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Protecting Action of Chemicals Related to Procaine on Ventricular Fibrillation During Cyclopropane Anesthesia.

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In a previous presentation[1] it was reported that procaine reduced the incidence of ventricular fibrillation following the intravenous injection of small doses of epinephrine into dogs during cyclopropane anesthesia. Since the injection of procaine solution into the circulation of man is frequently followed by untoward reactions, it seemed desirable to investigate the action of less toxic substances of the same chemical group. Para-amino benzoic acid, Paramon* and sodium para-amino benzoate were the drugs studied.

Fifty experiments were performed on 21 dogs. Preanesthetic medication, morphine sulphate one mg per kilo and scopolamine hydrobromide 0.04 mg per kilo was injected subcutaneously one hour before each experiment. The carbon dioxide absorption technic was utilized for cyclopropane anesthesia. An unobstructed airway was assured by an endotracheal tube fitted with an inflatable cuff. Depth of anesthesia was maintained at second plane as evidenced by the loss of the lid reflex and maintenance of intercostal activity. Electrocardiograms (lead II) were taken before, during and after drug administration.

The test injection of epinephine was 0.01 mg per kilo in 5 cc of normal saline, given intravenously at the rate of 1 cc per 10 seconds. Para-amino benzoic acid and Paramon were administered intravenously at the dose of 5 to 10 mg per kilo in 20 cc of normal saline injected at the rate of 5 cc in 10 seconds. Sodium p-amino benzoate was administered at the dose of 10 to 40 mg per kilo in 5 cc of normal saline at the rate of 1 cc in 10 seconds.

The effects of p-amino benzoic acid were studied in 13 experiments on 5 dogs. Administration of this drug during cyclopropane anesthesia prior to the injection of epinephrine showed a protecting action against the production of cardiac irregularities. When it

1 Burstein, Charles L., and Marangoni, Bruno A., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 210.

* Paramon is the calcium double salt of benzyl succinic and p-amino benzoic acids prepared and supplied by the Seydel Chemical Company.

was omitted, 4 out of 5 dogs died following ventricular fibrillation when epinephrine was injected during second plane cyclopropane anesthesia. Two test doses of epinephrine had been used in 2 of the cases and only one test dose in the other 2. All 4 of these animals had recovered from previous experiments in which they had been treated with p-amino benzoic acid prior to the injection of the same doses of epinephrine. In the animals that survived the administration of epinephrine alone, the cardiac irregularities were more severe than when the epinephrine injection was preceded by p-amino benzoic acid. One animal in this group developed ventricular fibrillation following the injection of one test dose of epinephrine preceded by p-amino benzoic acid. This animal, however, showed such marked emotional agitation prior to being anesthetized as to suggest the possibility of excess epinephrine secretion being an additive factor to the epinephrine administration.

The action of Paramon was studied in 21 experiments on 9 dogs. The results were similar to those obtained with p-amino benzoic acid. Noteworthy is the fact that when ventricular fibrillation developed in 2 of the animals following the injection of epinephrine alone, the intracardiac injection of 100 mg of procaine in 5 cc saline caused a change from ventricular fibrillation to auricular tachycardia and finally full recovery to sinus rhythm. Subsequently, the intracardiac injection of Paramon under the same conditions in the same animals was ineffective.

Sodium p-amino benzoate which is more soluble than the other 2 drugs permitted the use of larger quantities in less volume of solution. Doses of 10 to 40 mg per kilo were used and found to have effects similar to those of the other 2 dogs. Sixteen experiments on 7 dogs were performed with this drug. Five of the animals showed complete absence of cardiac irregularities when sodium p-amino benzoate was injected before one test dose of epinephrine whereas omission of sodium p-amino-benzoate resulted in ventricular fibrillation in 3 of the animals and ventricular tachycardia in the other 2. The remaining animals showed a few ventricular premature systoles when sodium p-amino benzoate was employed prior to epinephrine in contrast to the development of ventricular tachycardia in one case and ventricular fibrillation in the other when epinephrine alone was administered. In this group also, 2 of the animals that developed ventricular fibrillation were successfully treated by the intracardiac injection of procaine but succumbed when sodium p-amino benzoate was employed at the time of fibrillation.

Conclusions. The administration of p-amino benzoic acid, the calcium double salt of benzyl succinic and p-amino benzoic acids, or sodium p-amino benzoate prior to a test dose of epinephrine during cyclopropane anesthesia reduced the incidence of ventricular fibrillation. The intracardiac injection of procaine at the time when ventricular fibrillation developed effected a return to normal in a number of cases. Ventricular fibrillation was not ameliorated by the intracardiac injection of the other three p-amino benzoic acid derivatives.

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Anti-Catalase Activity of Sulfanilamide and Related Compounds. VI. Further Studies on Sulfonhydroxamides.

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In previous studies on the anti-enzymatic concept of the mode of action of sulfanilamide,[1-4] attention has been focused on catalase as one of the enzymes of importance. A time factor was postulated for the conversion of the inactive sulfanilamide to an active anti-catalase, which was presumed to result through oxidation to the hydroxylamino derivative. This furnishes an explanation of the characteristic lag period preliminary to the bacteriostatic action of sulfanilamide. It was therefore expected that p-hydroxylamino sulfanilamide, or a similar substance, would exert a bacteriostatic effect without this period of lag and that in addition the action would be more intensive. The sulfonhydroxamides contain a hydroxylamino group which, although located differently in the molecule, contributes anti-catalase activity. Hence they might

[1] Main, E. R., Shinn, L. E., and Mellon, R. R., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 272.

[2] Shinn, L. E., Main, E. R., and Mellon, R. R., PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 591.

[3] Main, E. R., Shinn, L. E., and Mellon, R. R., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 115.

[4] Mellon, R. R., Locke, A. P., and Shinn, L. E., *Publication No.* 11, *A. A. A. S.*, 1939, pp. 98-113.