Some Actions of Mercury Compounds on the Heart.* (18504)

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Severe impairment in cardiac function can be produced by the intravenous injection of mercurial diuretics(1-3). The object of the present investigation was to relate the dosage of the mercurials to the changes in the electrocardiogram and to determine differences in cardiac action of various types of mercury compounds.

Methods. All experiments were performed on mongrel dogs weighing 6 to 13 kg. The anesthetic used was Dial Urethane§ (0.6-0.7 cc per kg given intraperitoneally). The average arterial pressure was recorded from the common carotid or the femoral artery by means of a mercury manometer. Electrocardiographic tracings were obtained by means of subcutaneous leads, lead 2 being usually employed. Records were taken on an ink-writing oscillograph. In 3 experiments leads were taken directly from the auricle or ventricle by means of small metal clips attached to the respective organs. The mercurial to be studied was infused at a rate of 3 micromoles per kg per minute into the femoral vein by means of a constant rate infusion pump. The mercury compounds employed were mersalyl‖ (2-[(2-hydroxy-mercuri-3-methoxypropyl) carbamyl] phenoxy-acetic acid) mersalyl with theophylline,‖ Esidron acid§ (2-[2-hydroxy-mercuri-3-hydroxy-propyl-carbamyl] nicotinic acid) Esidron acid with theophylline,§ p-chloromercuribenzoate and mercury bichloride. Sodium salts of these compounds, except mercury bichloride, were prepared by the addition of equivalent quantities of sodium hydroxide.

Results. Following the infusion of a mercurial diuretic such as mersalyl or Esidron acid with and without theophylline, a fairly constant sequence of events occurred in the electrocardiograms taken either by conventional or by direct leads from the heart. The earliest changes observed were a depression and change in configuration of the ST segment, the "T wave" originating from the S wave. Changes in the height of the T wave were determined by the original state of this wave during the control period. If the T wave was upright, there were usually the ST changes and an increase in the height of the T wave; if inverted the main changes were the ST changes described above. The distance from S to the end of the T wave was

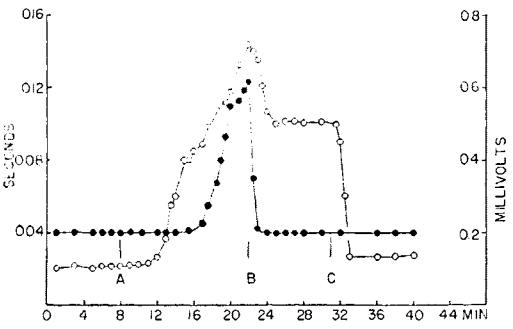

FIG. 1.

Effect of cysteine on electrocardiographic changes produced by free Esidron acid. Male dog 8.6 kg ECG Lead II. At A: infusion of Esidron (3 micromoles per kg per min.) was started. At B and C: 2 and 5 mg per kg cysteine hydrochloride respectively given by vein. Abscissa, time in min. Ordinates, the downward displacement of the ST segment in millivolts, or length of the QRS in sec. ●——● QRS in sec. ○——○ Displacement of the T wave in millivolts.

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1. DeGraff, A. C., and Lehman, R. A., *J.A.M.A.*, 1942, v119, 998.

2. Long, W., and Farah, A., *J. Pharmacol. Exp. Therap.*, 1946, v88, 388.

3. Chapman, D. W., and Shaffer, C. F., *Arch. Int. Med.*, 1947, v79, 449.

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TABLE I. Effect of Mercury Compounds on the ECG of the Anesthetized Dog. Constant infusion of the mercurial at a rate of 3 micromoles per kg per min. All values are in micromoles.

Compound	Min. T changes	Min. QRS changes	Toxic dose*	Lethal dose†	No. of exp.
Free salyrgan	16.8 ± 6.1	28.9 ± 3.2	44.2 ± 4	48.6 ± 5	6
Free Esidron	10.2 ± 3	16.9 ± 5.2	28.7 ± 32	33.5 ± 2.9	7
Esidron with theophylline	12.8 ± 2.7	18.8 ± 3.6	32.7 ± 2.8	37.9 ± 3.4	6
Mercury bichloride	11.8 ± 4.5	16.0 ± 5.0	28.0 ± 7.2	31.0 ± 6.1	3
P chloromercuribenzoate	25.2 ± 8	—	—	160 ± 20	5

* Dose which doubles the width of the QRS complex.
† Dose producing ventricular fibrillation or cardiac arrest.

not changed appreciably even during the severe stages of poisoning with the mercurial diuretics. Changes in the QRS wave occurred somewhat later than the T wave changes and were characterized by widening and notching of the QRS complex (Fig. 1). With lethal doses of the above mercurial diuretics there was a period of ventricular tachycardia followed by ventricular fibrillation. In Table I are given the dosages of some mercury compounds producing the various electrocardiographic changes described above.

It can be seen from Table I that with all compounds the T wave changes were the first to appear. All compounds except p-chloromercuribenzoate produced widening of the QRS wave. Parachloromercuribenzoate is unique in this series since in the doses employed it produced only T wave changes with no change in the width of the QRS even following lethal doses.

The other changes observed with the mercurial diuretics containing no aminophylline are widening of the P wave and prolongation of the PR interval. The prolongation of the PR interval may occur before or after the beginning of the QRS changes. With the aminophylline containing diuretics Esidron and mersalyl the PR changes are minimal or absent. All the above changes are readily reversed by an adequate dose of a cysteine HCl or 2,3-dimercuptopropanol (BAL)(2). The observation has been made that following the injection of a thiol the ST and T wave changes produced by the mercurial diuretics are slower to respond than the QRS complex. With small doses of cysteine it is possible to correct the QRS changes while the T wave is only partially corrected. By increasing the dose of the sulfhydryl compound the T wave changes also disappeared (Fig. 1).

Heart rate and PR interval changes produced by the various mercurial diuretics are not the same. With the aminophylline free mercurial diuretics mersalyl and Esidron acid, an increase in heart rate occurred only during the very late stages of poisoning and was due to ventricular tachycardia. The PR interval was increased with both the free compounds and both ventricular tachycardia and PR prolongation were readily reversed by the intravenous injection of cysteine (Fig. 2A). With the theophylline-containing mercurial preparations Esidron and mersalyl there was a 20 to 30% increase in sinus heart rate which started during the early stages of the injection period. The PR changes were minimal and a slight increase occurred only during the latter stages of the poisoning. The tachycardia could not be abolished by cysteine, thioglycolic acid or BAL. The PR interval was reduced below control levels by these thiols (Fig. 2B). Since the above differences could be due to the theophylline content of these compounds, aminophylline was infused in 2 dogs at a rate of 3 micromoles per kg per minute. There was first a cardiac slowing lasting 30 to 60 seconds followed by an increase in heart rate and some decrease in the PR interval. Neither heart rate increase nor PR change could be affected either by BAL or cysteine (5 and 10 mg per kg respectively).

The action of p-chloromercuribenzoate. The intravenous infusion of this compound at a rate of 3 micromoles per kg per minute resulted in marked ST and T wave changes. No QRS changes were observed even with doses 2 to 3 times as great as the lethal dose of the other mercurials studied (Table I

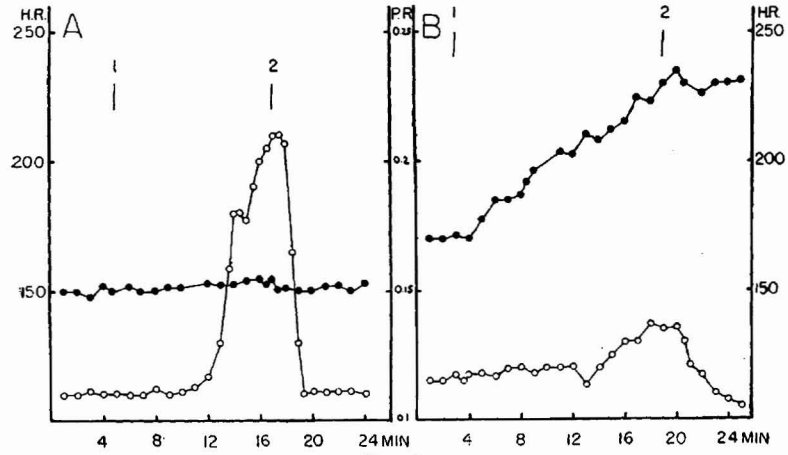

FIG. 2.

Effect of free Esidron and Esidron with theophylline on heart rate and PR interval in the anesthetized dog. A. Female dog 6.6 kg. 1: Start of the infusion of free Esidron (3 micromoles per kg per min.). 2: Intravenous inj. of 10 mg per kg of thioglycolic acid. B. Male dog 9.4 kg. 1: Start of infusion of Esidron with theophylline (3 micromoles per kg per min.). 2: Intravenous inj. of 10 mg per kg of thioglycolic acid. ○——○ PR interval in sec. ●——● Heart rate beats per min. Abscissa, time in min. Ordinate heart rate beats per min. or PR interval in sec.

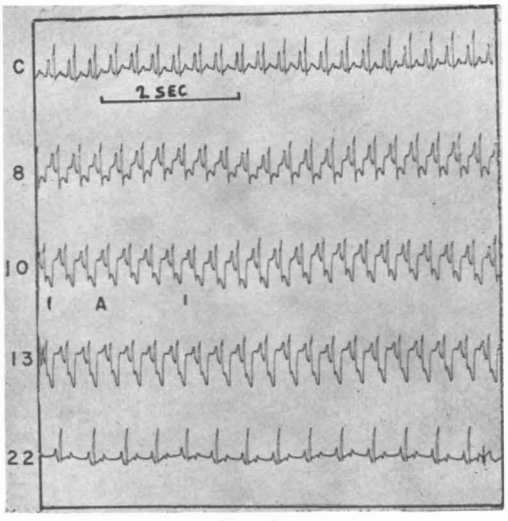

FIG. 3.

Effect of p-chloromercuribenzoate on the ECG of the dog. C. Control tracing. Between first and second tracing p-chloromercuribenzoate infused intrav. at 3 micromoles per kg per min. Numbers on left indicate time in min. following the start of infusion of p-chloromercuribenzoate. At A 20 mg per kg of cysteine hydrochloride was given intrav. At 21 min. 5 mg per kg of BAL was given intrav. Last tracing is after BAL inj.

and Fig. 3). With the mercurial diuretics and mercury bichloride death was due to ventricular fibrillation while with p-chloromercuribenzoate death was due to ventricular asystole. Prior to this ventricular asystole, there was a reduction in heart rate, a prolongation of the PR interval, followed by complete block, and appearance of slow ventricular extrasystoles. The slowing in heart rate and the prolonged PR interval could be corrected by the intravenous injection of cysteine hydrochloride (10-20 mg/kg) or BAL (5 mg per kg). Cysteine, even in large doses (20-40 mg/kg) had little effect on the T wave changes produced by toxic doses of p-chloromercuribenzoate while 5 mg per kg of BAL readily corrected these T wave changes (Fig. 3). The acute lethal dose of p-chloromercuribenzoate is about 160 micromoles and is high when compared with those of the mercurial diuretics and mercury bichloride (Table I). The probable reasons for this are the different mechanisms for the production of cardiac death described above.

Mercury bichloride has a cardiac action similar to that of the free mercurial diuretics and it produced the characteristic ST, T, QRS and PR changes. The administration of 10 to 20 mg per kg of cysteine corrected these changes only for 10 to 20 minutes, while with 10 mg per kg of BAL cardiac pro-

tection lasted several hours (3 experiments).

Discussion and summary. The various mercurials studied show both quantitative and qualitative differences in their cardiac action. In the case of the mercurial diuretics the aminophylline containing compounds produce an increase in the sinus rate as well as ventricular tachycardia while the free mercurials produce only a ventricular tachycardia (Fig. 2). The evidence presented makes it probable that the differences in response of the heart rate are due to the theophylline content of these preparations.

The ST and T wave changes described occurred somewhat prior to the QRS changes. ST and T wave changes are probably related to alterations in the process of repolarization of cardiac muscle while the QRS changes probably indicate mainly changes in intraventricular conduction. The mercurials studied are powerful inhibitors of enzymes containing essential SH groups(4,5). Thus the biochemical processes responsible for repolarization of cardiac muscle seem to be more sensitive to these SH inhibitors than the processes involved in intraventricular conduction.

The action of p-chloromercuribenzoate is of interest. It affects only the ST and T wave and thus probably interferes mainly with repolarization of the muscle but has no effect on intraventricular conduction processes. However, it does interfere with atrioventricular conduction and thus, with this enzyme poison it seems possible to inhibit selectively atrioventricular conduction. Differences in the histology and staining qualities of the atrioventricular and intraventricular conductile system have been described by Robb *et al.*(6) and pharmacological differences are thus not surprising.

4. Pitts, R. F., and Sartorius, O. W., *J. Pharmacol. Exp. Therap.*, 1950, v98, 161.

5. Handley, C. A., and Lavick, P. S., *J. Pharmacol. Exp. Therap.*, 1950, v100, 115.

6. Robb, J. S., personal communication.

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Prolongation and Potentiation of Anabolic and Androgenic Effects of Steroids: Testosterone and Methylandrostenediol.*† (18505)

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Carlinfanti *et al.*(1,2) have reported the potentiation and prolongation of the androgenic activity of testosterone in castrated male guinea pigs by the addition of aluminum phosphate to an aqueous suspension of the steroid. Margolin *et al.*(3) produced similar results in the albino rat. Both groups of workers have limited their reports to the androgenic effects. By use of a recently described assay procedure for anabolic activity (4), methylandrostenediol (MASD) has been found to be an anabolic agent which, in ordinary doses, has little androgenic activity (5). It was the purpose of our investigation to compare the duration and degree of action of the androgenic and anabolic properties of aqueous suspensions of MASD and of testo-

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1. Carlinfanti, E., D'Alo, F., and Cutolo, L., (Abstr.) *Chem. Abstr.*, 1949, v23, 3085.

2. Carlinfanti, E., D'Alo, F., and Cutolo, L., *Lancet*, 1949, v1, 479.

3. Margolin, S., Lee, S. W., and Tislow, R., PROC. SOC. EXP. BIOL. AND MED., 1950, v74, 649.

4. Eisenberg, E., and Gordan, G. S., *J. Pharm. and Exp. Therap.*, 1950, v99, 38.

5. Gordan, G. S., Eisenberg, E., Moon, H. D., and Sakamoto, W., *J. Clin. Endocrinol.*, in press.