Toxicological and Pharmacological Actions of Methacrylate Monomers III: Effects on Respiratory and Cardiovascular Functions of Anesthetized Dogs

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Abstract □ Methacrylic acid and 12 methacrylate esters were evaluated for their effects upon blood pressure, heart rate, electrocardiogram, and respiration in anesthetized dogs following intravenous administration. All of these compounds increased respiratory rate, decreased heart rate, and produced electrocardiographic changes. The compounds could be divided into three types according to their effects on blood pressure: I, those producing a biphasic response, *i.e.*, an abrupt fall followed by a secondary rise; II, those producing only a hypotensive effect; and III, one producing only a hypertensive response. The compounds comprising Type I were methacrylic acid; methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl, and hydroxyethyl methacrylates; and 1,3-butylene dimethacrylate. Type II compounds were 2-ethylhexyl, isodecyl, lauryl, and *tert*-butylaminoethyl methacrylates. Dimethylaminoethyl methacrylate produced the Type III response.

Keyphrases □ Methacrylate monomers—effects on respiratory and cardiovascular functions, anesthetized dog □ Biomaterials, methacrylate monomers—effects on respiratory and cardiovascular functions, anesthetized dog □ Toxicity—methacrylate monomers, effects on respiratory and cardiovascular functions, anesthetized dog

The use of acrylic polymers as biomedical materials has been well established over the past several years. Typical applications include dentures, bone substitutes, contact lenses, and, experimentally, artificial "implantable" teeth. The completely polymerized material appears to be reasonably well tolerated by various tissues *in vivo*, although there may be some degradation and/or solubilization of the polymer by the body's fluids or mechanical "wearing" of a device such as a Judet prosthesis (1, 2). The use of self-curing acrylics, however, may present problems associated with a residual monomer, an activator, an initiator, heat generated from the exothermic reaction, or a combination of these.

Some early toxicity studies (3, 4) were conducted on the methacrylate monomers, and the chronic oral toxicity of the methyl ester was studied in rats and dogs (5). Strain (6) suggested that the methyl methacrylate monomer was responsible for certain cases of hypersensitivity reactions to self-cured acrylics. Cohen and Smith (7) attributed the fall in blood pressure frequently seen from orthopedic use of a bone cement (self-curing methyl methacrylate cement) and occasional cardiac arrests to the methyl methacrylate monomer and/or small particles of the polymer, either as the primary or a contributory cause. Deichmann (3) reported a fall of blood pressure in the rabbit from the methyl methacrylate monomer and, more recently, a similar transient, hypotensive response in dogs was reported (8).

In previous articles of this series, it was reported that the methacrylate monomers tend to reduce rate and force of contraction of the isolated rabbit heart (9), to inhibit spontaneous contraction of the guinea pig ileum, and to antagonize the stimulant effect of acetylcholine and barium chloride upon the ileum (10). (Three of the higher members of the series were not active on the isolated ileum, while dimethylaminoethyl methacrylate produced an effect opposite to that described.)

The use of self-curing methyl methacrylate bone cement in fitting orthopedic prostheses has been associated with a significant number of transient hypotensive reactions in patients (7, 11–14), with a small incidence of cardiac arrests. Some investigators (7, 11) suggested that the monomer is responsible for, or at least a contributory factor in, the observed hypotensive states and cardiac arrests. Others (12, 13, 15–17) hypothesized that these result from factors other than the monomer such as fat emboli and temperature of reaction. The description by Deichmann (3) concerning the effect of the methacrylate monomer upon blood pressure of the rabbit, "When injected intravenously in doses of 0.03 or 0.04 cc./kg. body weight, the compounds produced a prompt and sudden fall in the arterial pressure (from about 90 to 50 mm. Hg.) followed by recovery during the following 3 to 4 minutes," is quite similar to that by Frost (13) concerning clinical use of bone cement. Frost commented: "In these cases the insertion of the cement into the femoral component was followed after approximately one minute by a precipitous fall in blood pressure to about 70 mm. Hg. In all cases recovery was rapid, unassisted by transfusion or vasopressors, and normal levels of blood pressure were regained in five to six minutes."

The following studies were undertaken in anesthetized dogs with a number of methacrylate monomers to supplement earlier data (3, 8) for methyl methacrylate and to extend the information to a number of its homologs.

EXPERIMENTAL

Methacrylic acid and 12 of its esters were included in this study[1]; these were: methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl, 2-ethylhexyl, isodecyl, lauryl (dodecyl), hydroxyethyl, *tert*-butylaminoethyl, and dimethylaminoethyl methacrylates and 1,3-butylene dimethacrylate.

The methacrylates were prepared for testing by dissolving the more soluble ones (methacrylic acid and hydroxyethyl and di-

[1] All of these compounds were obtained from Rohm & Haas, Philadelphia, Pa., except for *n*-propyl and 2-ethylhexyl methacrylates, which were obtained from K & K Labs, Plainview, N.Y.

methylaminoethyl methacrylates) in normal saline (5% v/v) and preparing a suspension of the others in normal saline with 0.1% gum acacia. Satisfactory suspensions of 5% (v/v) methacrylates were prepared with a blender[2].

Male mongrel dogs (9–12 kg) were anesthetized with 35–45 mg/kg ip of sodium pentobarbital which was supplemented, if needed, by small intravenous doses. By using standard techniques, the right common carotid artery was surgically exposed, cannulated, and attached to a pressure transducer[3] for determining systemic blood pressure; the trachea was cannulated and attached to another pressure transducer[4] to record respiratory pressure changes in the airway. The right femoral vein was cannulated to facilitate intravenous injections. Needle electrodes were placed subdermally in the four limbs of the dog for recording the electrocardiogram. All of these were connected to the appropriate preamplifiers and calibrated, and data were recorded using a polygraph[5].

Four dose levels of each methacrylate were tested; the highest was rapidly fatal to the dog, while the other three produced measurable changes in one or more of the vital functions being recorded.

RESULTS AND DISCUSSION

Blood Pressure—Based upon the pattern of blood pressure responses observed, these 13 compounds can be divided into three categories: Type I, those producing a biphasic response (an abrupt fall, followed by a more sustained rise); Type II, those producing a sustained hypotensive response; and Type III, one compound producing a sustained hypertensive effect. The compounds included in Type I were methacrylic acid; methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl, and hydroxyethyl methacrylates; and 1,3-butylene dimethacrylate. A Type II response was produced by isodecyl, 2-ethylhexyl, lauryl, and *tert*-butylaminoethyl methacrylates. Only dimethylaminoethyl methacrylate produced a Type III response. In an earlier report, using the isolated guinea pig ileum, dimethylaminoethyl methacrylate was also found to elicit an atypical type of response when compared to the other members of this series (10). These data are presented in Table I, which shows the mean values obtained as well as the range of responses noted. Test solutions and suspensions were prepared on a volume-to-volume basis; both the volume and moles of compound contained in the dose are presented in this table.

Type I Compounds—This group comprised the greatest number of compounds in the series tested. The responses observed were qualitatively similar, differing only quantitatively. Following an injection of the methacrylate, there was an abrupt fall in systemic pressure, ranging from 18 to 42% for the lowest doses used and from 39 to 79% for the highest doses. This hypotensive effect generally persisted for 2–4 min. Pressure then began to rise slowly until it reached a plateau somewhat higher than control values. The hypertensive phase was sustained for about 10–15 min at about 3.2–17.2% above control values for the low doses and at about 11.5–41.5% above control values for the highest of the three dose levels evaluated.

Type II Compounds—Four compounds in this series elicited only a hypotensive response. They also showed variation among compounds as to effective dose levels, with lauryl methacrylate being the least active and the *tert*-butylaminoethyl derivative being the most potent. The three dose levels of isodecyl and lauryl methacrylates reduced blood pressure by 5–25%, with a duration of 2–4 min. 2-Ethylhexyl methacrylate produced a more sustained hypotensive effect, lasting 20–30 min, with a 17–41% decrease in blood pressure. Much smaller doses of *tert*-butylaminoethyl methacrylate produced a 20–50% reduction in blood pressure, with a duration of 30–40 min.

Type III Compound—Only one of the compounds tested, dimethylaminoethyl methacrylate, elicited a hypertensive effect without a preceding fall in pressure. It was also the most potent compound, producing a 28–67% increase in pressure with smaller doses than required for the others. The hypertensive effect persisted for 30–40 min. Thus, this compound seems to be an atypical member of the series, both qualitatively and quantitatively.

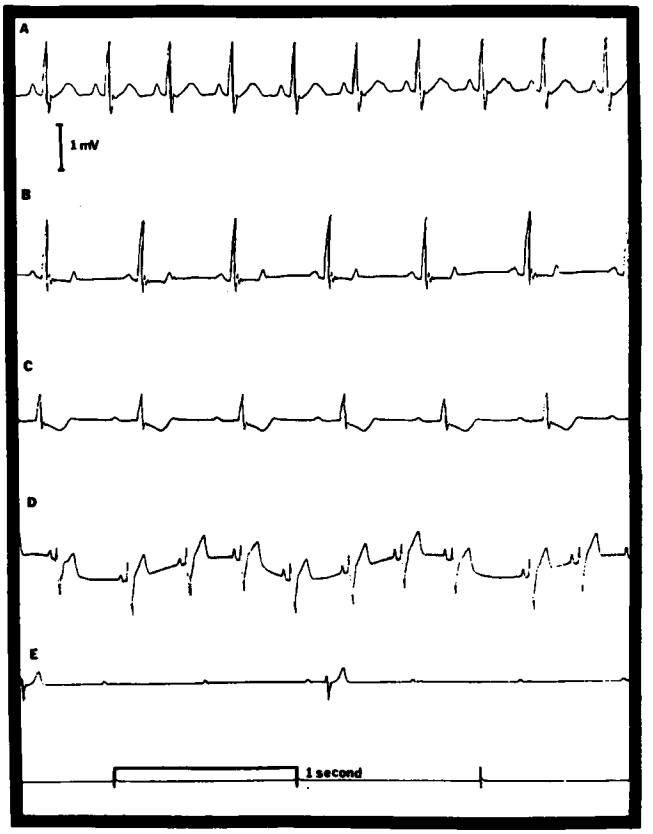

Figure 1—*Typical electrocardiographic changes produced by Type I methacrylate compounds. Key: A, control electrocardiogram; B, electrocardiogram after administering lowest dose of methacrylate; C, electrocardiogram after administering next higher dose of methacrylate; D, electrocardiogram after administering high dose of methacrylate; and E, electrocardiogram after administering highest (lethal) dose of methacrylate (mv = millivolt).*

Although the doses varied for the individual compounds, a dose-response relationship for each compound was observed within the three-dose range employed. Quantitatively, lauryl methacrylate was the least potent compound of the series in its effect upon blood pressure, while dimethylaminoethyl methacrylate was the most potent.

Heart Rate—The changes in heart rate following methacrylate administration are shown in Table I. All compounds produced a decrease in heart rate within the dosage range tested; however, the magnitude of change was usually less than noted for blood pressure. Propyl and isobutyl methacrylates appeared to reduce heart rate the most, while lauryl and isodecyl methacrylates seemed to cause the least reduction. The duration of effect upon heart rate was similar to that observed for blood pressure. Although the reduction in heart rate was dose related for each test agent, the magnitude of effect upon rate did not necessarily correlate with the magnitude of change in blood pressure.

Respiration—All tested compounds increased the respiratory rate (Table I). This increase was seen with all three dose levels for each compound, except with the two lowest doses of lauryl methacrylate, which produced no change. The magnitude of this increase ranged from 7 to 356% over control values. The duration of this effect was rather short for lauryl and isodecyl methacrylates; however, most compounds produced an effect lasting up to 20 min. Butyl and isobutyl methacrylates showed the most dramatic increase in respiratory rate.

Electrocardiogram—The effects of methacrylate injection upon the electrocardiogram of the dog fell into three patterns, as did the effects upon blood pressure.

Type I Compounds—The lower doses produced a slight increase

[2] Waring.
[3] Statham P23AC.
[4] Statham P23Dc.
[5] Grass, model 7.

Table I—Pharmacological Effects of Methacrylate Monomers

Dose per Kilogram	Test Sample	Number of Dogs	Blood Pressure					Heart Rate			Respiratory Rate		
			Control, mm Hg	Initial Response, mm Hg	Percent Change	Secondary Response, mm Hg	Percent Change	Control, beats/min	After Treatment, beats/min	Percent Change	Control, rate/min	After Treatment, rate/min	Percent Change
112×10^{-6} *M* (0.0095 ml)	Methacrylic acid	3	158.33[a] (155–160)[b]	101.66 (100–105)	−35.79	168.33 (165–170)	+6.31	104.00 (98–110)	102.66 (98–108)	−1.28	6.66 (6–8)	9.66 (9–10)	+45.40
224×10^{-6} *M* (0.0190 ml)		3	158.33 (155–160)	63.33 (60–65)	−60.00	173.33 (170–175)	+9.47	104.00 (98–110)	89.33 (86–96)	−14.10	6.66 (6–8)	12.66 (11–15)	+90.00
562×10^{-6} *M* (0.0476 ml)		3	158.33 (155–160)	33.33 (30–35)	−78.94	181.66 (175–185)	+14.74	102.33 (98–105)	80.00 (72–86)	−21.82	6.33 (6–7)	16.33 (12–18)	+157.97
1124×10^{-6} *M* (0.0952 ml)		(Lethal dose)											
140×10^{-6} *M* (0.0149 ml)	Methyl methacrylate	3	168.33 (165–175)	96.66 (95–100)	−42.57	181.66 (175–185)	+7.91	135.33 (130–142)	122.33 (120–125)	−9.61	9.66 (9–10)	16.00 (15–18)	+65.66
280×10^{-6} *M* (0.0299 ml)		3	168.33 (165–175)	76.66 (75–80)	−54.45	208.33 (200–215)	+23.76	134.00 (130–140)	120.00 (116–122)	−10.44	9.66 (9–10)	21.66 (21–22)	+124.22
560×10^{-6} *M* (0.0599 ml)		3	166.66 (160–175)	35.00 (30–40)	−78.99	216.66 (205–225)	+30.00	133.33 (130–140)	111.66 (105–120)	−16.25	10.00 (10–10)	23.66 (22–25)	+136.60
1120×10^{-6} *M* (0.1198 ml)		(Lethal dose)											
135×10^{-6} *M* (0.0171 ml)	Ethyl methacrylate	3	161.66 (160–165)	110.00 (105–115)	−31.95	173.33 (170–175)	+7.21	146.66 (142–152)	130.33 (125–136)	−11.13	14.66 (12–20)	19.66 (16–25)	+34.10
270×10^{-6} *M* (0.0342 ml)		3	161.66 (160–165)	88.33 (85–95)	−45.36	181.66 (180–185)	+12.37	145.33 (140–150)	115.66 (112–120)	−20.41	11.33 (11–20)	29.00 (25–36)	+155.95
540×10^{-6} *M* (0.3684 ml)		3	161.66 (160–165)	66.66 (65–70)	−58.66	201.66 (195–210)	+24.74	146.00 (142–148)	109.33 (104–116)	−25.11	13.66 (11–18)	33.66 (32–36)	+146.41
1080×10^{-6} *M* (0.1368 ml)		(Lethal dose)											
195×10^{-6} *M* (0.0280 ml)	Propyl methacrylate	3	170.00 (160–180)	113.33 (110–120)	−33.33	181.66 (170–190)	+6.85	140.00 (136–144)	122.00 (118–124)	−12.85	11.66 (10–15)	19.00 (15–26)	+62.95
390×10^{-6} *M* (0.0560 ml)			170.00 (160–180)	95.00 (95–100)	−44.11	208.33 (195–220)	+22.54	140.00 (135–145)	106.66 (105–115)	−23.81	11.66 (10–15)	26.00 (22–32)	+122.98
780×10^{-6} *M* (0.1120 ml)			168.33 (160–175)	55.00 (50–60)	−67.32	228.33 (225–230)	+35.64	140.00 (135–144)	93.33 (90–100)	−33.33	11.66 (10–15)	35.00 (30–40)	+200.17
1560×10^{-6} *M* (0.2240 ml)		(Lethal dose)											
135×10^{-6} *M* (0.0207 ml)	Butyl methacrylate	3	158.33 (150–165)	130.00 (120–135)	−17.89	163.33 (155–170)	+3.15	134.33 (125–145)	117.33 (100–130)	−12.65	13.00 (10–17)	34.33 (32–37)	+164.07
270×10^{-6} *M* (0.0415 ml)			158.33 (150–165)	111.66 (100–120)	−29.47	171.66 (165–180)	+8.41	134.00 (125–145)	112.00 (95–126)	−16.41	13.00 (10–17)	46.00 (45–48)	+253.84
540×10^{-6} *M* (0.0830 ml)			158.33 (150–165)	96.66 (95–100)	−38.95	176.66 (170–185)	+11.57	134.00 (125–145)	98.33 (80–115)	−26.61	13.00 (10–17)	52.33 (50–55)	+302.53
1080×10^{-6} *M* (0.1660 ml)		(Lethal dose)											
104×10^{-6} *M* (0.0167 ml)	Isobutyl methacrylate	3	155.00 (150–160)	103.33 (100–110)	−33.33	181.66 (175–190)	+17.20	127.33 (118–138)	114.66 (102–126)	−9.95	9.66 (8–10)	25.33 (25–26)	+162.21
208×10^{-6} *M* (0.0334 ml)			155.00 (150–160)	86.66 (85–90)	−44.09	196.66 (190–205)	+26.87	131.00 (115–140)	101.66 (90–115)	−22.39	9.33 (8–10)	40.33 (35–50)	+332.26
416×10^{-6} *M* (0.0668 ml)			151.66 (145–160)	61.66 (60–65)	−59.34	205.00 (200–210)	+35.17	125.33 (110–134)	85.66 (62–102)	−31.65	11.33 (10–14)	51.66 (45–62)	+355.95
832×10^{-6} *M* (0.1336 ml)		(Lethal dose)											
101×10^{-6} *M* (0.0124 ml)	Hydroxyethyl methacrylate	3	143.33 (135–150)	101.66 (100–105)	−29.07	160.00 (155–170)	+11.63	146.33 (135–164)	134.00 (130–144)	−8.42	12.33 (10–14)	17.33 (15–19)	+40.55
202×10^{-6} *M* (0.0248 ml)			140.00 (130–150)	81.66 (80–85)	−41.67	166.66 (155–180)	+19.04	143.33 (135–160)	127.00 (120–135)	−11.39	12.33 (10–14)	24.66 (22–26)	+100.00
404×10^{-6} *M*			136.66	63.33	−53.65	183.33	+34.15	138.33	115.33	−16.62	11.33	31.33	+176.52

Dose per Kilogram	Test Sample	Number of Dogs	Blood Pressure					Heart Rate			Respiratory Rate		
			Control, mm Hg	Initial Response, mm Hg	Percent Change	Secondary Response, mm Hg	Percent Change	Control, beats/min	After Treatment, beats/min	Percent Change	Control, rate/min	After Treatment, rate/min	Percent Change
(0.0496 ml)			(130–145)	(60–65)		(170–190)		(130–150)	(110–120)		(10–12)	(28–34)	
808×10^{-6} *M*			(Lethal dose)										
(0.0992 ml)													
200×10^{-6} *M*	1,3-Butylene dimethacrylate	3	143.33	101.66	−29.07	163.33	+13.95	113.33	103.66	−9.32	11.66	25.00	+114.40
(0.0449 ml)			(130–160)	(95–110)		(155–185)		(92–150)	(88–135)		(11–12)	(20–30)	
400×10^{-6} *M*			141.66	91.66	−35.29	173.33	+22.35	116.66	94.33	−23.67	10.66	30.33	+184.52
(0.0898 ml)			(130–165)	(80–100)		(155–200)		(90–145)	(76–125)		(10–12)	(24–25)	
800×10^{-6} *M*			136.66	63.33	−53.65	193.33	+41.46	108.66	85.66	−26.85	10.66	37.66	+253.28
(0.1796 ml)			(125–160)	(60–65)		(180–210)		(86–145)	(64–115)		(10–12)	(35–40)	
1600×10^{-6} *M*			(Lethal dose)										
(0.3592 ml)													
144×10^{-6} *M*	2-Ethylhexyl methacrylate	3	156.66	133.33	−14.89			145.33	132.00	−10.09	12.00	28.00	+133.33
(0.0326 ml)			(150–160)	(125–140)				(136–164)	(120–148)		(6–18)	(18–38)	
288×10^{-6} *M*			153.33	123.33	−19.56			142.33	122.33	−16.34	16.33	33.00	+102.08
(0.0652 ml)			(145–160)	(115–130)				(132–164)	(114–135)		(8–20)	(22–45)	
576×10^{-6} *M*			153.33	108.33	−29.34			139.33	112.00	−24.40	14.00	39.33	+180.92
(0.1304 ml)			(145–155)	(100–115)				(130–158)	(102–122)		(10–20)	(28–52)	
1152×10^{-6} *M*			(Lethal dose)										
(0.2608 ml)													
178×10^{-6} *M*	Isodecyl methacrylate	3	161.66	153.33	−5.15			149.33	141.33	−5.66	9.33	10.00	+7.18
(0.0461 ml)			(148–170)	(150–165)				(142–158)	(136–152)		(8–12)	(8–12)	
356×10^{-6} *M*			161.66	146.66	−9.27			147.66	135.66	−8.84	9.33	16.66	+78.56
(0.0922 ml)			(150–175)	(140–155)				(155–175)	(130–145)		(8–12)	(14–18)	
712×10^{-6} *M*			158.33	126.66	−20.00			146.33	130.33	−12.27	10.00	23.66	+136.60
(0.1844 ml)			(150–170)	(120–135)				(144–155)	(128–135)		(8–12)	(22–25)	
1424×10^{-6} *M*			(Lethal dose)										
(0.3688 ml)													
418×10^{-6} *M*	Lauryl methacrylate	2	147.50	140.00	−5.08			120.00	118.00	−1.66	11.00	11.00	0
(0.1550 ml)			(145–150)	(135–145)				(120–120)	(116–120)		(10–12)	(10–12)	
836×10^{-6} *M*			145.00	127.50	−12.06			120.00	115.50	−3.75	11.00	11.00	0
(0.3100 ml)			(140–150)	(120–135)				(120–120)	(115–116)		(10–12)	(10–12)	
1672×10^{-6} *M*			145.00	117.50	−18.96			120.00	107.50	−10.41	11.00	15.50	+40.90
(0.6200 ml)			(140–150)	(105–130)				(120–120)	(105–110)		(10–12)	(15–16)	
3344×10^{-6} *M*			(Lethal dose)										
(1.2400 ml)													
45×10^{-6} *M*	*tert*-Butylaminoethyl methacrylate	2	167.50	132.50	−20.89			153.00	138.00	−9.80	17.00	21.50	+26.47
(0.0095 ml)			(165–170)	(130–134)				(148–158)	(134–142)		(14–20)	(18–25)	
90×10^{-6} *M*			165.00	117.50	−28.78			151.00	128.00	−15.23	17.00	24.00	+14.17
(0.0190 ml)			(160–170)	(115–120)				(146–156)	(124–132)		(14–20)	(22–26)	
180×10^{-6} *M*			162.50	80.00	−50.76			150.50	116.00	−22.92	17.00	27.00	+58.82
(0.0380 ml)			(160–165)	(80–80)				(146–155)	(112–120)		(14–20)	(26–28)	
360×10^{-6} *M*			(Lethal dose)										
(0.0760 ml)													
15×10^{-6} *M*	Dimethylaminoethyl methacrylate	3	150.00	191.66	+27.77			143.33	123.33	−13.95	15.33	35.33	+130.26
(0.0026 ml)			(145–155)	(190–195)				(138–148)	(120–128)		(12–18)	(34–38)	
30×10^{-6} *M*			150.00	218.33	+45.55			140.66	112.66	−19.90	16.00	44.00	+175.00
(0.0052 ml)			(135–155)	(215–220)				(135–145)	(105–118)		(12–20)	(38–48)	
60×10^{-6} *M*			150.00	253.33	+66.88			140.00	111.66	−20.24	16.00	59.00	+268.75
(0.0104 ml)			(145–155)	(250–260)				(135–145)	(105–115)		(12–20)	(55–62)	
120×10^{-6} *M*			(Lethal dose)										
(0.0208 ml)													

[a] Mean value. [b] Range of responses noted.

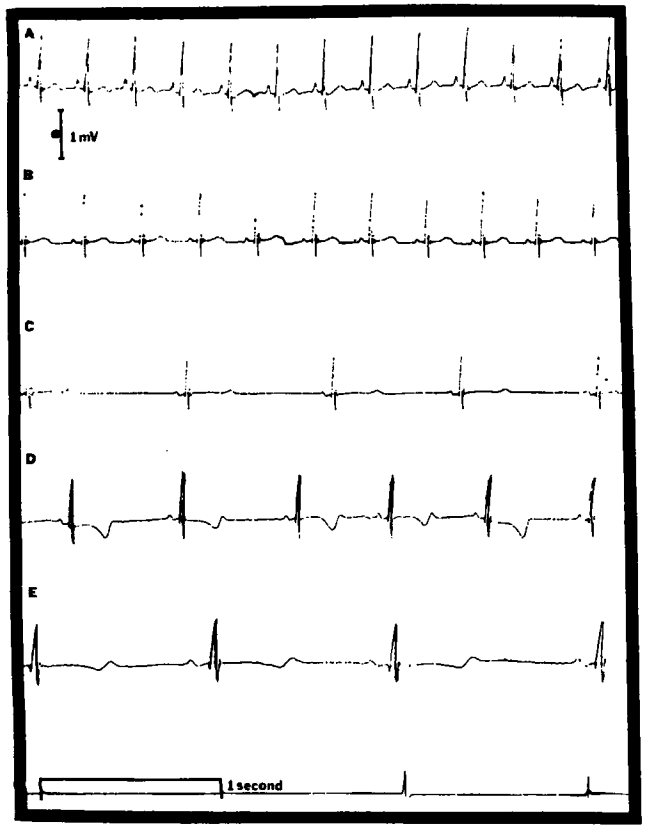

Figure 2—*Typical electrocardiographic changes produced by Type II methacrylate compounds. For key, see Fig. 1.*

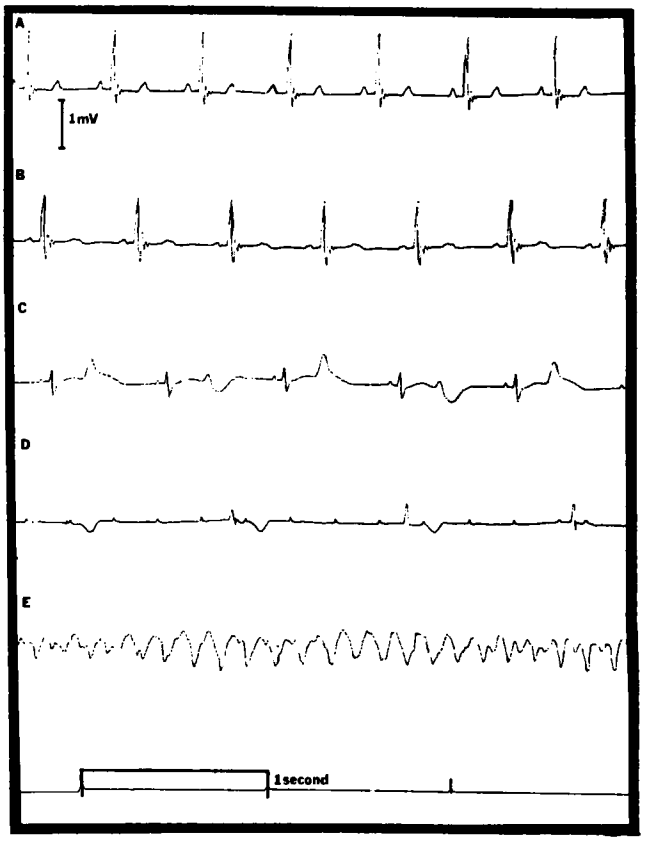

Figure 3—*Typical electrocardiographic changes produced by Type III methacrylate compound. For key, see Fig. 1.*

in the PR interval, an increase in the RR interval, prolongation of the ST segment, and a depression of the T wave (Fig. 1B). The median doses depressed and caused a marked sagging of the ST segment, inversion of the T wave, and further prolongation of the PR interval (Fig. 1C). Higher doses reduced the height of the R wave, increased the negativity of the S wave, and produced a prominent upright T wave (Fig. 1D). Premature ventricular contractions were frequently seen. With still higher (lethal) doses, the ventricular rate became very slow with a depressed QRS complex, an upright T wave, and a pattern of three P waves per QRS-T complex (Fig. 1E).

Type II Compounds—The lowest doses employed produced depression of the P wave, an increase in the RR interval, prolongation of the ST segment, and a slight depression of the T wave (Fig. 2B). The next higher doses produced a further increase in PR and RR intervals, with further depression of the T wave (Fig. 2C). Higher doses produced an increase in the PR interval, an increase in the RR interval, prolongation of the ST segment, and an inversion of the T wave (Fig. 2D). With the highest (lethal) doses, atrial–ventricular function was preserved in its proper sequence, although there was pronounced bradycardia and marked prolongation of the PR interval and ST segment (Fig. 2E). There was a suggestion of some electrical instability following these two highest doses, but it did not appear to be well-organized flutter or fibrillation (Figs. 2D and 2E).

Type III Compound—The lower doses produced a depression of the P wave, an increase in the PR interval, and a decrease in the amplitude of the R and T waves (Fig. 3B). The next higher dose produced a marked distortion of the electrocardiogram; the P wave was small and the ST segment was prolonged. The T wave appeared enlarged, upright, and "domed" in the first, third, and fifth cycles (Fig. 3C), while it was biphasic in the second and fourth cycles shown. With larger doses, there was a complete dissociation of the P waves from the QRS-T complexes (complete heart block), with the atrial rate approximately three times the ventricular rate (Fig. 3D). With the highest (lethal) dose, electrocardiographic abnormalities may be noted along with superimposed skeletal muscular contractions (Fig. 3E).

Thus, the electrocardiographic changes may be summarized as follows. Type I compounds showed a dose-related response in which there is bradycardia, a reduced rate of impulse transmission through the A-V node (increased PR interval), and possible acute cardiac ischemia. Higher doses produced premature ventricular contractions and incomplete A-V block.

The methacrylate esters with Type II action produced bradycardia, as well as a marked effect upon ventricular repolarization. As the dosage was increased, the T wave was reduced and then became inverted or biphasic with a considerable increase in the ST segment; the PR interval also became prolonged.

Dimethylaminoethyl methacrylate, the only Type III compound in this series, produced bradycardia, apparently also of sinus origin; as the dose was increased, abnormalities of the T wave were observed. In the next higher dose (Fig. 3D), complete A-V block was noted.

Administering suspensions by the intravenous route logically poses a question of whether the observed effects on blood pressure, heart rate, and the electrocardiogram are due to an intrinsic action of the compound injected or, secondarily, from physical blockage of small vessels by the suspension. The data obtained in this study suggest that the observed effects are due to the former and not to physical blockage of the coronary or other circulatory systems. Lauryl methacrylate was the least potent of these compounds in producing changes in these parameters; at the same time, it was the least water soluble and was injected in the largest quantities. Thus, if the effects were of a physical nature, this compound should have produced the greatest changes in these parameters.

Several authors (7, 11–14) reported cases of an abrupt fall in blood pressure in their patients immediately after the use of a bone cement containing methyl methacrylate monomer. Some authors (7, 11, 17) encountered cardiac arrest in a few patients. Homsy *et al.* (8) reported hypotensive effects of methyl methacrylate monomer (a member of the Type I series) when administered to dogs; however, they did not mention a secondary rise in pressure. Their figure depicting the blood pressure response of the dog to the monomer covered only the first 2 min postinjection.

during which we, too, observed only a hypotensive (initial) response to the monomer. In addition, a secondary rise in blood pressure, above control values, which occurred a few minutes after injection of the methacrylate, was observed in the present study.

Powell *et al.* (11) suggested that the hypotensive effect may result from a vasodilatory action of the methacrylate. In a previous study on the isolated guinea pig ileum (10), these methacrylates (Types I and II) induced relaxation of the smooth muscle of the intestine; thus Powell's postulate that such an effect may also be produced on the smooth musculature of the vascular system would not be inconsistent with the reported effects of these methacrylate monomers upon intestinal smooth muscle.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 9, 1973, from the *Materials Science Toxicology Laboratories, College of Pharmacy and College of Dentistry, University of Tennessee Medical Units, Memphis, TN 38163*

Accepted for publication October 12, 1973.

Supported in part by Research Grant DE 02944-05, National Institute of Dental Research, Bethesda, MD 20014

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Direct Estimation of Hexadecyltrimethylammonium-Ion Adsorption at Liquid Interfaces by a Radioisotope Technique I: Specific Ion Effects at Air–Water Interface

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Abstract □ The adsorption of the surfactant ^{14}C-hexadecyltrimethylammonium ion at the air-water interface was measured directly by detecting radioactivity emitted by adsorbed molecules. This was accomplished by placing a gas flow detector above the surface containing surfactant of known specific activity. Adsorption in the presence of potassium halide ions was found to change in the order bromide > chloride > fluoride, indicating specific ion interactions at the surface. Tetraalkylammonium halides produced the same order of effect for halide ions, but an inhibitory effect on adsorption was noted with increasing alkyl chain length. This effect appears to be related to their salting-in properties. Large hydrophobic anions, such as some alkyl- and arylsulfonates, produce two effects, depending on the concentration of surfactant and sulfonate. Ion association at the surface occurs at low sulfonate concentrations, whereas at higher sulfonate concentrations the ion association in bulk solution occurs, leading to less adsorption.

Keyphrases □ Hexadecyltrimethylammonium ion, adsorption—radioisotope technique for direct estimation at air–water interface, specific ion effects □ Surfactants, adsorption—radioisotope technique for direct estimation of hexadecyltrimethylammonium ion at air–water interface, specific ion effects □ Adsorption—radioisotope technique for direct estimation of hexadecyltrimethylammonium ion at air–water interface, specific ion effects □ Radiolabeling—used to measure hexadecyltrimethylammonium-ion adsorption at air–water interface

In recent years it has become increasingly apparent that the therapeutic potency of many drug molecules is related to their hydrophobic behavior or their tendency to leave an aqueous environment for one that is more nonpolar (1). At the molecular level, a number of processes may be responsible for this behavior. For example, *(a)* the drug may interact with a specific receptor or enzyme with a considerable contribution from hydrophobic interactions; *(b)* a rate-limiting barrier to the site of action may exist which is lipoidal and hence more limiting to less lipoidal molecules; and *(c)* there may be an interaction of the drug directly with biological membranes, causing a change in membrane permeability either by direct interaction with membrane molecules or by an indirect effect due to competition or