Delayed contact hypersensitivity and surgical glove penetration with acrylic bone cements

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Skin hypersensitivity was investigated in guinea-pig maximization tests with extracts from pellets of conventional polymethyl-methacrylate (PMMA) bone cements (Palacos R®, Simplex RO®) and a new methylmethacrylate/n-decylmethacrylate/isobornylmethacrylate (MMA/DMA/ IBMA) mixture (Boneloc®), but none of the three cements produced evidence of delayed contact hypersensitivity. Testings of the pure monomer compounds showed MMA to be an extreme sensitizer, whereas DMA and IBMA were only mild sensitizers. Fingers from three brands of surgical rubber gloves and a polystyrene-butadiene glove were immersed in water and filled with conventional MMA monomer, MMA/DMA/IBMA monomer or bone cements in the dough state, allowing cure inside the glove. In the surrounding water, no DMA or IBMA could be detected. The MMA concentrations were lower with MMA/DMA/IBMA monomer and curing Boneloc® cement. The most resistant to conventional PMMA cement was one of the rubber gloves, whereas the polystyrene-butadiene glove allowed the highest penetration, and even dissolved in MMA monomer. The potential occupational hazard of skin sensitization is reduced with MMA/ DMA/IBMA bone cement, preferably in combination with rubber gloves; but also polystyrene-butadiene gloves provide adequate protection.

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Skin sensitization following occupational exposure to acrylic cements has occasionally been reported with clinical symptoms such as eczema or even itching erythema and vesicles on the finger tips and palmar sides (Pegum and Medhurst 1971, Fisher 1975, Fregert 1983, Kassis et al. 1984), or burning sensations, tingling and slight numbness (Fisher 1975, 1979, Fregert 1983).

Ordinary surgical gloves are not impervious to methyl-methacrylate(MMA) monomer (Waegemaekers et al. 1983, Darre and Vedel 1984). Protective gloves of butyl rubber or a three-layer polyethylene/vinyl-ethylene/polyethylene glove have been suggested (Darre and Vedel 1984, Darre et al. 1987) to reduce exposure. Fregert (1983) has suggested a number of preventive measures and advocated development of a less sensitizing bone cement.

Our purpose was to evaluate this occupational hazard in relation to most frequently used conventional polymethylmethacrylate (PMMA) bone cements (Palacos R®, Simplex RO®) and contemporarily used surgical gloves, and to supply evidence for the reduction of risk by use of a new formulation of bone cement based on MMA/n-decyl-methacrylate (DMA)/isobornyl methacrylate (IBMA), registered as Boneloc®.

Materials

In the two conventional PMMA bone cements (Palacos R®, Simplex RO®), the liquid monomer consists of pure MMA with about 2–2.5 w/w% of the accelerator, N,N-dimethyl-p-toluidine (DMPT), and small amounts of a stabilizer, hydroquinone. The composition of the polymer powder is the major difference between the two products. Palacos R® contains MMA/MA(methylacrylate) copolymers with 15 w/w% of radiopaque zirconium oxide. Simplex RO® contains a mixture of PMMA and MMA/styrene copolymers with 10 percent radiopaque barium sulfate. Both brands contain an initiator, benzoyl peroxide in the amount of 0.5–1.3 percent.

Boneloc® differs in monomer composition, as mixed from about 50 percent MMA, 30 percent DMA, and 20 percent IBMA. The accelerator system consists of 0.5 w/w% DMPT and 1.0 w/w% N,N-dihydroxy-propyl-p-toluidine. Hydroquinone methyl ether is used as a stabilizer. The powder consists of MMA/butylmethacrylate(BMA) copolymers in the ratio 60/40 with 10 w/w% zirconium oxide and 1 w/w% benzoyl peroxide.

Monomer solutions and cements from commercially available cement kits (Palacos R®) or those supplied by the manufacturer (Boneloc®) were

tested. Mixing of the cement was performed according to the manufacturers' instructions before delivery with a cement gun into molds or gloves within 2 min after starting the admixing. From all three brands, cylindric cement pellets (D = 6.5 mm, L = 4 mm) were produced. Two hours after mixing, extraction from a 12.5-cm^2 surface area per mL medium (distilled water or paraffin oil) was performed by incubating at 37 °C for 72 hours. These extracts and the pure monomers MMA, DMA, and IBMA were investigated in sensitization tests.

For testing gloves, we included two brands of ordinary surgical rubber gloves (Ansell®, Sempermed®) and so-called low-allergy gloves of brown latex (Perry Microptic®) or polystyrene-butadiene (Elastyren®).

Methods

The concentrations of the monomers were determined for distilled-water extracts from cement pellets by high-performance liquid chromatography (HPLC, Perkin-Elmer, UK) applying a Licrosorb RP 18 column and a mobile phase consisting of acetonitrile and water, and for paraffin-oil extracts by Head-space (Perkin-Elmer, UK) gas chromatography.

The guinea-pig maximization test (GPM) consists of an induction and a challenge stage (Magnusson and Kligman 1970). The induction procedure consists of an intradermal and a topical exposure 1 week apart. The challenge procedure is a closed-patch topical application 2 weeks after the topical induction.

Forty female SPF albino guinea pigs of the Dunkin-Hartley strain (300–350 g, aged 6–7 weeks) were included in each study, and were divided into a test group and a control group. The two groups of 20 animals each were treated identically during the experiments, except for the administration of monomer or extracts during the induction stage of the treated group. In a preliminary study a slight to moderate concentration of the pure monomers were found for the intradermal injections and the topical inductions, and the highest nonirritating concentrations were found for the challenge application (Table 2). In the series of extracts from cements, a 100 percent concentration was selected for both induction and challenge purposes. After 24 h of topical challenge, the dressing was removed and the skin evaluated blindly after 24, 48, and 72 h for positive patch-test reactions (i.e., erythema and edema) on a 0–3 scale, with scores of 2 (moderate and confluent erythema) and 3 (intense erythema and swelling) being regarded as positive.

For testing monomer penetration, the third finger of gloves size no. 7 was cut off, suspended on a rig, and immersed in a glass container with 90 mL distilled water. In the water surrounding the glove finger, the concentrations of MMA, DMA, and IBMA were analyzed by HPLC. In the first test series, 10 mL monomer mixture was poured into a glove finger and measurements were performed after 1 and 2 min. The available content was 920 mg MMA/mL in MMA monomer, whereas the MMA/DMA/IBMA monomer contained 460 mg MMA/mL, 279 mg DMA/mL, and 186 mg IBMA/mL. The measured concentrations (ppm) in the surrounding water were recalculated into the fraction of µg MMA penetrating per mL of monomer solution applied. Further, the fraction of available MMA penetrating the glove was calculated. In the second series, cement was allowed to cure inside the glove finger, and measurements were performed after 30 min. A median of 13.5 (10.0–18.4) g of PMMA cement was applied as compared with 14.3 (8.1–17.2) g of MMA/DMA/IBMA cement. PMMA cement contains 315 mg MMA/g cement and MMA/DMA/IBMA cement 150 mg MMA/g, 90 mg DMA/g, and 60 mg IBMA/g. The concentrations were recalculated in the same fashion as for the monomers. Six experiments with each type of glove were performed in each series, totaling 96 experiments. For statistical purposes, the Mann-Whitney test was applied.

Results

Distilled-water extracts from cement pellets showed a considerable difference in MMA contents ($P < 0.0005$), the concentrations being more than 13–19 times lower with Boneloc® (Table 1). No DMA or IBMA could be detected.

The GPM tests (Table 2) showed that MMA was an extreme sensitizer, but DMA and IBMA were only mild sensitizers. Extracts with distilled water and paraffin oil of all three cements failed to produce any evidence of delayed contact hypersensitivity.

In the glove experiments in which pure MMA/DMA/IBMA monomer was used, DMA and IBMA could be detected in concentrations of only 0.1–1.2 ppm in 17/24 measurements, but could not be detected with curing cement. There was no correlation between the type of glove or the time lapsed after the beginning of the experiment.

Table 1. Median monomer concentrations (ppm) in extracts of bone cement pellets for GPM testing

	Paraffin oil			Distilled water		
	MMA	DMA	IBMA	MMA	DMA	IBMA
Boneloc®	297 (290–340)	< 1	< 1	52 (5–275)	< 1	< 1
Palacos R®	515 (455–575)			985 (730–1100)		
Simplex RO®	711 (594–828)			666 (562–1213)		

Table 2. Delayed contact hypersensitivity of pure monomers (GPM)

	MMA	DMA	IBMA
Percentage concentration for			
intraderm. induction	10	20	20
topical induction	100	100	100
challenge	50	50	25
Positive response at			
challenge (48)	18/20	5/20	3/20

Paraffin oil was used as a vehicle for the monomers.

Table 3. Monomer penetration through surgical gloves filled with concentrated monomer. Median (range)

	Ansell®	Sempermed®	Perry Microptic®	Elastyren®
Boneloc®				
1 min, µg/mL	5 (0–35)	9 (0–297)	0 (0–7)	22 (11–32)
‰ of MMA	0.01 (0–0.08)	0.02 (0–0.65)	0.00 (0–0.02)	0.05 (0.02–0.07)
2 min, µg/mL	34 (22–93)	106 (58–549)	126 (11–243)	248 (108–1116)
‰ of MMA	0.08 (0.05–0.20)	0.23 (0.13–1.19)	0.27 (0.02–0.53)	0.54 (0.23–2.43)
Palacos R®				
1 min, µg/mL x 10^{-3}	0.02 (0.05–0.15)	0.19 (0.08–1.7)	0.20 (0.02–0.43)	2.2 (0.03–920)
‰ of MMA	0.02 (0–1.67)	0.21 (0.09–1.83)	0.23 (0.02–0.47)	2.4 (0.03–1000)
2 min, µg/mL x 10^{-3}	0.50 (0.39–3.2)	1.67 (1.44–3.16)	1.3 (0.59–1.62)	6.0 (2.0–920)
‰ of MMA	0.55 (0.42–3.5)	1.8 (1.6–3.4)	1.4 (1.1–1.8)	6.5 (2.2–1000)
P-value, Boneloc® vs Palacos R®				
1 min	0.08	0.01	0.0005	0.007
2 min	0.002	0.002	0.002	0.002

µg/mL indicates µg MMA penetrated per mL monomer solution applied. The available MMA content was 460 mg/mL Boneloc® monomer and 920 mg/mL Palacos R® monomer.

The MMA concentrations in surrounding water (Table 3) was lower with MMA/DMA/IBMA monomer ($P = 0.0005–0.007$) for any type of glove, apart from Ansell® after 1 min. The recordings after 2 min with MMA/DMA/IBMA were lower or equivalent to those of MMA monomer after 1 min. With the polystyrene-butadiene glove, the highest concentrations were encountered ($P = 0.002–0.043$). In one experiment the pure MMA monomer dissolved the polystyrene-butadiene glove instantly; and in all the other experiments with concentrated MMA monomer, this glove dissolved within a few minutes after termination of the experiments. The Ansell® glove was the only brand being reasonably impervious to MMA monomer at 1 min ($P = 0.01–0.046$) and 2 min ($P = 0.002–0.012$). The concentrations at 2 min with MMA monomer were higher than with the combination of polystyrene-butadiene gloves and MMA/DMA/IBMA monomer at 2 min ($P = 0.019$). However, less than 0.2 percent of available MMA penetrated the rubber gloves within 2 min, and the amount was reduced about tenfold with the MMA/DMA/ IBMA monomer.

When the cement was delivered and cured inside the glove (Table 4), the concentrations in the surrounding water amounted to 1.2–1.9 percent of the available MMA, irrespective of the cement brand used. Because the content of MMA in PMMA is twice that of MMA/DMA/IBMA cement, a higher amount of MMA was naturally detected in the water ($P = 0.003–0.01$). In relation to MMA/DMA/IBMA cement, no significant differences among the glove brands were found; but with respect to PMMA cement, the Ansell® glove was superior to Perry Microptic® ($P = 0.009$) and Elastyren® ($P = 0.012$), but not with certainty to Sempermed® ($P = 0.055$). Sempermed®, however, gave no better protection than Elastyren® ($P = 0.315$).

Table 4. Monomer penetration through surgical gloves filled with curing cement. Median (range)

	Ansell®	Sempermed®	Perry Microptic®	Elastyren®
Boneloc®				
grams applied	15 (14–17)	14 (12–17)	14 (8–16)	14 (13–15)
30 min, mg/g	2 (1–4)	3 (2–3)	3 (2–5)	3 (1–4)
‰ of MMA	14 (7–27)	17 (10–19)	16 (11–31)	19 (9–24)
Palacos R®				
grams applied	13 (12–14)	14 (10–18)	13 (11–15)	16 (13–18)
30 min, mg/g	4 (2–4)	5 (2–9)	5 (3–14)	5 (3–8)
‰ of MMA	12 (8–14)	15 (7–27)	15 (10–43)	17 (10–26)
P-value				
Boneloc® versus Palacos R®	0.03	0.01	0.003	0.005

mg/g indicates mg MMA penetrating per gram cement applied. The available MMA content is 150 mg/g in Boneloc® cement and 315 mg/g in Palacos R® cement.

Discussion

The risk of delayed sensitization of patients is considered hypothetical even in cases with repeated revisions and thereby further cementations. Charnley (1970) reported no allergic reactions in a few patients who had evidence of severe radiolucency at the bone-cement interface, and who were tested with patches and subcutaneous injections. To our knowledge, no cases of skin sensitization have been reported in patients who have had implants fixed with acrylic bone cements.

Of much more concern is the risk of delayed skin sensitization of staff members who are repeatedly exposed to acrylic bone cements (Fregert 1983, Waegemaekers et al. 1983). MMA has previously been reported to be a moderate to strong sensitizer (Spealman et al. 1945, Pegum and Medhurst 1971, van der Walle et al. 1982, Christiansen 1983, Fregert 1983) depending on the induction concentration applied. This study confirmed that MMA is a potent sensitizer (Nyquist et al. 1972). Waegemaekers et al. (1983) claimed that the use of double-layer surgical gloves reduced the exposure. The penetrating MMA, however, increases the permeability of the inner glove, meaning that, although changing the outer glove after handling of the cement, the occlusive patch effect is increased and thereby the risk of delayed hypersensitivity (Magnusson and Kligman 1970).

The present study confirms (Brandrup and Immergut 1975) that the rubber gloves are not impervious to MMA (Pegum and Medhurst 1971, Fries et al. 1975, Fisher 1979, Darre et al. 1987) and that Elastyren® gloves (Waegemaekers et al. 1983, Darre et al. 1987) are insufficient for protection because of a high penetration velocity and even dissolution by MMA monomer. The exposure must be considered of significance by handling not only the concentrated monomer, but also the curing cements. Concentrations amounting to those obtained in extracts are a daily potential risk for orthopedic surgeons and nurses, although the fairly low concentrations did not cause delayed hypersensitivity in GPM tests.

The monomer concentrations ranged over a wide span. Such differences can only partially be explained by the experimental setup, the penetration depending on variations in the polymerization process and exotherm. Mass production of surgical gloves might result in imperfections, with areas of low material thickness or even small holes, which allow rapid penetration of monomer.

The use of impervious protective gloves (Darre and Vedel 1984, Darre et al. 1987) is rather impractical because of the lack of elasticity and finger touch (Waegemaekers et al. 1983). We do, however, agree with Fregert (1983) that measures should be undertaken to reduce the occupational exposure, primarily by emphasizing nontouch techniques.

As demonstrated, the exposure to MMA can be reduced considerably by applying a bone cement that contains not only less MMA but also less sensitizing monomers (DMA, IBMA). These do not penetrate the gloves, and further inhibit the penetration of MMA. In spite of imperfections in manufacturing of surgical gloves and less resistance to MMA monomer for a frequently used polystyrene-butadiene glove, the potential occupational hazard may be minimized by the use of MMA/DMA/IBMA bone cement, which has been available for clinical use since the summer of 1990.

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References

Brandrup J, Immergut E H. *Polymer Handbook.* John Wiley & Sons, New York 1975.

Charnley J. *Acrylic cement in orthopaedic surgery.* Churchill Livingstone, Edinburgh 1970.

Christiansen M L. Acrylater og methacrylater. *Arbete och Hälsa* 1983; 21.

Darre E, Vedel P. Surgical rubber gloves impervious to methylmethacrylate monomer. *Acta Orthop Scand* 1984; 55 (3): 254–5.

Darre E, Vedel P, Jensen J S. Skin protection against methylmethacrylate. *Acta Orthop Scand* 1987; 58 (3): 236–8.

Fisher A A. Contact dermatitis in surgeons. *J Dermatol Surg* 1975; 1 (3): 63–7.

Fisher A A. Paresthesia on the fingers accompanying dermatitis due to methylmethacrylate bone cement. *Contact Dermatitis* 1979; 5 (1): 56–7.

Fregert S. Occupational hazards of acrylate bone cement in orthopaedic surgery (editorial). *Acta Orthop Scand* 1983; 54 (6): 787–9.

Fries I B, Fisher A A, Salvati E A. Contact dermatitis in surgeons from methylmethacrylate bone cement. *J Bone Joint Surg* (Am) 1975; 57: 547-9.

Kassis V, Vedel P, Darre E. Contact dermatitis to methyl methacrylate. *Contact Dermatitis* 1984; 11 (1): 26–8.

Magnusson B, Kligman A K. *Allergic contact dermatitis in the guinea pig.* C C Thomas Ill, Springfield 1970.

Nyquist G, Koch G, Magnusson B. Contact allergy to medicaments and materials used in dentistry. 3. Sensitization and sensitivity study in guinea pigs on methyl methacrylate used in a dentifrice. *Odontol Revy* 1972; 23 (2): 197–204.

Pegum J S, Medhurst F A. Contact dermatitis from penetration of rubber gloves by acrylic monomer. *Br Med J* 1971; 2 (754): 141-3.

Spealman C R, Main R J, Haag H B, Larson P S. Monomeric methyl methacrylate studies on toxicity. *Indust Med* 1945; 14 (4): 292–8.

Waegemaekers T H, Seutter E, den Arend J A, Malten K E. Permeability of surgeons' gloves to methyl methacrylate. *Acta Orthop Scand* 1983; 54 (6): 790–5.

van der Walle H B, Klecak G, Geleick H, Bensink T. Sensitizing potential of 14 mono (meth) acrylates in the guinea pig. *Contact Dermatitis* 1982; 8 (4): 223–35.