

Are concomitant patch test reactions to epoxy resin and BIS-GMA indicative of cross-reactivity?

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Background: Despite rare simultaneous exposure, concomitant sensitisation to bisphenol A diglycidyl methacrylate (BIS-GMA) and epoxy resin frequently occurs. Immunological cross-reactivity has not been proven by animal experiments so far.

Objective: Our objective was to examine cross-reactivity epidemiologically by analysing data of the Information Network of Departments of Dermatology (IVDK).

Patients/Methods: From 2001 to 2005, 3,777 patients were patch tested with epoxy resin and BIS-GMA in the IVDK. We retrospectively analysed concomitant reactions to these allergens and to BIS-GMA and selected methacrylates. Additionally, we compared clinical characteristics of patients reacting to both, epoxy resin and BIS-GMA, with those of patients reacting to epoxy resin or BIS-GMA only.

Results: 185 patients reacted to epoxy resin, and 40 to BIS-GMA. Of the latter, 34 reacted to epoxy resin. There was no difference concerning exposure between the above-mentioned groups of patients. Concomitant reactions to BIS-GMA and methacrylates hardly ever occurred.

Conclusions: Considering the fact that very few patients had been potentially exposed to BIS-GMA and that 85% of those reacting to BIS-GMA also reacted to epoxy resin, we conclude that our data are presumably indicative of immunological cross-reactivity. A verification of this hypothesis by animal experiments would be promising.

Key words: BIS-GMA; bisphenol A diglycidyl methacrylate; CAS 1565-94-2; cross-reaction; diglycidyl ether of bisphenol A; epoxy resin; methacrylates. © Blackwell Munksgaard, 2007.

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Contact sensitisation to epoxy resins can be acquired by exposure to adhesives or coatings, in the construction industry, in the boat and aeroplane building industry, in wind turbine construction and several other industries and trades (1–3). Bisphenol A diglycidyl methacrylate (BIS-GMA) is commonly used in dental composite materials, and sensitisation to BIS-GMA by contact with denture materials has been reported (4, 5). A few cases of contact allergy to BIS-GMA also occurred from contact to ultraviolet-cured paints and lacquers, for example in the printing industry (6, 7). Recently, we found BIS-GMA declared in a gel nail preparation brought in by a patient. However, according to an overview published in 2005, contact allergy to BIS-GMA is uncommon

among patients with adverse reactions to artificial nails (8). Although there is only a small overlap of the exposure fields, concomitant sensitisation to BIS-GMA and epoxy resin based on diglycidyl ether of bisphenol A (DGEBA resin) is frequent, according to the literature (9, 10). In many cases, clinical relevance of the BIS-GMA reaction could not be established convincingly (9). Immunological cross-reactivity has been discussed as a possible explanation for these concomitant reactions, but never been proven by animal experiments.

On the other hand, BIS-GMA is chemically related to methacrylates (Fig. 1). Hence, cross-reactivity with this group of allergens, although not proven by animal experiments either, might be suspected. Against this background, data of the

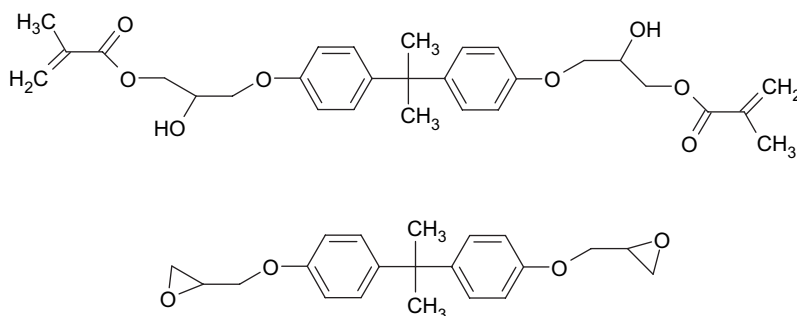


Fig. 1. Chemical structures of bisphenol A diglycidyl methacrylate (BIS-GMA; on top), and diglycidyl ether of bisphenol A (DGEBA; at the bottom). Note the methacrylate groups at both ends of the BIS-GMA molecule and the epoxy groups at both ends of the DGEBA molecule.

Information Network of Departments of Dermatology (IVDK) was analysed to examine cross-reactivity epidemiologically. In particular, we wanted to know if clinical data of patients sensitized to BIS-GMA point to special allergen sources.

Material and Methods

IVDK data from 2001 to 2005 was analysed retrospectively. First, we looked at the results of parallel patch tests with epoxy resin 1% petrolatum (pet.) (DGEBA resin) in the standard series and BIS-GMA 2% pet. in special series. Second, we analysed cross-reactions between BIS-GMA and selected methacrylates. Third, we compared clinical characteristics of patients reacting to both, epoxy resin and BIS-GMA, with those of patients reacting to epoxy resin only, but not to BIS-GMA, or vice versa.

In the years mentioned, altogether 44,480 patients have been patch tested in the departments of dermatology forming the IVDK. Of these, 3,777 were patch tested with DGEBA resin and BIS-GMA, constituting the study group for the present analysis. Patch tests were performed according to the guidelines of the German Contact Dermatitis Research Group (11). Patch test preparations were obtained from Hermal, Reinbek, Germany, except for 2-hydroxypropyl methacrylate (HPMA), which was purchased from Chemo-technique, Tygelsjö, Sweden. The raw material used for the BIS-GMA patch test preparation was analysed with regard to a possible contamination with DGEBA. For this purpose, a high-pressure liquid chromatography (HPLC) was performed. The detection limit for DGEBA was 0.1%. Reproducibility of this result and calibration in the presence of BIS-GMA was determined by analysing BIS-GMA, to which DGEBA was added. HPLC analysis of the BIS-GMA used for the production of patch test preparation BIS-GMA 2% pet. gave no signal at the respective retention time. It can be deduced, therefore, that the BIS-GMA raw material contained less than 0.1% DGEBA. This means that there was less than 0.002% (=20 ppm) DGEBA in the test preparation.

Data was collected and processed according to the IVDK routine procedure (12). Data analysis was carried out on the basis of day 3 patch test reactions at the IVDK data centre using SAS[®] 9.1 software (SAS Institute, Cary, NC, USA), following current guidelines (13).

Results

Of the 3,777 patients tested, 185 (4.9%) reacted positively to DGEBA epoxy resin, and 40 (1.1%) to BIS-GMA. Of these, 34 reacted to both test preparations, representing 85% [exact 95% confidence interval (95% CI): 70–94%] of those reacting to BIS-GMA, and 18% (95% CI: 13–25%) of those reacting to epoxy resin, respectively (Table 1). Significantly more patients reacted to DGEBA resin but not to BIS-GMA than vice versa ($P < 0.0001$, exact McNemar test). Of those 185 patients reacting to epoxy resin, 112 (61%) had a strong positive reaction with vesicles, that is ++ or +++, and 73 (39%) showed a reaction with erythema and infiltration or papules only, that is +. Of the latter subgroup, only 6 patients (8%) reacted to BIS-GMA, while of those 112 patients with a strong reaction to DGEBA resin, 28 (25%) reacted to BIS-GMA, which is a significantly greater proportion ($P = 0.004$; Fisher's exact test). Reactivity to BIS-GMA was distributed equally (2/3 +; 1/3 ++) among all degrees of reactivity to epoxy resin.

The great majority of patients had been patch tested additionally with methyl methacrylate (2% pet.), ethyleneglycol dimethacrylate (2% pet.), 2-hydroxyethyl methacrylate (1% pet.), triethyleneglycol methacrylate (2% pet.), or (HPMA; 2% pet.). In all, 3,722 of the 3,777 patients had been patch tested with BIS-GMA and at least 1 of the 5 methacrylates mentioned, including all 40 patients who reacted to BIS-GMA. Among these 3,722 patients, 125 (3.4%) had positive reactions to 1 or more methacrylate(s). Significantly more patients reacted to at least 1 methacrylate but not to BIS-GMA than vice versa ($P < 0.0001$, exact McNemar test). Reactions to BIS-GMA and

methacrylates very rarely occurred concordantly: only 3 patients reacted to both, BIS-GMA and a methacrylate, which is a share of 7.5% (95% CI: 2–20%) of those reacting to BIS-GMA, and 2.4% (95% CI: 0.5–7%) of those reacting to any of the methacrylates (Table 1).

When comparing the group of patients reacting to both, epoxy resin and BIS-GMA ($n = 34$; group 1), with those reacting to epoxy resin, but not to BIS-GMA ($n = 151$; group 2), there were no significant differences concerning professions or suspected allergen sources (Table 2). In particular, there was no increased proportion of dental technicians or patients tested because of suspected allergy to denture materials in group 1 ($P > 0.05$, Fisher's exact test). Among those 6 patients reacting to BIS-GMA, but not to epoxy resin (group 3), clinical data did not show typical allergen sources for BIS-GMA, except for artificial nails in 1 case (Table 2). 1 of these patients was a dental assistant with generalized atopic dermatitis who showed positive patch test reactions to 10 substances, most of them without clinical relevance. Hence, an angry back with false-positive reactions seemed

probable. Denture materials had been tested to rule out occupational dermatitis in this case.

Discussion

In 1984, Björkner et al. reported on guinea-pig sensitisation experiments with methacrylates based on bisphenol A and epoxy resin (14). Of 15 animals sensitized with a commercial BIS-GMA product, 13 (87%) reacted when challenged with the same product as a whole. 8 animals (53%) reacted when challenged with an impurity fraction of the product, which was free of BIS-GMA, but no animal reacted to the challenge with a purified fraction containing BIS-GMA. However, 12 of the 15 guinea-pigs reacted when challenged with a DGEBA epoxy resin [molecular weight (MW) 340]. From chromatography, it could be seen that the commercial BIS-GMA product was contaminated, probably with epoxy resin MW 340. Thus, the authors concluded that these reactions were not because of BIS-GMA, but because of epoxy resin, which was probably a residue from the BIS-GMA production (14).

Table 1. Cross tabulation of dichotomized test reactions at day 3 to BIS-GMA 2% pet., and epoxy resin (DGEBA resin 1% pet.) and selected methacrylates, respectively

		Epoxy resin			Methacrylates		
		Negative, ?, and irr.	Positive	Total	Negative, ?, and irr.	Positive	Total
BIS-GMA 2% pet.	Negative, ?, and irr.	3,586	151	3,737	3,560	122	3,682
	Positive	6	34	40	37	3	40
	Total	3,592	185	3,777	3,597	125	3,722

BIS-GMA, bisphenol A diglycidyl methacrylate; DGEBA, diglycidyl ether of bisphenol A; pet., petrolatum; MMA, methyl methacrylate (2% pet.); EGDMA, ethyleneglycol dimethacrylate (2% pet.); HEMA, 2-hydroxyethyl methacrylate (1% pet.); TEGDMA, triethyleneglycol methacrylate (2% pet.); and HPMA, 2-hydroxypropyl methacrylate (2% pet.); irr, irritant.

Table 2. Occupations and suspected allergen sources in patients reacting to both epoxy resin and BIS-GMA, in patients reacting to epoxy resin only, and in patients reacting to BIS-GMA only

	Group 1: epoxy resin + BIS-GMA + ($n = 34$)	Group 2: epoxy resin + BIS-GMA – ($n = 151$)	Group 3: epoxy resin – BIS-GMA + ($n = 6$)
Occupation			
Bricklayers, tile setters etc.	8 (24%)	26 (17%)	0
Painters, spray painters	3 (9%)	16 (11%)	0
Plastic industry (polymer processing)	1 (3%)	6 (4%)	0
Dental technicians	0	2 (1%)	1 (17%) ^a
Printers	0	3 (2%)	0
Suspected allergen source			
Construction materials	6 (18%)	44 (29%)	0
Adhesives	12 (35%)	37 (25%)	0
Plastic materials	9 (26%)	32 (21%)	2 (33%)
Paints, lacquers	5 (15%)	32 (21%)	0
Denture materials	1 (3%)	5 (3%)	1 (17%) ^a
Artificial nails	0	0	1 (17%)

BIS-GMA, bisphenol A diglycidyl methacrylate.

^aIn group 3, there were no dental technicians but 1 dental assistant with suspected angry back. Denture materials were tested to rule out occupational dermatitis.

To our knowledge, no further animal studies addressing the question of cross-reactivity between DGEBA resin and BIS-GMA have been published so far. In particular, no studies performing induction with DGEBA resin and challenge with BIS-GMA have been carried out, as far as we know.

From HPLC analysis, it was known that the BIS-GMA test preparation used in the IVDK contained less than 20 ppm DGEBA resin. This is 1/500 of the common DGEBA resin patch test concentration. To our knowledge, there is no established elicitation threshold for patch testing with DGEBA resin, but it seems unlikely that 20 ppm DGEBA resin will elicit any positive patch test reaction, even in high-grade sensitized individuals. Hence, contamination cannot be the reason of simultaneous reactions to epoxy resin and BIS-GMA that we observed in our study. Considering the fact that very few of our patients had had potential exposure to BIS-GMA, namely denture materials, and that 85% of those reacting to BIS-GMA also reacted to epoxy resin, we conclude that our data are presumably indicative of immunological cross-reactivity. This conclusion is supported by the finding that the proportion of patients reacting to BIS-GMA is significantly greater among those with a strong sensitisation to epoxy resin indicated by a strong patch test reaction, compared with those sensitized to DGEBA resin more weakly. We assume that most of the patients reacting to BIS-GMA have primarily been sensitized to epoxy resin (DGEBA resin), which would be plausible from the exposure data. In contrast, the clinical relevance and possible allergen source of BIS-GMA remained unclear in 5 of the 6 patients with positive reactions (4 +, 1 ++) to BIS-GMA but not to DGEBA resin (group 3). The only probable BIS-GMA exposure was professional contact with artificial nails in 1 female patient with a + reaction to BIS-GMA.

Almost no concomitant reactions to BIS-GMA and methacrylates occurred which is in line with findings in dental technicians with occupational dermatitis (15). This constellation is insofar remarkable as BIS-GMA has 2 methacrylate groups and cross-reactivity between certain methacrylates is very common (16). However, in contrast to these cross-reacting methacrylates, there is no similarity between BIS-GMA and the tested methacrylates regarding a common or structurally closely related epitope. Therefore, it might be speculated that BIS-GMA is metabolized in a different way, leading to intermediates other than those derived from methacrylates. It has been pointed out that immunological cross-reactivity between DGEBA resin and BIS-GMA is improbable because BIS-GMA has no epoxy group (10).

Of course this is true, and certainly, chemical reactivity of BIS-GMA differs from DGEBA resin. But it is not proven that the reactive epoxy group is indeed the (only) part of the molecule rendering it a hapten. Moreover, in the process of protein binding, that is formation of the full allergen, relevant structural or spatial similarities between these 2 chemical components may ensue.

In conclusion, our data probably point to an immunological cross-reactivity between epoxy resin based on DGEBA and BIS-GMA. Animal sensitisation experiments with induction of contact allergy to DGEBA resin and a challenge with pure BIS-GMA would be highly interesting to test this hypothesis. Maybe results from experiments of this kind are as surprising as the finding of a quasi 'unidirectional' cross-reactivity of DGEBA resin and phenyl glycidyl ether (PGE), leading to allergic reactions to PGE in animals sensitized to DGEBA resin, but not vice versa (17).

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Letter to the Editor

Addendum to Geier J, Lessmann H, Uter W, Schnuch A. Are concomitant patch test reactions to epoxy resin and BIS-GMA indicative of cross reactivity? *Contact Dermatitis* 2007: 57: 376–380

Dear Sir,

When discussing one's own study results, it is good scientific practice to cite and describe all relevant and important scientific literature concerning the topic. In this regard, in our recent publication (1), we did not consider an American study (2) of which we have now been made aware by one of its authors. Lee et al. (2) patch tested 41 patients known to have contact allergy to bisphenol A epoxy resin, with several epoxy methacrylates and acrylates. They found positive reactions to bisphenol A diglycidyl methacrylate (BIS-GMA) in 7 of these 41 patients (17%), which is a similar proportion to that found in the Information Network of Departments of Dermatology (IVDK) data (34 of 185, i.e. 18%). In the American study, only a very few patients reacted to methyl methacrylate or ethyl acrylate, which also corresponds to our results. Lee et al. discussed the possibility of true immunological cross-reactions between bisphenol A epoxy resin and BIS-GMA but also considered the possibility that these reactions may be

because of contamination of BIS-GMA with bisphenol A epoxy resin monomers.

We consider this American study to be relevant, and it should have been mentioned in our paper. We apologize for having overlooked this important work.

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