16584

Production of Positive Inotropism in the Dog Heart by Some Constituent of Intocostrin.*

CARL W. FISHER AND LESLIE L. BENNETT.

From the Division of Physiology, the Institute of Experimental Biology, and the Subdivision of Anesthesiology, University of California, Berkeley and San Francisco.

Recent clinical and laboratory work in connection with curare as an adjuvant to anesthesia has disclosed little significant action of this drug on the myocardium. Older experimental work is rather inconclusive because of the impure preparations used. Carlson[1] reported that in the Limulus heart curare produces an inhibtory effect by acting on the heart ganglion but that it does not affect the heart muscle or the intrinsic motor nerve fibers. Jullien[2] found a negative inotropic effect on the oyster heart. Hauschild[3] stated that curin has a negative inotropic, chronotropic, and dromotropic effect on the frog heart, but Tillie[4] described the action of curin on the frog heart as being like that of veratrin or glucosides of the digitalis group. It is the purpose of this paper to report the effects produced by certain curare preparations in the isolated dog heart.

Method. The dog heart-lung preparation was used in these studies and was arranged for the recording of right atrial pressure, aortic pressure, pulmonary arterial pressure, and cardiac output.† Ventricular volume was recorded mechanically upon smoked kymograph paper by means of a Henderson cardiometer and a piston-type volume recorder. No alterations were made in venous return or the peripheral resistance during the course of an observation, and the curare preparations were introduced directly into the venous return.

Two curare preparations were used: *d*-tubocurarine chloride (Squibb) and a less highly purified curare preparation, Intocostrin (Squibb). It should be noted that according to the manufacturer, 50% of Intocostrin is *d*-tubocurarine and that the *d*-tubocurarine content accounts for all of its paralytic activity. The remainder of the Intocostrin is unidentified residue from *Chondodendron tomentosum.*

Results. Intocostrin was used 15 times in 10 different heart-lung preparations in amounts above 5 units and in every instance there was a prompt reduction in both systolic and diastolic heart size without a change in cardiac rate. In one case there was a slight fall in aortic pressure and cardiac output. When the effect was most marked there was a transient rise in aortic pressure associated with the momentary increase in cardiac output. The reduction in heart size was not permanent, the heart gradually returning to its normal volume. Maximal effects were obtained with about 20 units, larger amounts producing little additional effects. This effect was obtained both in fresh heart-lung preparations and in those in which some degree of heart failure was present, seeming to be more striking when failure was present.

The pure drug *d*-tubocurarine chloride was introduced at a comparable dose level 7 times in 5 different heart-lung preparations and in each instance it was without any effect upon the observed pressures, the cardiac output, the cardiac rate, or the heart size, except in one case in which it produced a slight increase in heart size. The preservative, cholorobutanol, was used in amounts identical with those amounts present in the Intocostrin solution, and it likewise was without effect. In Fig. 1

* Aided by grants from the Research Board of the University of California.

1 Carlson, A. J., *J. Gen. Physiol.*, 1894, **34**, 147.

2 Jullien, A., *C. R. Soc. de Biol.*, 1936, **121**, 1002.

3 Hauschild, F., *Arch. f. exp. Path. u. Pharmakol.*, 1934, **174**, 742.

4 Tillie, J., *Arch. f. exp. Path. u. Pharmakol.*, 1890, **27**, 1.

† The experimental procedure used is described in greater detail elsewhere (*J. Pharm. and Exp. Therap.*, in press).

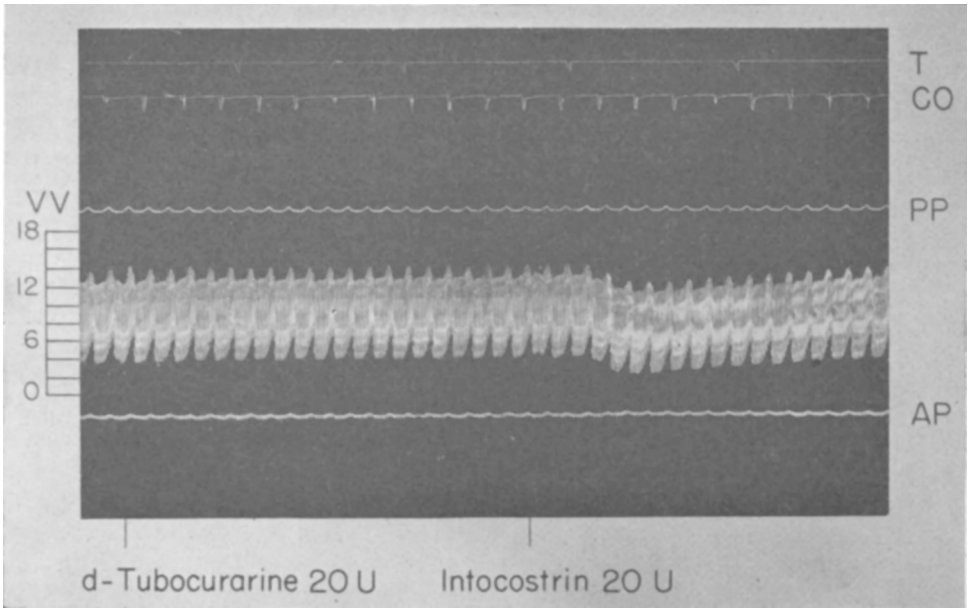

FIG. 1.

T, time in minutes; CO, cardiac output; PP, pulmonary arterial pressure; AP, aortic pressure; VV, ventricular volume change calibrated in cc; diastolic size is indicated by the upper part of the stroke, systolic size by the lower.

TABLE I.

Effect of Curare upon Aortic Pressure, Cardiac, Output, and Ventricular Volume of the Dog Heart-lung Preparation.

Curare preparation used and dose	Effect on aortic pressure	Effect on cardiac output	Effect on ventricular volume
d-T* 5μ	None	None	None
d-T 20μ (5 experiments)	"	"	"
d-T 20μ	"	"	½ cc increase
Int.† 5μ (2 experiments)	"	"	None
Int. 20μ (2 experiments)	"	"	1½ cc decrease each
Int. 20μ (2 experiments)	"	"	2 " " "
Int. 20μ (2 experiments)	"	"	3 " " "
Int. 20μ	"	"	4 " "
Int. 20μ (2 experiments)	Transient rise of 4-6 mm of Hg.	"	4 " " each
Int. 20μ	Transient rise of 10 mm of Hg.	Transient rise‡	10 " "
Int. 10μ§	None	None	1½ " "
1 min later 10μ	"	"	½ " "
1 min later 80μ	Transient fall of 6 mm of Hg.	Transient fall‡	3 " "
4 min later 100μ	Transient rise of 4 mm of Hg.	Not determined	5 " "
3 min later 100μ	None	" "	1 " "

* *d*-tubocurarine chloride.

† Intocostrin.

‡ Because of the nature of the recording apparatus, transient changes could not be quantitated.

§ All subsequent administrations were to the same heart-lung preparation at time intervals as indicated. After the 80μ dose and subsequently, there was partial recovery before the next administration.

is shown a representative kymograph tracing from the series of experiments illustrating the contrast between the two preparations. In Table I is presented a summary of the several experiments.

The average apnic dose for a dog is approximately 20 μ while 200 μ will produce apnea in about 80% of normal humans. Thus, the dose levels of Intocostrin producing significant effects in the dog heart-lung preparation are, in terms of units per mass of tissue, considerably in excess of the amounts required for the desired paralyzing action in intact animals or man.

Conclusion. A highly purified curare preparation (Intocostrin) produces a positive inotropic effect in the isolated dog heart. This effect is not due to the *d*-tubocurarine content of the preparation or to the preservative and, therefore, must be due to some unidentified component.

16585

Antibiotic Studies on Beta Hemolytic Streptococci.* V. Streptomycin Resistance Acquired by Group A, B, and C Organisms.†

HORACE M. GEZON AND ELIZABETH E. CRYST. (Introduced by C. Phillip Miller.)

From the Department of Pediatrics, University of Chicago, Chicago, Ill.

The development of *in vitro* resistance to streptomycin has been reported for a number of organisms including staphylococci, meningococci, gram negative enteric bacilli, chromogenic bacteria, Klebsiella, and *Hemophilus influenzae*. Miller and Bohnhoff,[1] for example, demonstrated approximately a 2000 fold rise in resistance in four strains of gonococcus and nine of meningococcus after 4 to 6 daily transfers on streptomycin medium. Seligmann and Wassermann[2] described a 50,000 fold increase in streptomycin resistance by a strain of *Staphylococcus aureus* after 7 transfers on antibiotic medium and a change in excess of 50,000-fold in one strain of *B. prodigiosus* after 9 transfers.

Resistance by streptococci has not been thoroughly studied. In a group A, type 14 organism reported by Chandler and Schoenbach,[3] a 5-fold rise in resistance after 6 daily transfers on streptomycin medium was observed. No other reference to streptomycin resistance of beta hemolytic streptococci has been found.

The present study compares the rate at which resistance develops among strains of Lancefield group A, B, and C streptococci. In addition we have attempted to compare the hemolytic, antigenic and virulence behavior of streptomycin resistant strains with that of penicillin resistant strains described in preceding communications.[4,5,6]

The streptomycin sensitivity range in our laboratory[7] for recently isolated strains of beta hemolytic streptococci has been found to be 10 to 50 μg/ml for 275 strains of group A, 30 to 400 μg/ml for 20 strains of group B, and 10 to 50 μg/ml for 47 strains of group C

* These studies were partially supported by the Fenger Memorial Fund of the University of Chicago.

† This report was presented in part at the meeting of the American Association for the Advancement of Science in Chicago, December 30, 1947.

1 Miller, C. P., and Bohnhoff, M., *J. Am. Med. Assn.*, 1946, **130**, 485.

2 Seligman, E., and Wassermann, M., *J. Immunol.*, 1947, **57**, 351.

3 Chandler, C. A., and Schoenbach, E. B., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 208.

4 Gezon, H. M., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 208.

5 Gezon, H. M., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 212.

6 Gezon, H. M., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 215.

7 Unpublished data.