testing is done on this occasion with the substance diluted 10-100 × as compared to the original test concentration and the test turns out positive, active patch test sensitization must be considered likely (23). However, it has been shown that patch test reactivity to nickel in nickel-allergic women can vary 250 times from one time to another (24), and other sensitizers may also exhibit this pattern.

Moreover, this study not only elucidates the duration of positive patch test reactions to 2-HEMA and EGDMA but also the nature of reactions appearing after 10 days.

Three such reactions were seen in 3 patients (in pat. nos. 1 and 6 to 2-HEMA, in pat. no. 2 to EGDMA). In 1 patient (no. 1), the reaction to 2-HEMA was the first reaction to appear with a morphology consistent with an allergic reaction, i.e. a reaction that could be suggestive of active sensitization in a non-sensitized individual. On an earlier occasion prior to this study the patient had tested positively to 2-HEMA both on D3 and D7. However, in the other 2 patients higher test concentrations (nos. 2 to EGDMA and no. 6 to 2-HEMA) gave positive reactions within the first week, speaking against active sensitization if tested in a non-sensitized person. Furthermore, the 11 patients were all positive to 2-HEMA and EGDMA on the previous test occasion prior to this study within the 1st week and the 12th patient, who did not react to either 2-HEMA or EGDMA in the present study, only reacted to them on D13 on the previous occasion. Establishing of contact allergy and assessment of clinical relevance may thus be much more difficult in these cases.

It has been postulated that active sensitization is proven when a flare-up reaction at retesting is followed by a positive test within 2-4 days (22). However, it may not always be true. Looking at patient no. 2 and the reactions to EGDMA, she reacted positively with a papular reaction to the concentration 2.0 and 0.2% v/v on D3, while the concentration of 0.02% showed up as a late-appearing reaction after 2 weeks indicative of patch test sensitization. However, she was known from prior patch testing to be hypersensitive to EGDMA, and in this study there was a contact allergic reaction already on D3 but from a concentration 10 and 100 × higher. Thus, there is a narrow concentration range, meaning that one particular dose may give a positive test reaction on one test occasion within the first week and a slightly lower dose will result in a late-appearing reaction that could be interpreted as a flare-up reaction. The same applies for pat no. 6 allergic to 2-HEMA. She reacted to 2.0 % v/v on D3 with a papular reaction, while the 10× lower concentration of 0.2% showed up as a late-appearing reaction after 2 weeks. Considering biological and technical variations, this means

that the same patch test concentration tested on different occasions might lead to a positive test reaction first seen on different reading days, i.e. sometimes a positive reaction is seen on D7 or even later for the first time and then at retesting on D3, a pattern that easily can be misinterpreted as active sensitization.

In summary, this study shows that many epicutaneous tests to the methacrylates 2-HEMA and EGDMA are long-lasting. 12/25 (48%) of the 2-HEMA reactions and 10/19 (53%) of the EGDMA reactions remained after 1 month. Some were also late appearing, especially the reactions evoked from the low test concentrations, i.e. not the concentrations used in the commercial acrylate series. Overall, 16% of all 2-HEMA reactions appeared after 1 week compared to 5.3% for EGDMA. The late appearing and long-lasting test reactions to 2-HEMA and EGDMA are not easily explained. Slow penetration could account for the late appearance. Also, metabolism and processing of the allergens might differ from other allergens. Long duration may be due to slow elimination of the allergen from the skin site of reaction. Taken together, however, the internationally recommended patch test concentrations of 2-HEMA (2.0%) and EGDMA (2.0%) may thus be continually used in our dental and acrylate series, and late-appearing patch test reactions that show up as flare-up reactions may be seen without having to be patch test sensitization. However, to distinguish with the highest possible degree of likelihood between active sensitization with a flare-up reaction and a late elicitation reaction the most appropriate way is to retest with the allergen in question in a dilution series (23).

Table 1. Positive patch test reactions to 2-hydroxyethyl methacrylate and ethyleneglycol dimethacrylate in the 11 patients

Patient no.	Substance	Concentration (%)	Reading day							
			3	7	10	14	17	21	24	28
1.	2-HEMA*	2.0				+	++	++	+	+
		0.2								
	EGDMA**	2.0								
2.	2-HEMA	2.0	+++	+++	++	++	++	++	++	++
		0.2	++	++	++	+	++	++	+	+
		0.02			+	+				
		0.002								
	EGDMA	2.0	+++	+++	++	++	++	++	++	++
		0.2	++	++	++	++	++	++	+	+
		0.02				+				
		0.002								
3.	2-HEMA	2.0	+++	+++	+++	+++	++	++	++	++
		0.2	++	++	++	++	++	+	+	+
		0.02	++	+	+	+	+	(+)		
		0.002								
	EGDMA	2.0	+++	+++	+++	+++	++	++	++	++
		0.2	++	++	++	++	+	+	+	+
		0.02								
4.	2-HEMA	2.0	+++	++	++	++	+	+	(+)	
		0.2	++	++	(+)	(+)	(+)	(+)	(+)	
		0.02								
	EGDMA	2.0	+++	++	++	++	+	+	(+)	
		0.2	(+)							
		0.02								
5.	2-HEMA	2.0	+++	+++	++	++	++	++	++	+
		0.2	++	++	++	++	++	++	+	
		0.02			+	+	(+)			
		0.002								
	EGDMA	2.0	+++	+++	++	++	++	++	+	+
		0.2	++	++	++	++	+	+		
		0.02								
6.	2-HEMA	2.0	++	++	++	++	++	++	++	+
		0.2				+				
		0.02								
	EGDMA	2.0	++	++	++	++	++	++	++	+
		0.2								
7.	2-HEMA	2.0	+++	+++	+++	++	++	++	+	+
		0.2	+++	+++	+	+	+	+	+	?
		0.02	++	++	+	(+)	(+)	(+)	?	
		0.002								
	EGDMA	2.0	+++	+++	+++	++	++	++	+	+
		0.2	+++	+++	++	+	+	+	+	?
		0.02	++	+	+	(+)	(+)	?		
		0.002								
8.	2-HEMA	2.0	+++	++	++	++	+	+	+	+

		0.2	+++	++	+	+	(+)	(+)	(+)	(+)
		0.02	(+)	+	?					
		0.002								
	EGDMA	2.0	+++	+++	++	++	++	++	+	+
		0.2	+++	++	+	+	+	(+)	(+)	(+)
		0.02	(+)	(+)						
		0.002								
9.	2-HEMA	2.0	+++	+++	+++	++	+	+	+	+
		0.2	++	++	++	+	(+)	?	?	?
		0.02	(+)	(+)						
		0.002								
	EGDMA	2.0	+++	+++	++	++	++	++	++	+
		0.2	+	(+)	(+)	(+)	?	?	?	
		0.02	(+)							
		0.002								
10.	2-HEMA	2.0	+++	+++	+	+	+	+	+	+
		0.2	++	++	+	+	+	(+)	(+)	(+)
		0.02								
	EGDMA	2.0	++	++	+	+	+	+	(+)	(+)
		0.2	+	+	+	+	(+)	+	?	?
		0.02								
11.	2-HEMA	2.0	++	++	+	+	+	+	+	+
		0.2								
	EGDMA	2.0	(+)	+	+	+	+	+	+	+
		0.2								

*2-HEMA= 2-hydroxyethyl methacrylate; **EGDMA= ethyleneglycol dimethacrylate.

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