activity *in vivo* against *C. albicans* and *A. fumigatus*. Like clotrimazole, it was inactive against *Crypt. neoformans*.

The data obtained in this study indicate that Compound 27 is endowed with good inhibitory activity *in vitro* and *in vivo*, which is only slightly inferior to that of clotrimazole.

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▲ To whom inquiries should be directed.

Toxicological and Pharmacological Actions of Methacrylate Monomers I: Effects on Isolated, Perfused Rabbit Heart

G. N. MIR, W. H. LAWRENCE, and J. AUTIAN▲

Abstract □ A series of 12 methacrylate esters and methacrylic acid was investigated for activity upon the isolated, perfused rabbit heart. Each compound was dissolved in the perfusing fluid and tested at concentrations of 1:1000, 1:10,000, and 1:100,000 (v/v). All compounds reduced heart rate and force of contraction at one or more of these concentrations, and most, but not all, of the compounds reduced coronary flow rate.

Keyphrases □ Methacrylate monomers—toxicological and pharmacological actions, isolated, perfused rabbit heart □ Medical devices—toxicity and pharmacological actions of methacrylate esters from dental and surgical uses □ Methyl acrylic acid esters—toxicity and pharmacological actions, related to use in dentistry and surgery, cardiovascular effects, isolated, perfused rabbit heart □ Toxicity—methacrylate monomers, effects on isolated, perfused rabbit heart

Methacrylate esters are esters of methyl acrylic acid, $CH_2{=}CH(CH_3)COOH$, and the lower members of the series have a penetrating, disagreeable odor which may be recognized in tissues of treated animals (1). These esters may be polymerized by heat, oxygen, and oxygen-yielding compounds. The methacrylate polymers are widely used in dentistry and surgery as well as in many industrial applications.

Toxicity studies by Deichmann (1) and by Spealman *et al.* (2) indicated that lower members of the methacrylate esters were acutely lethal to laboratory animals due to respiratory depression by all routes of administration employed. Lawrence *et al.* (3) subjected 11 of the present 13 compounds to structure–toxicogenic analyses and found eight of these 11 compounds to be consistent with the hypothesis of a common mode of lethal activity.

Various investigators have reported a mild to marked irritant effect from application of some methacrylate monomers to skin, rabbit eye, wall of the stomach, respiratory membranes, and peripheral nerve tissue (1, 2, 4, 5). Strain (6) reported contact allergic reactions in sensitive patients to the residual monomer from incompletely polymerized methyl methacrylate dentures. Chronic toxicity feeding studies were conducted on rats and dogs by Borzelleca *et al.* (7) over a 2-year period. They did not find an increased mortality in the methacrylate-treated animals and, in fact, noted only a few instances of abnormal findings.

Acrylic polymers, primarily self-curing methyl methacrylate, have found some use as "bone cements" in orthopedics, especially for intramedullary placement of prosthetic devices. Hypotensive responses in patients shortly after clinical use of the cement have been reported by several workers (8–10). Cardiac arrests, some of which were fatal, have been reported in a few patients undergoing such treatment (9, 10) in which methyl methacrylate monomer was suggested as the primary or contributory cause of the cardiac arrest (10).

The present study was undertaken to investigate the pharmacological and toxicological effects of methacrylate monomers upon cardiac function, independent of their effect upon respiration and peripheral vasodilator activity.

Table I—Response of Isolated Rabbit Heart to Methacrylate Perfusion (Mean ± *SE*)

	Cardiac Rate per Minute			Force of Contraction, g.			Coronary Flow, ml./min.		
	Control	Response[a]	Change	Control	Response[a]	Change	Control	Response[a]	Change
Methacrylic acid									
1:100,000	182.8 ± 3.9	170.2 ± 4.2[b]	−6.9%	2.36 ± 0.05	1.90 ± 0.12[b]	−19.4%	10.4 ± 1.0	10.0 ± 0.3	−3.8%
1:10,000	180.0 ± 3.5	90.4 ± 16.8[b]	−49.0%	2.28 ± 0.37	1.00 ± 0.30[b]	−56.1%	10.8 ± 0.9	10.3 ± 0.5	−5.0%
1:1000	181.6 ± 2.7	0.0[b]	−100.0%	2.34 ± 0.15	0.00[b]	−100.0%	9.8 ± 1.4	0.0[b]	−100.0%
Methyl methacrylate									
1:100,000	184.0 ± 2.8	163.6 ± 1.6[b]	−10.9%	2.44 ± 0.15	1.26 ± 0.15[b]	−48.3%	10.1 ± 0.5	7.0 ± 0.6[b]	−30.5%
1:10,000	181.6 ± 2.6	79.6 ± 10.4[b]	−56.2%	2.36 ± 0.11	0.62 ± 0.21[b]	−73.7%	10.3 ± 0.8	5.0 ± 0.7[b]	−51.4%
1:1000	183.2 ± 2.1	0.0[b]	−100.0%	2.34 ± 0.08	0.00[b]	−100.0%	10.1 ± 1.3	0.0[b]	−100.0%
Ethyl methacrylate									
1:100,000	184.6 ± 3.5	173.8 ± 7.5[c]	−5.8%	2.42 ± 0.04	1.94 ± 0.08[b]	−19.8%	10.4 ± 0.6	7.6 ± 0.5[b]	−26.1%
1:10,000	184.4 ± 5.3	151.6 ± 11.7[b]	−17.8%	2.38 ± 0.04	0.66 ± 0.11[b]	−72.2%	9.7 ± 0.4	4.1 ± 0.4[b]	−57.9%
1:1000	184.0 ± 2.8	0.0[b]	−100.0%	2.48 ± 0.13	0.0[b]	−100.0%	11.0 ± 1.1	0.0[b]	−100.0%
n-Propyl methacrylate									
1:100,000	184.0 ± 3.7	177.2 ± 3.6	−3.7%	2.36 ± 0.08	2.02 ± 0.04[b]	−14.4%	9.48 ± 1.0	9.40 ± 0.5	−0.84%
1:10,000	185.2 ± 3.0	164.8 ± 4.3[b]	−11.0%	2.38 ± 0.08	1.32 ± 0.10[b]	−44.5%	10.7 ± 0.8	10.3 ± 0.4	−3.5%
1:1000	186.4 ± 4.3	145.2 ± 6.9[b]	−22.1%	2.38 ± 0.04	0.74 ± 0.08[b]	−68.9%	11.7 ± 1.7	10.0 ± 1.0[b]	−14.1%
n-Butyl methacrylate									
1:100,000	184.0 ± 3.1	169.2 ± 2.2[b]	−8.0%	2.38 ± 0.17	2.00 ± 0.15[b]	−15.9%	10.3 ± 0.4	10.2 ± 0.4	−0.38%
1:10,000	184.8 ± 3.0	159.2 ± 1.0[b]	−13.8%	2.44 ± 0.15	1.14 ± 0.25[b]	−53.3%	10.3 ± 0.2	6.1 ± 0.2[b]	−41.2%
1:1000	183.2 ± 2.2	132.4 ± 4.5[b]	−27.7%	2.44 ± 0.05	0.76 ± 0.11[b]	−68.8%	10.3 ± 0.5	4.9 ± 0.1[b]	−51.7%
Isobutyl methacrylate									
1:100,000	183.2 ± 2.6	166.4 ± 2.6[b]	−9.1%	2.44 ± 0.11	2.16 ± 0.08[b]	−11.4%	10.1 ± 0.2	10.0 ± 0.1	−1.1%
1:10,000	183.6 ± 2.1	151.6 ± 2.6[b]	−17.4%	2.50 ± 0.15	1.86 ± 0.05[b]	−25.6%	10.8 ± 0.4	10.5 ± 0.3	−2.0%
1:1000	184.8 ± 1.7	128.4 ± 1.6[b]	−30.5%	2.38 ± 0.08	0.44 ± 0.05[b]	−81.5%	10.1 ± 0.1	9.1 ± 0.1[c]	−9.5%
1,3-Butylene dimethacrylate									
1:100,000	184.0 ± 3.1	181.2 ± 5.2	−1.5%	2.32 ± 0.13	2.08 ± 0.22[c]	−10.3%	10.2 ± 0.4	9.7 ± 0.4	−5.8%
1:10,000	184.0 ± 3.7	166.0 ± 6.7[c]	−9.7%	2.30 ± 0.07	1.74 ± 0.11[b]	−25.6%	10.2 ± 0.2	9.5 ± 0.4	−6.4%
1:1000	183.8 ± 3.0	131.2 ± 5.9[b]	−28.6%	2.40 ± 0.07	0.68 ± 0.04[b]	−71.6%	11.3 ± 0.1	10.2 ± 0.5[c]	−9.5%
2-Ethylhexyl methacrylate									
1:100,000	184.8 ± 1.7	180.0 ± 1.4	−2.5%	2.52 ± 0.33	2.36 ± 0.11[c]	−6.7%	10.0 ± 0.3	10.1 ± 0.4	+0.6%
1:10,000	184.0 ± 2.8	172.4 ± 3.8[c]	−6.3%	2.40 ± 0.07	1.96 ± 0.05[b]	−18.3%	9.9 ± 0.2	11.0 ± 0.8	+11.0%
1:1000	182.8 ± 1.7	153.2 ± 1.7[b]	−16.1%	2.40 ± 0.07	1.54 ± 0.05[b]	−35.8%	10.0 ± 0.2	12.9 ± 1.4[b]	+28.1%
Isodecyl methacrylate									
1:100,000	184.0 ± 2.4	179.6 ± 1.6	−2.4%	2.40 ± 0.12	2.34 ± 0.13	−2.5%	10.4 ± 0.4	11.6 ± 0.8[c]	+12.3%
1:10,00	184.0 ± 3.7	173.8 ± 3.0[c]	−5.5%	2.44 ± 0.05	2.16 ± 0.13[b]	−11.4%	10.3 ± 0.4	11.8 ± 0.7[c]	+14.7%
1:1000	182.6 ± 1.9	162.6 ± 1.9[b]	−10.9%	2.40 ± 0.07	1.78 ± 0.08[b]	−25.8%	10.2 ± 0.2	12.2 ± 1.7[c]	+18.9%
Lauryl methacrylate									
1:100,000	183.6 ± 3.5	183.0 ± 4.1	−0.21%	2.38 ± 0.08	2.36 ± 0.08	−0.84%	10.2 ± 0.1	10.4 ± 0.1	+2.1%
1:10,000	184.4 ± 3.5	179.6 ± 1.6	−2.6%	2.34 ± 0.19	2.18 ± 0.10[c]	−6.8%	10.1 ± 0.1	10.4 ± 0.1	+2.7%
1:1000	184.8 ± 2.2	170.0 ± 2.4[c]	−8.0%	2.40 ± 0.07	1.94 ± 0.11[b]	−19.1%	10.0 ± 0.2	11.1 ± 0.7[b]	+11.6%
Substituted Methacrylates:									
Hydroxyethyl methacrylate									
1:100,000	183.6 ± 3.2	163.2 ± 2.6[b]	−11.1%	2.42 ± 0.04	2.28 ± 0.22	−5.7%	9.7 ± 0.4	9.8 ± 0.4	+1.0%
1:10,000	183.6 ± 2.9	144.8 ± 3.9[b]	−21.1%	2.38 ± 0.08	1.56 ± 0.05[b]	−34.4%	9.7 ± 0.3	10.8 ± 1.3	+11.0%
1:1000	181.6 ± 1.6	106.4 ± 3.5[b]	−41.4%	2.36 ± 0.05	0.42 ± 0.04[b]	−82.2%	9.5 ± 0.8	10.8 ± 0.3[b]	+13.3%
tert-Butylaminoethyl methacrylate									
1:100,000	184.0 ± 3.1	172.8 ± 3.3[c]	−6.0%	2.42 ± 0.08	2.32 ± 0.14	−4.1%	10.0 ± 0.2	10.0 ± 0.1	0.0
1:10,000	181.8 ± 2.0	163.8 ± 3.0[b]	−9.9%	2.42 ± 0.04	1.96 ± 0.05[b]	−19.0%	10.2 ± 0.6	10.1 ± 0.4	−0.39%
1:1000	182.2 ± 2.2	143.6 ± 3.5[b]	−21.8%	2.36 ± 0.20	1.64 ± 0.15[b]	−30.5%	11.0 ± 1.1	10.3 ± 0.9	−5.6%
Dimethylaminoethyl methacrylate									
1:100,000	184.2 ± 3.1	149.2 ± 12.9[b]	−19.0%	2.26 ± 0.20	1.02 ± 0.08[b]	−54.8%	9.8 ± 1.1	9.6 ± 1.1	−2.4%
1:10,000	181.6 ± 1.6	0.0[b]	−100.0%	2.38 ± 0.16	0.0[b]	−100.0%	9.4 ± 1.1	0.0[b]	−100.0%
1:1000	183.2 ± 4.8	0.0[b]	−100.0%	2.34 ± 0.15	0.0[b]	−100.0%	10.2 ± 0.6	0.0[b]	−100.0%

[a] Response represents the stabilized level of altered activity within the first 3 min. following methacrylate perfusion and return to normal Locke's solution. [b] $p < 0.01$ when compared to control. [c] $p < 0.05$ when compared to control.

Table II—Reversibility of Heart Response to Methacrylates

Group	Effect
I: Methacrylic acid, Methyl methacrylate, Ethyl methacrylate, Dimethylaminoethyl methacrylate	Produced an irreversible effect on the isolated heart at all three concentrations
II: *n*-Propyl methacrylate, *n*-Butyl methacrylate, Isobutyl methacrylate, Hydroxyethyl methacrylate, *tert*-Butylaminoethyl methacrylate	Produced an irreversible effect on the isolated heart at the 1:1000 concentration but not at lower concentrations
III: 1,3-Butylene dimethacrylate, 2-Ethylhexyl methacrylate, Isodecyl methacrylate, Lauryl methacrylate	Produced a reversible effect on the isolated heart at all three concentrations

MATERIALS AND METHODS

Materials—The monomers included in this study are all liquids at room temperature, and they constitute the following: methacrylic acid[1]; methyl[1], ethyl[1], *n*-butyl[1], isobutyl[1], isodecyl[1], lauryl[1] (dodecyl), hydroxyethyl[1], *tert*-butylaminoethyl[1], dimethylaminoethyl[1], *n*-propyl[2], and 2-ethylhexyl[2] methacrylates; and 1,3-butylene dimethacrylate[1].

Methods—Isolated rabbit hearts were perfused using an Anderson coronary perfusion apparatus. A twin reservoir system was employed, one containing normal Locke's solution and the other the test substance dissolved in Locke's solution[3], in which a uniform hydrostatic pressure was maintained to provide a constant perfusion pressure and to permit rapid changes from one solution to the other. Heart rate and force of contraction were recorded with a polygraph[4] by placing a small hook in the apex of the heart and passing a ligature over a pulley to a force-displacement transducer[5] which was calibrated to produce 1 cm. deflection/g. of force applied. The outflow from the heart was collected in a small graduated cylinder at specified time intervals to determine the coronary flow rate.

Hearts from small rabbits (1.5–2.0 kg.) were used throughout this study. Each heart was perfused for a 20-min. equilibration period prior to initiating the experiment, with the tests being conducted during the following 90 min. Preliminary studies using only normal Locke's solution did not reveal any functional abnormality in the isolated, perfused heart for approximately 2 hr. or more.

All compounds were tested at three fixed concentrations, 1:1000, 1:10,000, and 1:100,000 (v/v), in Locke's solution. When cardiac activity had stabilized, the test solution was introduced as the perfusate for 1 min. and immediately thereafter normal Locke's solution was perfused to permit recovery of the heart. The effect of a test solution was deemed "irreversible" if cardiac activity had not made a significant return toward control levels within 30–35 min. of perfusion with normal Locke's solution. If at any time the heart failed to return to control levels of activity, it was replaced with a fresh one before proceeding with the next test. Each methacrylate concentration was tested five times. Effects of the test solution were determined by quantitating the three parameters (rate and force of contraction and coronary flow rate) of the heart at its stabilized activity immediately prior to perfusion of test solution and comparing these to the values obtained from the heart at its plateau activity near the end of, or immediately following, perfusion with the test solution.

[1] Rohm & Haas, Philadelphia, Pa.
[2] K & K Labs., Inc., Plainview, N. Y.
[3] The Locke solution contained 9.0 g. NaCl, 0.42 g. KCl, 0.24 g. $CaCl_2$, 0.15 g. $NaHCO_3$, and 1.0 g. glucose/l. It was oxygenated with 95% oxygen and 5% carbon dioxide, and the perfusate temperature was maintained at 37 ± 0.3°.
[4] Grass model 7.
[5] Grass FT 03C.

RESULTS

When dissolved in Locke's solution and perfused through isolated rabbit hearts, methacrylic acid and the 12 methacrylate esters produced significant effects upon the heart at one or more of the three concentrations employed. A summary of the mean values and standard errors is presented in Table I for cardiac rate, force of contraction, and coronary flow. The data also show which changes are significant by Student's *t* test and the magnitude of the change as percent change from control values. The methacrylate perfusion produced cardiac standstill in five of the test solutions employed. In these cases, the heart stopped in systole and coronary flow ceased or was reduced to negligible amounts (responses were recorded as zero), with a −100% change from control.

These methacrylates may be rather equally divided into three categories (Table II) as to those which, under the conditions of these experiments: (*a*) produced irreversible effects upon the isolated heart at all three concentrations tested, (*b*) produced irreversible effects on the isolated heart at highest concentrations but reversible effects at lower concentrations, and (*c*) produced reversible effects upon the isolated heart at all three concentrations tested.

DISCUSSION

Although the acute lethality of methacrylate monomers has been reported to result from respiratory depression (1, 2), more information was needed concerning the pharmacodynamic (or toxicological) activity of these compounds upon a relatively simple system: the isolated, perfused rabbit heart. Examination of the data in Table I reveals that most of the methacrylate-containing perfusing solutions produced a significant ($p \leq 0.05$) reduction in cardiac rate and force of contraction, with the effect upon contraction generally being of a greater magnitude. This was true whether or not the effect was reversible. In approximately one-half of the test groups, there was also a significant ($p \leq 0.05$) change in coronary flow rate; this change was usually a reduction but, in several instances, it was an increase.

From the toxicological aspect, it would be desirable to rate or rank such compounds according to their toxicological liability. However, there appears to be no single criterion upon which to base such a comparison since the magnitude of change in these three characteristics varies from one methacrylate to another. For example, the 1:10,000 concentration of *n*-butyl methacrylate reduced heart rate by 13.8%, force of contraction by 53.3%, and coronary flow by 41.2%, while the same concentration of isobutyl methacrylate reduced rate by 17.4%, force by 25.6%, and flow by 2.0%; this concentration of ethyl methacrylate reduced rate by 17.8%, force by 73.3%, and flow by 57.9%. Thus, while the reduction of rate was comparable for all three monomers (13.8, 17.4, and 17.8%), the reduction in force of contraction and coronary flow varied tremendously (force = 53.3, 25.6, and 73.7%, respectively; flow = 41.2, 2.0, and 57.9%, respectively). For any particular methacrylate, the response obtained demonstrated a concentration-dependent relationship for each experimentally measured variable.

Table III presents these 13 methacrylates ranked in order of their relative effects upon the parameters indicated. The compounds are listed in decreasing order of acute toxicity to mice (intraperitoneally), with the acute LD_{50} values for each. The effect of the compound upon each function of the isolated heart was expressed as the average mean response to the three standard concentrations, and this value is given in parentheses following each ranking number. These were ranked from 1 to 13, with 1 producing the greatest reduction and 13 the least reduction. Examination of these data or the more detailed data in Table I suggests a relatively greater reduction in force of contraction and cardiac rate than upon coronary flow.

The data presented, their reproducibility, and discussions to this point have been based upon volume quantities or concentrations of methacrylates. To obtain an estimate of the activity of each methacrylate upon these three parameters by molar concentrations of the compounds, the mean percent change from control was plotted against the molar concentration in the perfusate and a "best-fit" curve was drawn through these three points. The molar concentrations *versus* percent change for heart rate, force of contraction, and coronary flow rate are shown in Figs. 1, 2, and 3, respectively. It is readily apparent that these three-point curves are estimates;

Table III—Relative Activity of Methacrylates of Equal Volume to Volume Dilutions[a]

Compound (Monomer)	Acute LD_{50}, Intraperitoneal, Mice, ml./kg.	Relative Effect upon Isolated Rabbit Heart: Rate	Contraction	Coronary Flow
Methacrylic acid	0.048	3 (−52.0%)	4 (−58.5%)	4 (−36.3%)
Dimethylaminoethyl methacrylate	0.104	1 (−73.0%)	1 (−84.9%)	1 (−67.5%)
tert-Butylaminoethyl methacrylate	0.190	9 (−12.6%)	11 (−17.9%)	9 (−2.0%)
Hydroxyethyl methacrylate	0.497	5 (−24.5%)	7 (−40.8%)	+11 (+8.4%)[b]
n-Propyl methacrylate	1.121	10 (−12.3%)	6 (−42.6%)	7 (−6.1%)
Methyl methacrylate	1.198	2 (−55.7%)	2 (−74.0%)	3 (−60.6%)
Isobutyl methacrylate	1.340	6 (−19.0%)	8 (−39.5%)	8 (−4.2%)
Ethyl methacrylate	1.369	4 (−41.2%)	3 (−64.0%)	2 (−61.5%)
n-Butyl methacrylate	1.663	7 (−16.5%)	5 (−46.0%)	5 (−31.1%)
2-Ethylhexyl methacrylate	2.614	11 (−8.3%)	10 (−20.3%)	+12 (+13.2%)[b]
1,3-Butylene dimethacrylate	3.598	8 (−13.3%)	9 (−35.8%)	6 (−7.2%)
Isodecyl methacrylate	3.688	12 (−6.3%)	12 (−13.2%)	+13 (+15.3%)[b]
Lauryl methacrylate	24.897	13 (−3.6%)	13 (−8.9%)	+10 (+5.5%)[b]

[a] Relative activity determined by using the mean responses obtained at the three standard concentrations tested (1×10^{-3}, 10^{-4}, and 10^{-5} v/v). [b] + indicates an increase over controls, with higher numbers indicating a greater increase.

Table IV—Relative Effect of Perfusing Methacrylates upon Three Functions of the Isolated Heart at Equimolar Concentration

Compound (Monomer)[a]	Acute LD_{50}, Intraperitoneal, Mice, moles/10^6 g.	Relative Effect upon Isolated Heart[b]: Rate	Contraction	Coronary Flow
Methacrylic acid	0.564	3 (−63.5%)	5 (−64.9%)	7 (−7.5%)
Dimethylaminoethyl methacrylate	0.618	1[c]	1[c]	1[c]
tert-Butylaminoethyl methacrylate	0.937	10 (−16.5%)	11 (−28.0%)	9 (−1.9%)
Hydroxyethyl methacrylate	4.060	5 (−28.5%)	7 (−48.0%)	+11 (+11.5%)
n-Propyl methacrylate	7.821	9 (−17.4%)	6 (−57.5%)	6 (−7.9%)
Isobutyl methacrylate	8.398	6 (−23.5%)	9 (−43.9%)	8 (−5.0%)
n-Butyl methacrylate	10.481	8 (−20.0%)	4 (−65.5%)	4 (−48.9%)
Ethyl methacrylate	10.896	4 (−36.9%)	2 (−85.5%)	2 (−70.5%)
Methyl methacrylate	11.217	2 (−75.0%)	2 (−85.5%)	3 (−64.5%)
2-Ethylhexyl methacrylate	11.571	11 (−13.0%)	10 (−30.4%)	+13 (+20.4%)
Isodecyl methacrylate	14.251	12 (−11.0%)	12 (−21.9%)	+12 (+18.0%)
1,3-Butylene dimethacrylate	16.063	7 (−21.0%)	8 (−47.0%)	5 (−8.0%)
Lauryl methacrylate	84.531	13 (−8.0%)	13 (−17.3%)	+10 (+8.9%)

[a] Compounds listed in decreasing order of lethal potency on a mole basis. [b] Ranking is based upon relative effects produced by the compound at a concentration of 2×10^{-3} mole/l. in the perfusing solution as estimated from Figs. 1–3. A rank of 1 represents the greatest depressant effect, while that of 13 is the least depressant. In the case of coronary flow rate, a plus value indicates an increase in flow rate, with the higher number representing the greater increase. Percentage change from control is given in parentheses. [c] This compound produced cardiac standstill at a concentration of 0.59×10^{-3} *M*, while a concentration of 0.059×10^{-3} mole/l. reduced rate by 19%, contraction by 55%, and coronary flow by 2%.

arguments for other "lines of best fit" could be made for some, particularly those in which cardiac standstill has occurred, since the −100% point could readily be shifted to the left by data intermediate between those presented. Such a shift would, of course, show an increased potency for the compound upon the parameters in question. Although only approximate, the curves show the patterns of activity and the relative magnitudes of potency of the various compounds on a molar basis.

Examination of these figures reveals considerable similarity between the effects that a compound produces upon heart rate and force of contraction; this appears to be true on a qualitative basis for all compounds in this series. When comparing these to changes in coronary flow rate, a few of the compounds (*e.g.*, methyl and ethyl methacrylates) still produce similar curves; however, many of these compounds produce response curves of a grossly different shape or magnitude.

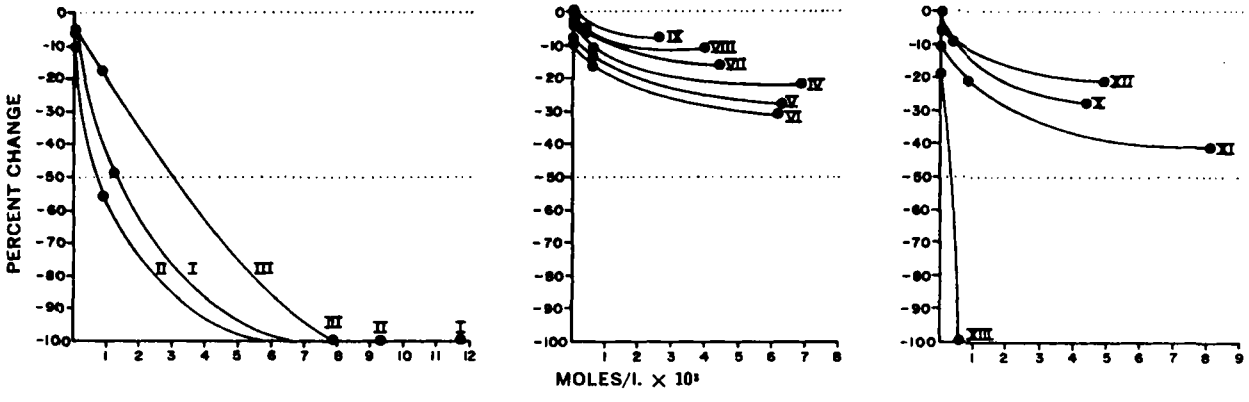

Figure 1—*Effects of methacrylates upon rate of contraction of isolated rabbit heart. Key: I = methacrylic acid, II = methyl methacrylate, III = ethyl methacrylate, IV = n-propyl methacrylate, V = n-butyl methacrylate, VI = isobutyl methacrylate, VII = 2-ethylhexyl methacrylate, VIII = isodecyl methacrylate, IX = lauryl methacrylate, X = 1,3-butylene dimethacrylate, XI = hydroxyethyl methacrylate, XII = tert-butylaminoethyl methacrylate, and XIII = dimethylaminoethyl methacrylate.*

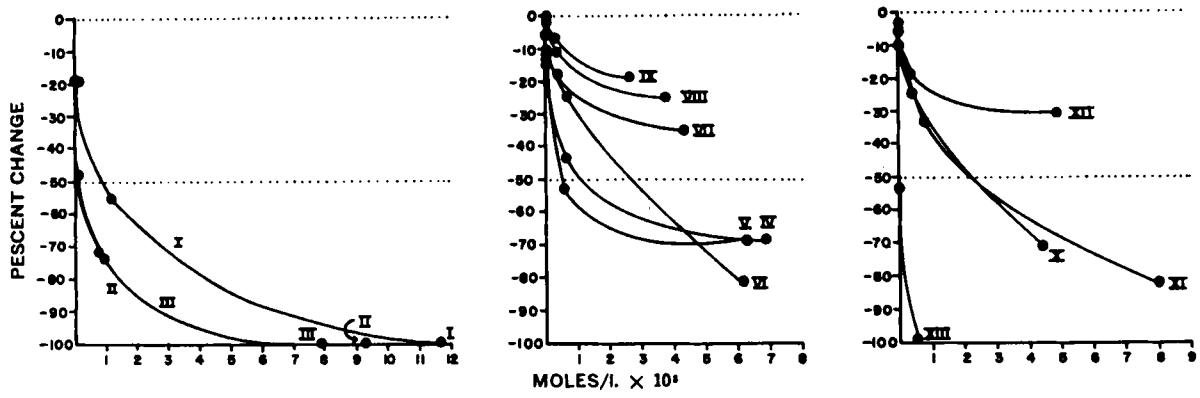

Figure 2—*Effects of methacrylates upon force of contraction of isolated rabbit heart. (For Key, see Fig. 1.)*

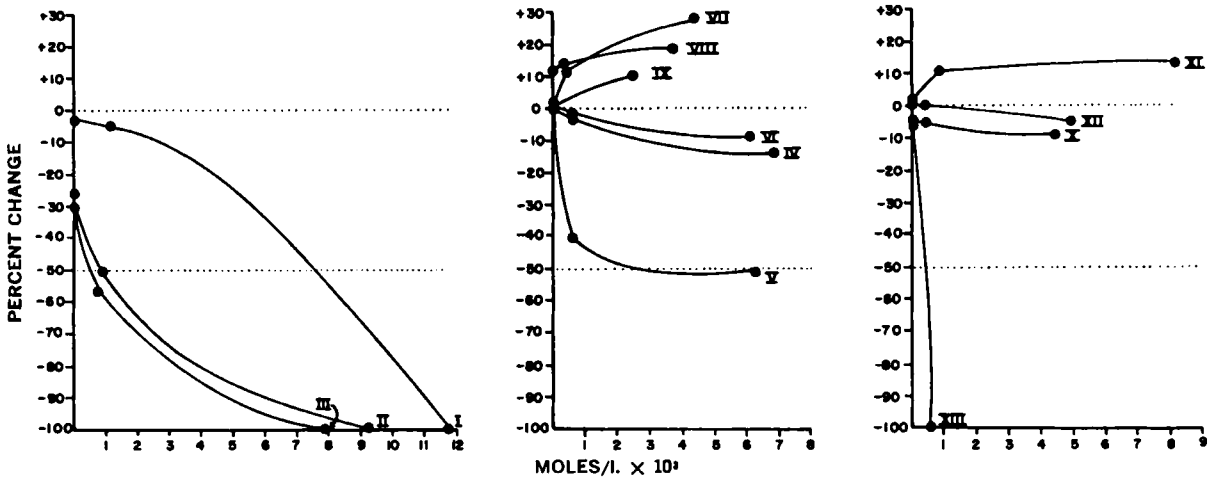

Figure 3—*Effects of methacrylates upon coronary flow rate of isolated rabbit heart. (For Key, see Fig. 1.)*

To facilitate equimolar comparisons, a perfusate concentration of 2×10^{-3} mole/l. was selected and the approximate responses were obtained from the curves shown in Figs. 1–3 and ranked for each cardiac parameter. These data are presented in Table IV, in which the monomers are ranked in order of decreasing acute intraperitoneal toxicity to mice, with LD_{50} values expressed as moles/10^6 g. of mouse.

A comparison of Table IV with Table III indicates that most of the compounds exhibited similar ranking according to their effect upon the isolated heart, whether they were considered on the basis of average response to the three standard volume to volume concentrations (Table III) or response produced by a 2×10^{-3} *M* solution (Table IV). The relative ranking of these compounds by these two methods of comparison differed by more than the adjacent rank in only one case (effect of methacrylic acid upon coronary flow rate). There were a number of instances, however, where the rank moved up or down to the adjacent number.

SUMMARY

The action of a number of methacrylates was examined using the isolated, perfused rabbit heart. Dimethylaminoethyl methacrylate exhibited the most potent effect upon the isolated heart, producing cardiac standstill at a dilution of 1:10,000 (v/v) (0.59×10^{-3} mole/l.), while lauryl methacrylate showed the least depressant effect upon the isolated heart at the concentrations tested. All of the methacrylates tested, at all concentrations employed, produced a relative increase in coronary flow (coronary flow per gram of contraction) or did not alter it when compared to pretreatment control values. The only exception observed was when the test solution produced cardiac standstill. Although cardiac failure may not be the primary cause of death from methacrylate esters in animals, these compounds do show some marked effects upon the isolated heart, and some clinicians have implicated one of them (methyl methacrylate) in certain clinical cases of cardiac arrests observed during the use of "acrylic bone cement." Dose-response data are presented based upon both molar concentrations and volume dilutions of these compounds.

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▲ To whom inquiries should be directed.