# Effectiveness of Procaine Amide in Digitalis-Induced Ventricular Tachycardia.* (18912)

L. I. GOLDBERG† AND M. DEV. COTTEN. (Introduced by R. P. Walton.)

*From the Department of Pharmacology, Medical College of South Carolina, Charleston.*

Procaine amide (Pronestyl, Squibb) has been shown to be effective in the treatment of ventricular arrythmias(1-3). The pharmacology of procaine amide and its physiological disposition has recently been reported(1,4,5). The present report was designed to determine the value and limitations of procaine amide in the treatment of ventricular tachycardia produced acutely by large intravenous doses of cardiac glycosides.

*Experimental.* Twenty mongrel dogs weighing between 5 and 13 kg were anesthetized with 50 mg/kg (i.v.) of Dial-Urethane. Supplemental pentobarbital was administered in a few cases to induce an adequate level of anesthesia. Thirteen of the dogs were subjected to bilateral cervical vagosympathectomy; final analysis, however, indicated no differences in the procaine amide action in the vagotomized and non-vagotomized animals. Seven of the vagotomized animals were artificially respired with oxygen at rates of 16 to 20 per minute by means of a rhythmic interrupter interposed between the animals and a constant pressure tank. Frequent electrocardiograms were taken in all experiments from standard Lead II with a direct writing E.P.L. Cardiotron. Digitoxin (Digitaline Nativelle, Varick) was administered to 12 dogs and Ouabain (Penick, U.S.P.) to 8 dogs. The glycosides were administered intravenously in divided doses until either A-V block with a slow ventricular rate or ventricular tachycardia had developed. The dose of glycoside necessary to produce such effects ranged from 0.75 to 1.25 cat units/kg administered within a period of 2 hours. Procaine amide in a 10% solution was administered by rapid intravenous injection in doses of 10 or 20 mg/kg to those animals in ventricular tachycardia and was repeated when necessary. In most instances, the drug was not injected until at least 10 minutes of tachycardia with no appearance of normal sinus complexes was recorded. This procedure was intended to minimize the possibility of spontaneous remissions of the arrhythmias. Such requirements necessitated relatively high doses of cardiac glycosides and resulted, in most instances, in tachycardia of multifocal origins. The criteria for reversion of the tachycardia, arbitrarily adopted, was a period of at least 2 minutes of ectopic-free, normal sinus rhythm.

Blood pressures were recorded in 12 of the 20 experiments. In 7 cases, the recordings were made by means of a standard mercury manometer and in 5 cases by a Statham Transducer in conjunction with a Brush strain analyzer (Model B1-310) and oscillograph (Model B1-202).

In addition to the dog experiments, the effect of procaine amide on the "cat-unit" of ouabain (Hatcher-Brody method) was determined in 7 cats. End points were obtained electrocardiographically. The procaine amide was administered by continuous intravenous infusion in 5 experiments and by rapid intravenous injections in the others. A similar "cat-unit" study was carried out with procaine and other drugs by Emerson(6).

* This investigation was supported by a research grant from the National Institute of Health, U. S. Public Health Service.

† Fellow of the American Foundation for Pharmaceutical Education.

1. Mark, L. C., Kayden, H. J., Steele, J. M., Cooper, J. R., Berlin, I., Rovenstine, E. A., and Brodie, B. B., *J. Pharm. Exp. Therap.*, 1951, v102, 5.

2. Kinsman, J. M., Clay, H. L., Coe, W. S., and Best, M. M., *J. Kentucky State Med. Assn.*, 1950, v48, 509.

3. McCawley, E. L., Stanwood, J. E., and David, N. A., *Fed. Proc.*, 1950, v9, 82.

4. Newman, P. J., and Clark, B. B., *Fed. Proc.*, 1950, v9, 304.

5. Newman, P. J., and Clark, B. B., *Fed. Proc*, 1951, v10, 326.

6. Emerson, G. A., PROC. SOC. EXP. BIOL. AND MED., 1943, v53, 12.

TABLE I.

| Exp No. | Glycoside and dose in cat unit/kg* | Initial dose of procaine amide in mg/kg and No. of init. inj | Results following initial dose of procaine amide | Additional injections | Total dose of procaine amide, mg/kg | Time of final ecg in hr† |
|---|---|---|---|---|---|---|
| 3‡§ | Digitoxin 1.25 | 10 (1) | Reversion to NSR‖ | 5 | 80 | 1 |
| 5‡§ | Digitoxin 1 | 10 (1) | " " " | 7 | 120 | 11+ |
| 6‡§ | Digitoxin 1 | 10 (2)<br>20 (1) | " " " | 5 | 100 | 12+ |
| 7 | Digitoxin .75 | 10 (1) | " " " | 0 | 10 | 12+ |
| 11 | Ouabain .75 | 10 (2) | " " " | 4 | 60 | 12+ |
| 15 | Ouabain .75 | 10 (1) | " " " | 0 | 10 | 12+ |
| 16 | Ouabain .75 | 10 (5) | Coupling after second inj; NSR after fifth injection | 0 | 50 | 12+ |
| 1‡ | Digitoxin 1.25 | 10 (1) | Reversion to NSR | 1 | 20 | 1 |
| 13 | Ouabain 1 | 10 (2) | Coupling after first inj; complete A-V block after second inj; then cardiac arrest | 0 | 20 | — |
| 12 | Ouabain .75 | 10 (1) | Complete A-V block; then 8-min period of cardiac arrest | 7 | 80 | 12+ |
| 2‡ | Digitoxin 1 | 10 (1) | Complete A-V block | 4 | 60 | 12+ |
| 4‡ | Digitoxin 1 | 10 (2) | Slow idioventricular rhythm with no auricular activity | 3 | 50 | 3+ |
| 17‡ | Digitoxin 1 | 10 (1) | Cardiac arrest | 0 | 10 | — |
| 14 | Ouabain 1 | 10 (1) | Complete A-V block; then cardiac arrest | 0 | 10 | — |

* .33 mg digitoxin = 1 cat unit; .11 mg ouabain = 1 cat unit.
† Time in hours after first procaine amide injection; in all instances, normal sinus rhythm was recorded at these times.
‡ Vagotomy.
§ Artificial respiration.
‖ NSR = normal sinus rhythm.

*Results.* The results of procaine amide administration to 14 dogs in digitalis-induced ventricular tachycardia are presented in Table I. Procaine amide was not administered to 6 other digitalis-treated dogs because of the development of slow idioventricular rhythms in 4 and fatal ventricular fibrillation in 2 instances.

*Reversion to normal sinus rhythm.* In 8 of the 14 experiments ventricular tachycardia reverted to normal sinus rhythm following procaine amide. In 5 of these, a single procaine amide injection produced initial reversion; in the other experiments additional injections were necessary. The reverted rhythm remained ectopic-free in 2 experiments; in the remaining, the initial reversion was temporary, lasting on an average of 10 minutes before the reappearance of ventricular tachycardia or the appearance of numerous premature ventricular contractions. The recurring arrhythmias were generally not as severe as the pre-

vious tachycardia, being usually from a single focus and mixed with normal complexes. Procaine amide, administered at the appearance of these and subsequently occurring arrhythmias, was effective in re-establishing normal sinus rhythm. The incidence of ectopic rhythms progressively decreased during the course of these experiments and in all cases were absent during observations over at least a 60-minute interval before termination of the experiment. This diminishing incidence of arrhythmias was probably the result of decreasing cardiac glycoside intoxication and cumulative effectiveness of procaine amide.

In all of these experiments, a prolonged P-R interval was recorded following the initial reversion. This change was probably due to the action of the cardiac glycosides since subsequent injections of procaine amide did not appreciably lengthen the interval and also because, in most experiments, a prolonged P-R interval was recorded before the onset of ventricular tachycardia. No significant ECG changes which could be directly attributed to cumulative procaine amide toxicity were seen in those experiments with numerous administrations. Transient bundle branch block, however, occurred in 4 experiments following injection of procaine amide. This change commonly reappeared with succeeding administrations in the same experiment. Similar bundle branch block was seen after procaine amide therapy in humans by Kinsman *et al.*(2).

Ventricular fibrillation occurred suddenly in one experiment (No. 5) after procaine amide had reverted 3 episodes of ventricular tachycardia to normal sinus rhythm. The fibrillation was coarse in character and was followed by a 4-minute period of asystole, after which time the heart resumed beating in ventricular tachycardia. This tachycardia then reverted to normal sinus rhythm following an injection of procaine amide. Subsequent appearances of ventricular premature contractions were treated with 5 additional injections of procaine amide during the remainder of this experiment. As has been pointed out, ventricular fibrillation also occurred in 2 other experiments before any administration of procaine amide.

*Development of Slow Idioventricular Rhythms and Cardiac Arrest After Procaine Amide Administration.* In 6 of the 14 experiments with digitalis-induced tachycardia, procaine amide administration was followed by slow idioventricular rhythms and cardiac arrest. In 3 experiments (Nos. 12, 17, and 14) cardiac arrest followed shortly after a first procaine amide injection. In 2 of these (Nos. 12 and 14) a period of slow idioventricular rhythm associated with complete A-V block was recorded before the asystole. In 2 (Nos. 14 and 17), the arrest was permanent; in the other (No. 12), the heart resumed beating in normal sinus rhythm after 8 minutes. In this latter experiment, ventricular tachycardia recurred and was subsequently reverted to normal sinus rhythm by procaine amide with no further occurrences of A-V dissociation or of cardiac arrest. In Experiment No. 13 cardiac arrest followed a second injection of procaine amide. The initial injection had converted a multifocal ventricular tachycardia to coupling. Procaine amide administration, repeated for this latter arrhythmia, resulted in the development of second degree A-V heart block with infrequent ventricular responses and then permanent ventricular arrest.

In 2 experiments (Nos. 2 and 4), idioventricular rhythms, without the development of cardiac arrest, occurred after procaine amide administration. In No. 2, the idioventricular rhythm was associated with complete A-V heart block; in No. 4, there was no evidence of auricular activity associated with the idioventricular rhythm. Cutting the vagi in the latter experiment resulted in a slight increase in ventricular rate, but did not otherwise alter the conditions. Additional administrations of procaine amide in each of these experiments at the reappearance of ventricular tachycardia restored the previous forms of idioventricular rhythms without the occurrence of cardiac arrest. In both experiments, the electrocardiographic picture improved and a period of normal sinus rhythm was recorded before termination.

*Effects of Procaine Amide on Blood Pres-*

*sure.* The blood pressure usually fell about 10 to 20 mm Hg following doses of 10 mg/kg and about 30-40 mm Hg following doses of 20 mg/kg. Such hypotensive effects were, in most instances, of short duration and were occasionally followed by slight hypertensive effects when a tachycardia was reverted.

*Effect of Procaine Amide on the "Cat Unit" of Ouabain.* Procaine amide failed to increase the lethal dose of ouabain in cats. In 5 experiments, the drug was infused concomitantly with the cardiac glycoside at rates of from 2 mg/cc/min. (total dose of 23 mg/kg) to 20 mg/cc/min. (total dose of 157 mg/kg). In 2 other experiments, procaine amide was injected repeatedly in a 10% solution in doses of 10 and 20 mg/kg (total doses of 70 and 80 mg/kg) beginning with the first appearance of ventricular tachycardia and continuing until the end of the experiment. The ouabain was constantly infused as in the other cat experiments. The "cat unit" values, as determined with ouabain and procaine amide, were compared with the values obtained with a previously conducted series of 11 cats in which ouabain alone was used. The value for the ouabain-procaine amide "cat unit" as well as the standard deviation was the same as that obtained with the ouabain series (0.11 mg/kg SD$\pm$0.015).

*Summary.* Rapid intravenous administration of procaine amide was found effective in reverting ventricular tachycardia, produced in dogs by large doses of cardiac glycosides, to normal sinus rhythm. In most instances, the reversion was temporary and additional injections of procaine amide were necessary in order to maintain the normal rhythm. Such additional injections, repeated several times in these experiments, did not produce electrocardiographic signs of cumulative toxicity.

Although procaine amide effectively reverted ventricular tachycardia in the dog experiments, the same agent failed to increase the lethal dose as determined by limited "cat unit" studies. A similar relation was noted by Emerson in studies on procaine(6) and by Stanbury and Farah(7) in studies on magnesium.

The development of slow idioventricular rhythms and cardiac arrest in several experiments following procaine amide administration demonstrates a danger of drug termination of digitalis-induced ventricular tachycardia. As Gold(8) has emphasized, complete A-V heart block concomitantly produced by the digitalis may be masked in the electrocardiogram by the ventricular tachycardia and the abolition of the latter arrythmia by quinidine or other drugs may result in ventricular arrest.

We are obliged to Dr. P. C. Gazes for his review of the electrocardiographic interpretations.

7. Stanbury, J. B., and Farah, A., *J. Pharm. Exp. Therap.*, 1950, v100, 445.

8. Cornell Conference on Arrhythmias, *Am. J. Med.*, 1948, v5, 110.

Received July 17, 1951. P.S.E.B.M., 1951, v77.

## Effect of Vitamin $B_{12}$, Folic Acid, and Nicotinamide on Urinary Coproporphyrin Excretion in Photosensitized Rabbits.* (18913)

R. PIMENTA DE MELLO.† (Introduced by C. J. Watson.)

*From the Department of Medicine, University of Minnesota Hospital. Minneapolis, Minn.*

Nicotinic acid has been claimed to cause a decrease in the urinary coproporphyrin in certain pathologic states. Thus Spies and co-workers reported marked diminution in patients with pellagra(1) and in painters(2).

* Aided by Research Grant No. 345, U. S. Public Health Service.

† Fellow of the Guggenheim Foundation, New York City (from the Instituto Oswaldo Cruz, Rio de Janeiro, Brazil).

1. Grant, J. M., Zschiesche, E., and Spies, T. D., *Lancet*, 1938, v234, 939