EFFECTS OF PROCAINE AMIDE ON CARDIAC IRREGULARITIES DURING CYCLOPROPANE ANESTHESIA * † ‡

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CARDIAC irregularities of ventricular origin are frequently present during the clinical administration of cyclopropane. This possible occurrence of ventricular ecoptic beats or ventricular tachycardia is viewed with serious alarm by many anesthetists because such irregularities are thought occasionally to be the precursor of fatal ventricular fibrillation. Although actual foundation for this fear seems to be of a circumstantial nature only, conservative attitudes have limited the use of this agent. Many anesthetists would use it more freely if during administration of cyclopropane cardiac irregularities could be minimized or eliminated completely. There has been, therefore, much interest among anesthetists and pharmacologists in finding a way to prevent or treat these abnormalities of the cardiac conduction system. Many drugs have been studied in the laboratory for their effects in preventing the cyclopropane-epinephrine-induced arrhythmias (1, 2, 3). The results of some of these investigations have been sufficiently encouraging so that clinical studies were made with some of these drugs as protective agents (4, 5).

Procaine amide (pronestyl-Squibb)§ has been reported to be capable of protecting against epinephrine-induced ventricular tachycardia during cyclopropane anesthesia in dogs (6). This drug also has been recommended for the prevention and treatment of cardiac irregularities of ventricular origin during clinical anesthesia. In this paper the results of the use of this drug in both clinical and laboratory studies will be reported.

LABORATORY STUDY

Twenty-five experiments were made on 13 healthy, unpremedicated mongrel dogs ranging in weight from 7 to 20 kg. Cyclopropane in

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§ Supplies of procaine amide (pronestyl-Squibb) used in this study were kindly supplied by E. R. Squibb and Sons.

TABLE 1

ADMINISTRATION OF EPINEPHRINE IN CONSCIOUS ANIMALS BEFORE AND AFTER ADMINISTRATION OF PROCAINE AMIDE

Dog No.	Control Epinephrine, mg.	Irregularity Produced	Procaine Amide, mg. (total)	Subsequent Epinephrine, mg.	Irregularity Produced
1	0.01	V.T.* (60 sec.)	100	after 15 min. 0.01	V.T. (20 sec.)
2	0.02	V.T. Burst	200	after 16 min. 0.02	BBB** and V.R.†
2	0.02	V.T. Burst	1000.0 slowly over 40 min.	after 15 min. 0.02	V.T. Burst
3	0.01	V.T. (25 sec.)	200	after 5 min. 0.01	V.T. (20 sec.)
3	0.01	V.T. (25 sec.)	200	after 15 min. 0.01	V.T. (40 sec.)

* Ventricular tachycardia.
** Bundle branch block.
† Ventricular rhythm.

an oxygen atmosphere was the only anesthetic agent used in this series. Unanesthetized dogs also were tested. Anesthesia was induced and maintained by a closed to-and-fro absorption system and an endotracheal catheter was used to provide a free airway. Third plane anesthesia was maintained for thirty minutes before using the trial drugs in order that approximate equilibration at that level might be achieved. Adequate ventilation was carefully maintained throughout. Epinephrine was administered according to a standard technic (7). With a direct writing electrocardiograph, control records of the three stand-

TABLE 2

EFFECT OF PROCAINE AMIDE ON EPINEPHRINE-CYCLOPROPANE VENTRICULAR TACHYCARDIA IN DOGS

Dog No.	Control Adrenalin		Procaine Amide	Adrenalin		Procaine Amide	Adrenalin		Protection
	mg/Kg	Result	Total Dose gm.	mg/Kg	Result	Total Dose gm.	mg/Kg	Result	
1(9.4K)	Time* 0 / 0.0125	+31 V.T. (burst)	+42 0.3	+53 0.0125	V.T. 65 sec.	-	-	-	0
4(10.0K)	0 / 0.01	+30 V.T. 60 sec.	+37 0.1	+50 0.01	V.T. 70 sec.	+57 0.2	+79 0.01	VT-VF died	0
5(7.8K)	0 / 0.01	+35 V.T. 25 sec.	+50 0.2	+63 0.01	AVB PVC	-	-	-	+?
6(7.0K)	0 / 0.01	+30 V.T 25 sec.	+43 0.3	+57 0.01	V.T. 60 sec.	-	-	-	0
7(10.4K)	0 / 0.01	+30 V.T. 70 sec.	+42 0.3	+60 0.01	VT-VF	Defibrillated by direct electric shock Survival 30 hours			0
8(16.8K)	0 / 0.01	+43 V.T. 85 sec.	+61 0.3	+76 0.01	V.T. 75sec.	-	+89 0.01	V.T. 60 sec.	0
9(19.8K)	0 / 0.01	+30 V.T. 120 sec.	+38 0.3	+50 0.01	V.T. 70 sec.	+64 0.3	+84 0.01	V.T. 120 sec.	0
10(16.0K)	0 / 0.02	+60 V.T 50 sec.	+67 1.0	+74 0.02	V.T. 150 sec.	-	+94 0.02	V.T 70 sec.	0

*0= Time of induction with Cyclopropane
Other time figures represent elapsed time after induction

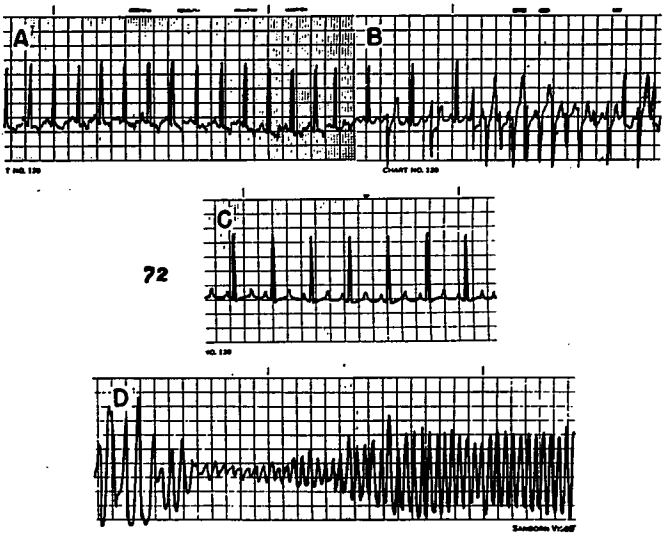

FIG. 1. Effect of procaine amide on epinephrine-cyclopropane-induced ventricular tachycardia in a dog weighing 10.4 kg. A. Sinus rhythm after induction with cyclopropane. B. Ventricular tachycardia thirty seconds after beginning injection of epinephrine, 0.01 mg. per kilogram of body weight. C. Sinus rhythm thirty minutes later and fifteen minutes after administration of 300 mg. of procaine amide. D. Two minutes later, after again injecting epinephrine, 0.01 mg. per kilogram, ventricular tachycardia is rapidly followed by ventricular fibrillation.

TABLE 3

EFFECT OF EPINEPHRINE DURING CYCLOPROPANE ANESTHESIA IN DOGS WHICH RECEIVED INTRAVENOUS PROCAINE AMIDE FIFTEEN TO THIRTY MINUTES BEFORE INDUCTION OF ANESTHESIA

Dog. No.	Control Epinephrine, mg./kg. body wt.	Irregularities Produced	Procaine Amide gm.	Epinephrine, mg./kg. body wt. 30 min. after Induction with Cyclopropane	Irregularities Produced
8	0.01	V.T.† (85 sec.)	1.0	0.01	V.T.—V.F.*
1	0.01	V.T.(60 sec.)	1.0	0.005	V.T. (150 sec.)
5	0.0125	V.T. (25 sec.)	1.0	0.0075	V.T. (40 sec.)
6	0.01	V.T. (25 sec.)	1.0	0.005	V.T. (120 sec.)

† Ventricular tachycardia.
* Ventricular fibrillation.

ard leads were taken at the beginning of each experiment and frequent records were taken from lead II at suitable intervals while observation of the deflection of the stylus was continued throughout.

From a large series of dogs in which epinephrine-induced arrhythmia had previously been studied, 3 animals were found in which the intravenous injection of small doses of epinephrine (10 to 20 gamma per kilogram of body weight) in the conscious animal regularly

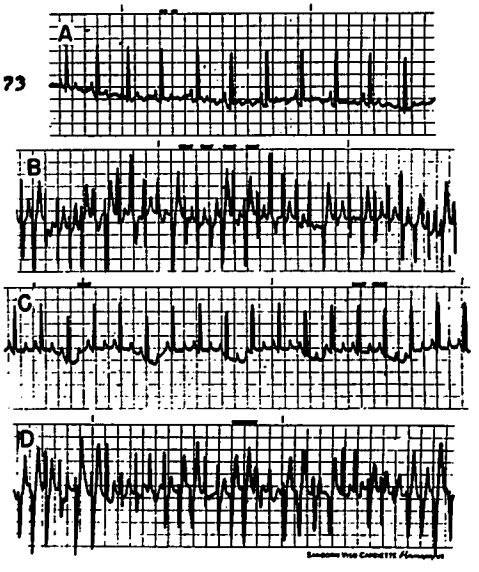

FIG. 2. Effect of procaine amide on epinephrine-cyclopropane-induced ventricular tachycardia in a dog weighing 16.8 kg. A. Sinus rhythm in standard lead II. B. After thirty minutes of cyclopropane anesthesia, epinephrine, 0.01 mg. per kilogram, produced ventricular tachycardia. C. Sinus rhythm after 300 mg. of procaine amide. D. Fifteen minutes after intravenous administration of procaine amide, injection of epinephrine, 0.01 mg. per kilogram again produced ventricular tachycardia.

produced ventricular tachycardia. These animals were given a control injection of epinephrine sufficient to produce ventricular tachycardia. Procaine amide was injected approximately ten minutes after the control dose of epinephrine. After administration of procaine amide, the same individually standardized dose of epinephrine was again injected and electrocardiographic observations made. Ventricular tachycardia appeared with the same frequency as in the control group. The results of five experiments are shown in table 1.

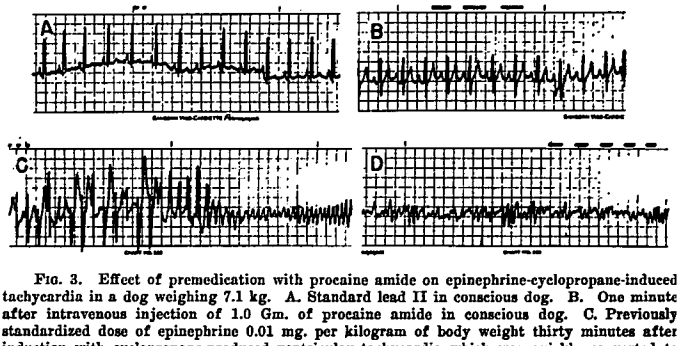

FIG. 3. Effect of premedication with procaine amide on epinephrine-cyclopropane-induced tachycardia in a dog weighing 7.1 kg. A. Standard lead II in conscious dog. B. One minute after intravenous injection of 1.0 Gm. of procaine amide in conscious dog. C. Previously standardized dose of epinephrine 0.01 mg. per kilogram of body weight thirty minutes after induction with cyclopropane-produced ventricular tachycardia which was quickly converted to ventricular fibrillation. D. Ventricular fibrillation.

Eight animals were anesthetized with cyclopropane and, after equilibration was achieved, the amount of epinephrine which would regularly produce ventricular tachycardia was determined for each dog. Procaine amide was then given intravenously in dosages of from 10 to 60 mg. per kilogram of body weight. The maximal total dose was 1.0 Gm. Subsequently, injections of the individually standardized

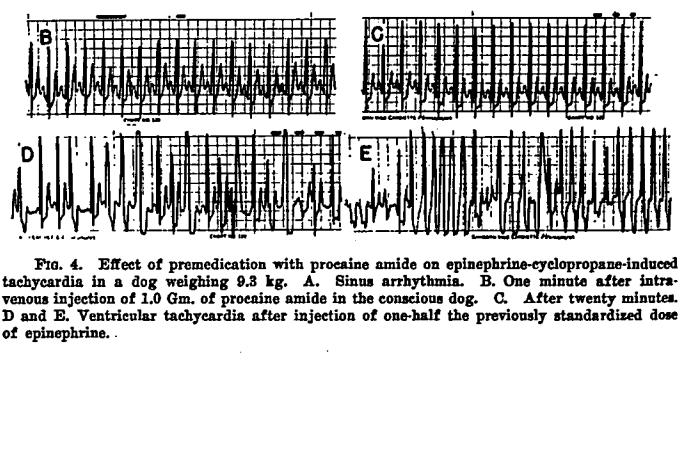

FIG. 4. Effect of premedication with procaine amide on epinephrine-cyclopropane-induced tachycardia in a dog weighing 9.3 kg. A. Sinus arrhythmia. B. One minute after intravenous injection of 1.0 Gm. of procaine amide in the conscious dog. C. After twenty minutes. D and E. Ventricular tachycardia after injection of one-half the previously standardized dose of epinephrine.

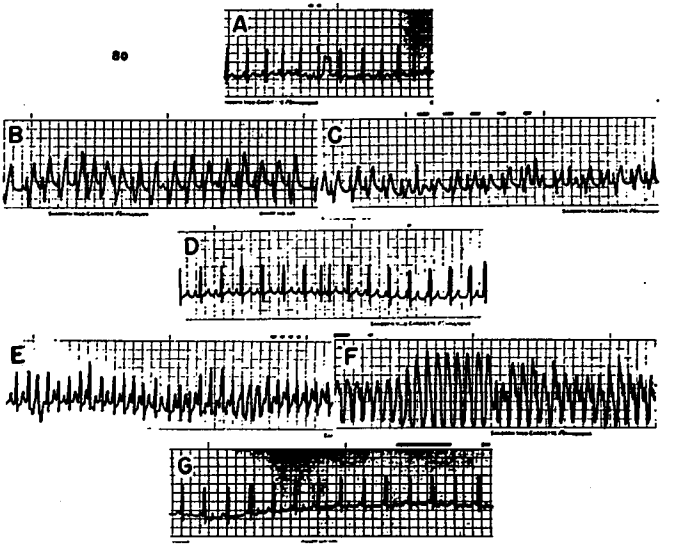

FIG. 5. Effect of premedication with procaine amide on epinephrine-cyclopropane-induced tachycardia in a dog weighing 7.1 kg. A. Standard lead II in normal conscious dog. B and C. Ventricular irregularities after slow, intravenous injection of 1.0 Gm. of procaine amide in a conscious dog. D. Standard lead II thirty minutes after induction of cyclopropane anesthesia. E and F. Ventricular tachycardia caused by injection of epinephrine, 0.005 Gm. per kilogram which is half the previously standardized dose. G. Return of sinus rhythm.

TABLE 4

COMPARISON OF CARDIAC IRREGULARITIES OBSERVED IN PATIENTS DURING CYCLOPROPANE ANESTHESIA SOME OF WHOM RECEIVED PROCAINE AMIDE

		Procaine Amide Administered			
	Control Group	Oral (1.0 gm.)	Oral (1.0 gm.) and I.V. (1.0 gm.)	I.V. (0.3 gm.)	Total
Total No. Patients	19	16	8	8	(24)
No. Irregularities	7	-	-	1	1
Sinus Tachycardia	-	-	-	1	1
Sinus Bradycardia	4	7	-	2	9
SA EXS	1	2	-	1	3
AVR	5	5	4	3	11
AVB	1	-	-	-	0
AVEXS	2	2	1	2	4
(VEXS) PVC	8	9	3	5	14
VR	-	1	1	-	2
VT	3	2	2	1	4

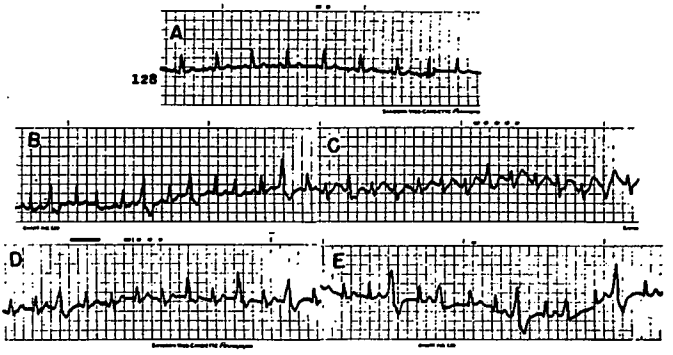

FIG. 6. A. Standard lead II in a woman aged 47 years after oral premedication with 1.0 Gm. of procaine amide. B. Occurrence of ventricular irregularities half an hour after induction with cyclopropane. C. One minute after intravenous injection of 1.0 Gm. of procaine amide. D. Five minutes later. E. Thirty-five minutes later premature ventricular beats still present.

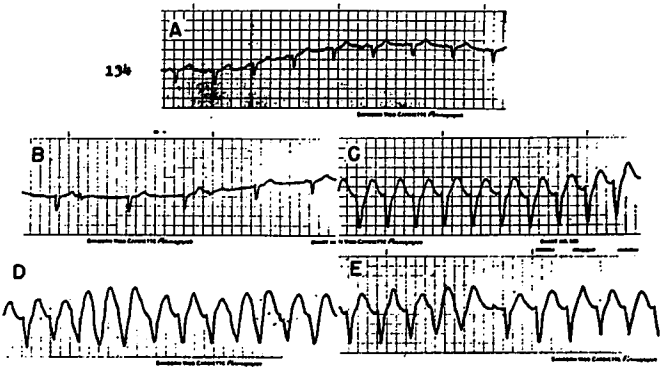

FIG. 7. A. Standard lead II in a woman aged 19 years after premedication with 1.0 Gm. of procaine amide orally. Right bundle branch block which existed before anesthesia. B. Premature ventricular contractions observed fifteen minutes after administration of cyclopropane. C, D and E. Effect observed after intravenous injection of 1.0 Gm. of procaine amide.

dose of epinephrine were made. Seven of the 8 animals exhibited ventricular tachycardia and 2 died of ventricular fibrillation (figs. 1 and 2). The results are shown in table 2.

In four additional experiments 1 Gm. of procaine amide (dose of

60 to 140 mg. per kilogram of body weight) was given intravenously as preanesthetic medication fifteen to thirty minutes before induction. This amount consistently produced retching or emesis in five to ten minutes. In all these dogs there was an apparently generalized sedative effect and it was thought that less cyclopropane was necessary to accomplish induction of anesthesia than had been required in the same dogs when they were not premedicated in this way. After in-

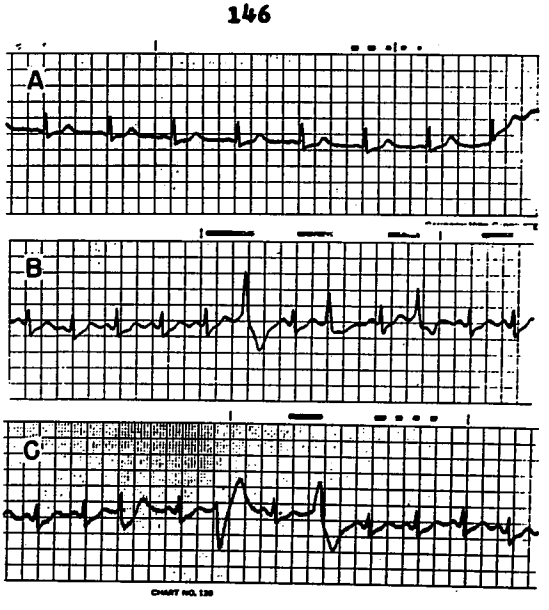

FIG. 8. A. Standard lead II in a woman aged 53 years who had been given procaine amide, 1.0 Gm. orally, for premedication. During first forty minutes of administration of cyclopropane no irregularities were observed. B. Three minutes after intravenous injection of an additional 0.3 Gm. of procaine amide, premature ventricular contractions occurred. C. One minute later.

jection of procaine amide the normal electrocardiographic complex showed a pronounced depression of the RS-T segment and an increased amplitude of the T wave. In the animals which received larger dosages, bundle branch block and ventricular tachycardia were observed after the injection. Equilibration in deep surgical anesthesia with cyclopropane was then achieved. In the first animal when the standard dose of epinephrine was injected ventricular tachycardia occurred

and was immediately converted to ventricular fibrillation (fig. 3). Therefore, in the other three experiments an injection was made containing 5 gamma less of epinephrine than the individually standardized dose which had been determined previously (figs. 4 and 5). In all three instances ventricular tachycardia occurred which was of longer duration than had been present following the control injections of larger amounts of epinephrine. These results are shown in table 3.

In six instances of ventricular fibrillation during cyclopropane anesthesia attempts were made to reverse the fibrillation by direct injection of procaine amide into the fibrillating heart during the period of artificial circulation. Defibrillation occurred after forty minutes of artificial circulation in one of these animals following the administration of 300 mg. of procaine amide. In another animal defibrillation was accomplished by direct application of electric shock after the use of procaine amide. Defibrillation did not occur in the other 4 animals.

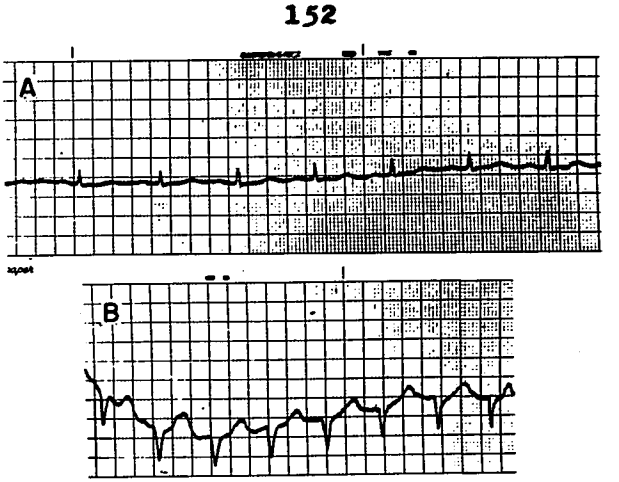

FIG. 9. A. Standard lead II during cyclopropane anesthesia in a woman aged 75 years. B. During the two and one-half hours of anesthesia no ventricular irregularities were observed. Procaine amide, 1.0 Gm. (total dose), was given in successive small doses during the last hour. Ten minutes after the last dose of procaine amide was given and while the patient was waking this ventricular rhythm was observed.

CLINICAL STUDY

Electrocardiographic tracings were taken on 43 gynecologic patients anesthetized with cyclopropane. Twenty-four of these 43 patients

were given procaine amide either as premedication orally (1.0 Gm. one hour before induction of anesthesia), or intravenously during anesthesia, or by a combination of both routes with a maximal dosage of 2.0 Gm. Those patients who received procaine amide orally were given scopolamine (0.2 or 0.3 mg.) in addition about one-half hour before induction of anesthesia. All other patients in this study received scopolamine or a morphine-scopolamine combination as preanesthetic medication. It was noted that many of the patients who received pro-

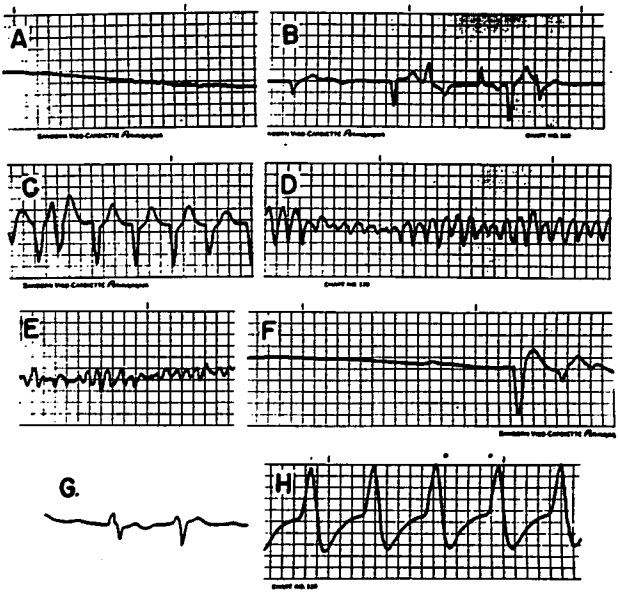

FIG. 10. A. Asystole recorded after cardiac arrest in 63-year-old woman. B and C. Bizarre rhythms observed during resuscitation efforts. D and E. Ventricular fibrillation. F, G and H. After 500 mg. of procaine amide was injected into the heart asystole occurred and was followed by ineffective ventricular rhythms.

caine amide orally seemed less alert and more lethargic than those who received scopolamine alone. It also seemed that possibly less cyclopropane than usual was required for induction and maintenance of anesthesia at an adequate level. The average age of the patients was about 60 years and the age distribution was similar in the control group to that of the group which was given procaine amide. The anesthetics were administered by various members of the resident staff.

The cardiac irregularities which were recorded are listed in table 4. Premature ventricular contractions occurred in 14 and ventricular tachycardia was observed in 14 of the 24 patients who received procaine amide. This incidence of ventricular irregularities is not significantly different from that of the control group. Representative electrocardiographic tracings from some of these cases are shown in figures 6, 7, 8 and 9.

Procaine amide was used in 2 clinical cases in which ventricular fibrillation had occurred during resuscitative efforts on anoxic hearts. In each instance after the injection of 0.5 Gm. of procaine amide, asystole occurred and was followed by slow ventricular rhythms. In neither instance did the patient survive, but the period of artificial circulation had been lengthy and inadequate in each. Electrocardiographic records from one of these cases are shown in figure 10. Procaine and direct electric shock were used in unsuccessful attempts at defibrillation during the thirty minutes before procaine amide was injected.

COMMENT

The results of the laboratory study consistently failed to show that any degree of protection against epinephrine-induced irregularities was provided by procaine amide. The 4 animals which were given large intravenous doses of this drug as preanesthetic medication actually seemed to show an increased sensitivity to epinephrine.

The incidence of spontaneous ventricular irregularities which occurred in patients who had received procaine amide was similar to that in the control group and to that which has been reported to occur during cyclopropane anesthesia (8). These clinical data were subjected to analysis by the method of chi-square which substantiated the impression gained from inspection that there was no significant decrease in incidence of ventricular arrhythmias in the group which received procaine amide as compared with the control group. No protection against ventricular tachycardia or premature ventricular contractions was provided by the use of procaine amide.

Attempts to cause defibrillation of the ventricles by the use of drugs, including procaine (9, 10) and procaine amide (11), have usually been described as unsuccessful. Fibrillation is encountered frequently as an additional difficulty during attempts at artificial circulation. Spontaneous reversal of this fibrillation is rare. Therefore, a drug which may possibly provide reversal of fibrillation may be of clinical value as part of the armamentarium of resuscitation.

SUMMARY

Procaine amide was studied to determine its effectiveness in preventing epinephrine-induced ventricular tachycardia in dogs during cyclopropane anesthesia. No protection was observed.

Spontaneous irregularities during clinical anesthesia with cyclopropane were not prevented by procaine amide in the 24 patients studied.

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Eclampsia—Managed with Conduction Anesthesia.
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Evaluation of Curarizing Agents in Man.
Doctors Klaus R. Unna and Max S. Sadove, University of Illinois College of Medicine, Chicago.

Continuous Segmental Analgesia in Obstetrics and Surgery.
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