8. Campbell, P. M., Stove, N. E., *Biochem. J.*, 1957, v66, 19.

9. Straub, W., *J. Clin. Invest.*, 1962, v42, 130.

10. Pool, J. G., Robinson, J., *Am. J. Physiol.*, 1959, v196, 423.

11. Barnhart, M. I., *ibid.*, 1960, v199, 360.

12. Aydin, A., Sokal, J. E., *Am. J. Physiol.*, 1963, v205, 667.

13. Owren, P. A., Aas, K., *Scand. J. Clin. and Lab. Invest.*, 1951, v3, 201.

14. Stormorken, H., *ibid.*, 1957, v9, 273.

15. Biggs, R. G., Douglas, A. S., *J. Clin. Path.*, 1953, v6, 23.

16. Ambrus, J. L., Ambrus, C. M., Back, N., Sokal, J. E., Collins, G. L., *Ann. N. Y. Acad. Sci.*, 1957, v68, 97.

17. Ambrus, J. L., Ambrus, G. M., Sokal, J. E., Markus, G., Back, N., Stutzman, L., Razis, D., Ross, C. A., Smith, B. H., Rekate, A. C., Collins, G. L., Kline, D. L., Fishman, J. B., *Am. J. Cardiol.*, 1960, v6, 462.

18. Ambrus, J. L., Ambrus, C. M., Sokal, J. E., Back, N., Metzger, R. S., A Progress Report in *Anticoagulants and Fibrinolysins*, Lea & Febiger, Philadelphia, 1961, 413.

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Conversion of Acetyl Strophanthidin-induced Ventricular Tachycardia to Sinus Rhythm by Isopropyl Methoxamine.* (29162)

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Digitalis toxicity is manifested by a multiplicity of changes in the electrocardiogram, usually terminating in ventricular tachycardia and ventricular fibrillation. Clinically, such drugs as quinidine, procaine amide and potassium are used to treat ventricular arrhythmias caused by digitalis but these drugs are not always effective and many times prove dangerous in themselves. Thus, the search continues for other drugs to treat digitalis toxicity. This paper is a report of the drug isopropyl methoxamine, found to be effective in the conversion of acetyl strophanthidin-induced ventricular tachycardia to sinus rhythm.

Acetyl strophanthidin,† a synthetic ester of the aglycone strophanthidin, was chosen because of its very rapid action. Pharmacologic and clinical studies have revealed that acetyl strophanthidin produced essentially the same effects as those of digitalis glycosides(1-4).

Methods. Mongrel dogs weighing between 8 and 12 kg were anesthetized with 30-35 mg/kg pentobarbital sodium intravenously or intraperitoneally. They were intubated with a cuffed Portex endotracheal tube under direct vision and ventilated with 100% oxygen at a tidal volume of 250 ml and at a rate which varied from 12 to 20 per minute with a Harvard respirator pump, depending upon the minute volume required to maintain controlled respiration. Arterial blood pressure, electrocardiogram, lead 2, and a right atrial lead were monitored continuously at a paper speed of 25 mm/min. At intervals, short runs of 25 mm/sec were taken in order to interpret the electrocardiogram properly. Acetyl strophanthidin was infused at a constant rate of 6 μg/kg/min in 9 dogs. Within 8 minutes of the onset of ventricular-initiated beats, isopropyl methoxamine‡ was injected intravenously at various dose levels. In all experiments the acetyl strophanthidin was infused until death of the animal occurred as evidenced by absence of blood pressure. In 4 experiments blood samples were taken for analysis of serum potassium.

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† Acetyl strophanthidin was kindly supplied by Eli Lilly Co., Indianapolis, Ind.

‡ BW 61-43 or *dl*-erythro-α-(2,5-dimethoxyphenyl)-β-isopropylaminopropanol hydrochloride kindly supplied by Burroughs Wellcome & Co., Tuckahoe, N. Y.

TABLE I. Effects of Isopropyl Methoxamine, Administered After Initiation of Ventricular Tachycardia by Infusion of Acetyl Strophanthidin, 6 μg/kg/min., in Dogs.

Before infusion	After infusion		After isopropyl methoxamine			
Dog No.	Heart rate (beats/min.)	Max. sinus bradycardia (beats/min.)	V.T. (beats/min.)	Dose of isopropyl methoxamine (mg/kg)	Sinus rate after conversion (beats/min.)	Terminal event	Survival time (min.)
A-I-F-13	210	120	215	2	110 (2)*	VF	30
2	120	80	175	4	155 (4)	VF	64
4	130	115	190	6	80 (10)	VF	55
11	190	140	210	6	140 (15)	VF	50
8	180	75	240	8	115 (8)	VF	50
9	195	155	180	9	130 (13)	VF	62
14	125	120	195	10	90 (4)	VF	65
1	155	100	195	12	120 (13)	Asystole	30
15	150	125	170	12	90 (13)	VF	58
Mean	162	114	197		114 (9)		52

* Figures in parentheses represent duration of sinus rhythm in min.

Results. The control sinus rate prior to infusion of acetyl strophanthidin averaged 162 beats per minute (Table I). After the infusion of acetyl strophanthidin, the following sequence of events occurred: 1) a slowing of the heart rate to a mean of 114 beats per minute, 2) a shift in the pacemaker site from the S-A node to a ventricular site as evidenced by the presence of fusion beats, capture and prolongation of the Q R S complex. This occurred after an average of 14 minutes (range 8-18 minutes) from the start of the infusion and was characterized by a rapid rate of firing which reached a mean maximum of 197 beats per minute. Two to eight minutes after onset of this ventricular rhythm, isopropyl methoxamine was administered intravenously at dose levels ranging from 2 to 12 mg/kg body weight (Table I). This resulted in an immediate conversion to sinus rhythm in all dogs, which lasted from 2 to 15 minutes. Six of these dogs then reverted back to a ventricular-initiated rhythm and developed ventricular fibrillation (A-I-F-2, 8, 11, 13, 14, 15). One had a very slow sinus rate of 15 to 20 per minute, then developed nodal rhythm, then ventricular rhythm and finally ventricular fibrillation (A-I-F-4, Fig. 1. Isopropyl methoxamine administered at time 21). A-I-F-9 developed complete heart

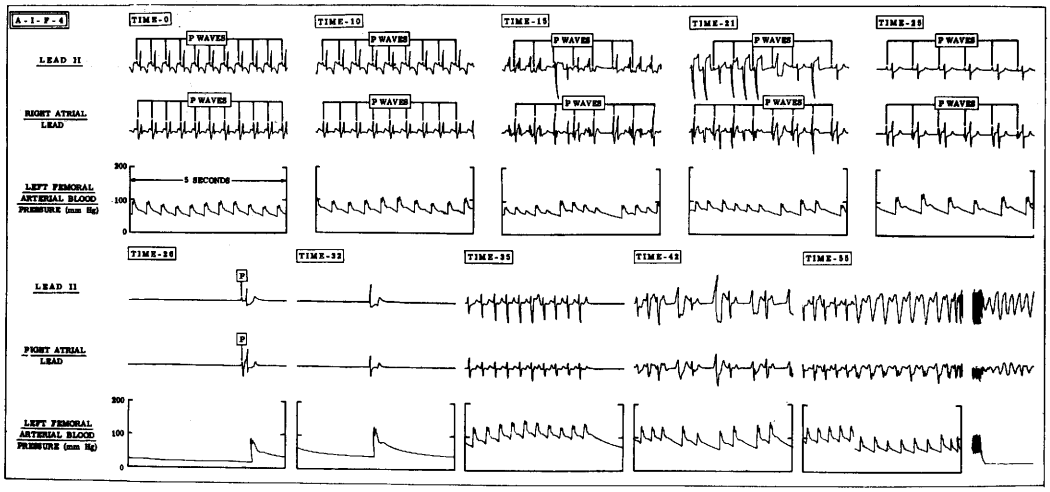

FIG. 1. Infusion of acetyl strophanthidin 6 μg/kg/min I. V. until death of dog. Isopropyl methoxamine 6 mg/kg administered I. V. 21 min after start of infusion.

block, nodal rhythm, ventricular rhythm and finally ventricular fibrillation. In A-I-F-1 complete heart block was the terminal event as evidenced by the presence of P waves and absence of Q R S complexes. Ventricular fibrillation did not occur in this dog. Mean survival time in this group of 9 dogs was 52 minutes, in sharp contrast to a mean survival time of 34 minutes found in 15 dogs under the same conditions except for omission of the isopropyl methoxamine(5). All 15 of the untreated dogs developed ventricular tachycardia and ventricular fibrillation as the terminal event.

The mean serum potassium value before infusion of acetyl strophanthidin was 3.65 meq/l. Twenty-five to 30 minutes after infusion, the mean value rose to 5.08 meq/l. This rise in serum potassium is characteristic of acute digitalis intoxication.

Discussion. Administration of 2 to 12 mg/kg isopropyl methoxamine during ventricular tachycardia, induced by acetyl strophanthidin, has resulted in conversion to sinus rhythym in all 9 dogs. The mechanism of this conversion is not understood although evidence has been obtained which indicates that the sympathetic nervous system may be involved in the production of ventricular-initiated beats after infusion of acetyl strophanthidin(5). This evidence consists mainly of the fact that conversion of acetyl strophanthidin-induced ventricular tachycardia to sinus rhythym can be accomplished by total epidural blockade with lidocaine, a procedure which suppresses sympathetic innervation of the heart.

Isopropyl methoxamine has been shown to be capable of blocking some actions of the adrenergic mediators such as the epinephrine-induced positive inotropic response in turtle and rabbit heart(6) and the norepinephrine-induced rise in plasma free fatty acids, glucose and liver triglycerides(7) but was not able to block the norepinephrine-induced rise in arterial blood pressure and rise in heart triglycerides(7).

Whether isopropyl methoxamine acts by inhibition of the sympathetic innervation of the heart, perhaps by preventing access of catecholamines to their receptor sites as with adrenergic blocking agents, or whether it acts by a direct action on the ectopic ventricular pacemaker is at present not known.

Summary. Acetyl strophanthidin was infused intravenously into 9 dogs at a constant rate of 6 μg/kg/min until death occurred. After the establishment of ventricular tachycardia, isopropyl methoxamine was administered intravenously at dose levels ranging from 2-12 mg/kg. This resulted in temporary conversion to sinus rhythm in all cases.

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1. Chen, K. K., Elderfield, R. C., *J. Pharm. & Exp. Therap.,* 1942, v76, 81.

2. Greiner, T., Reilly, J., PROC. SOC. EXP. BIOL. AND MED., 1952, v81, 141.

3. Root, M. A., Chen, K. K., *ibid.,* 1953, v84, 131.

4. Gold, H., Otto, H. L., Modell, W., Halpern, S. L., *J. Pharm. & Exp. Therap.,* 1946, v86, 301.

5. Wilson, D., Paradise, R. R., Stoelting, V. K., *Anesth. and Analg.,* 1964, in press.

6. Meester, W. D., Hardman, H. F., Barboriak, J. J., *Pharmacologist,* 1963 v5, 249.

7. Maling, H. M., Williams, M. A., Highman, B., Garbus, J., Hunter, J., *ibid.,* 1963, v5, 257.

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