The Effects of Intravenous Procaine and Procaine Amide (Pronestyl) upon Ectopic Ventricular Tachycardia Accompanying Acute Myocardial Infarction

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In tests using dogs with ectopic ventricular tachycardia resulting from myocardial infarction, procaine has been found to be without practical value as an ectopic impulse suppressor agent. Procaine amide has proved to be very effective in reducing the ectopic rate of high frequency tachycardias to low levels, thus eliminating danger of death from the tachycardia. Procaine amide usually does not produce an entirely normal rhythm but this is of little practical importance. The toxicity of procaine amide is relatively low. For approximately equivalent results, in the tachycardias studied, the dosage of procaine amide must be two to three times that of quinidine.

The development of a standard technic for producing rapid ectopic ventricular tachycardia associated with myocardial infarction in dogs has provided a valuable preparation for studies upon the nature and treatment of this kind of arrhythmia.

Comparison of the types of ventricular arrhythmias that develop in association with myocardial infarction in dogs with those found in a large series of patients with myocardial infarction, and comparisons of the reactions of dogs and men exhibiting these ventricular arrhythmias to intravenous quinidine have revealed striking similarities. These similarities appear to justify confidence that results obtained in the dog with myocardial infarction and ectopic ventricular tachycardia can be valuable in deriving principles which would be of value as guides to improvement in the management of patients with ventricular arrhythmias resulting from this cause. Reports from investigations upon the effects of diphenylhydantoin sodium (Dilantin) and phenobarbital, of upper thoracic sympathectomy and of quinidine lactate and gluconate upon ventricular tachycardias produced in this manner have been completed.

The experiments to be reported were planned for the purpose of critically evaluating procaine and procaine amide (Pronestyl) as suppressors of ectopic ventricular tachycardia associated with myocardial infarction. Mautz demonstrated that locally applied procaine, Metycaine, cocaine and potassium chloride significantly increase the electrical threshold for extrasystoles at a constant time in diastole. In another paper Mautz reported that the use of intravenous and locally applied procaine aids in the resuscitation of the heart from ventricular fibrillation by the use of the electric defibrillator and massage. As a result of these studies, the use of procaine prophylactically during surgery in the region of the heart has been recommended.

Wiggers and Wegria have shown that intravenous procaine raises the electrical threshold for ventricular fibrillation produced in dogs by brief direct current stimuli delivered during the vulnerable period. Since ventricular fibrillation is induced by repetitive ectopic impulses, their results obviously were measurements of the relative thresholds for ectopic beats during an unstable stage of repolarization when repetitive
responses often follow a single effective stimulus.\textsuperscript{19} This stage of recovery is characterized by oscillations in excitability.\textsuperscript{11}

Procaine has been reported to be effective in preventing ventricular tachycardia and fibrillation in dogs upon administration of a test dose of Adrenalin in the presence of cyclopropane anesthesia.\textsuperscript{12–14} These results were not confirmed by Huggins and co-workers in dogs in which ventricular tachycardia and fibrillation were produced by chloroform-epinephrine\textsuperscript{15} and cyclopropane-epinephrine\textsuperscript{16} technics. Procaine afforded no practical protection against ventricular tachycardia and fibrillation to animals of either series. Experiences with intravenous procaine for the control of arrhythmias during anesthesia in a series of cases reported by Burstein\textsuperscript{17} indicate that procaine probably does have value for this purpose, though its duration of action is brief. Zapata Díaz and co-workers\textsuperscript{18} terminated auricular paroxysmal tachycardia and ventricular premature systoles by intravenous procaine in a few cases but failed in paroxysmal ventricular tachycardia and in chronic auricular fibrillation.

\textit{Procaine amide} has recently been found to be effective in protecting dogs against cyclopropane-epinephrine arrhythmias, and in suppressing premature ventricular systoles and ventricular tachycardia in human cardiac patients.\textsuperscript{19, 20} Plasma levels decline slowly, about 10 to 20 per cent per hour; therefore long duration of action may be expected. Metabolic changes bring about part of the decrease but the greater part of the procaine amide is excreted in the urine.\textsuperscript{19} Procaine amide, used prophylactically, has reduced the incidence and severity of arrhythmias during cyclopropane anesthesia in patients, but did not fully prevent them.\textsuperscript{21}

\textbf{Technics}

The preparation of animals and the methods of testing will be described briefly. They have been presented somewhat more completely in previous papers.\textsuperscript{1, 3, 4} Under pentobarbital sodium anesthesia (30 mg. per kilogram) and with aseptic surgical precautions the anterior descending artery of the dog is dissected free for a distance sufficient to pass ligatures under it at the level of the free edge of the left auricular appendage. A doubled ligature is then passed under the artery and cut, making two ligatures. A partial occlusion is produced by tying one ligature snugly, but not tightly, around the artery together with a 20 gage hypodermic needle, and withdrawing the needle. The second ligature is tied tightly around the artery after an interval of 30 minutes. By this two stage technic, losses by ventricular fibrillation during the danger period of the first 10 minutes which follows abrupt occlusion are avoided. The chest is closed and the animal is given fluids and other routine postoperative care.

On the following morning, 16 to 20 hours after occlusion and after the animal has completely recovered from anesthesia, a number of control electrocardiograms are made and then testing is begun. At this time the animals characteristically have a rapid ectopic ventricular tachycardia which is persistent and exhibits only minor changes in frequency from hour to hour. If untreated, the ventricular tachycardia continues for two to four days, and in some animals there are ventricular premature beats on the fifth postoperative day. In about 5 to 10 per cent of the animals, the ectopic ventricular activity is not sufficiently rapid or sufficiently constant to be considered suitable for valid testing.

The principal testing is done on the first postoperative day when the ventricular ectopic activity is most intense and most difficult to control. In some animals testing is continued on subsequent days. The term test is used to denote all of the doses of the test drug and all procedures and observations performed during any one day of testing.

Effects of morphine in conjunction with procaine and with procaine amide were tested in some experiments. It was found in the earlier study with quinidine compounds that morphine prevented some of the toxic side reactions (vomiting and diarrhea) but did not prevent convulsions. Morphine may have increased the ectopic suppressor effect of quinidine in some experiments.

\textbf{Results}

\textit{Procaine}

Procaine was used alone in five dogs, and in combination with morphine in four others. In the experiments with procaine alone, doses were 10 or 20 mg. per kilogram, the dose being diluted with Locke’s solution to 20 cc. and injected slowly during a period of five minutes. Doses of 10 mg. per kilogram administered at 30-minute intervals until six doses had been given failed to alter significantly the ectopic ventricular frequency. Doses of 20 mg. per kilogram usually produced a quick reduction in ectopic frequency following each dose. The reduction was of brief duration in all cases, usually lasting less than five minutes after the
completion of the injection. Convulsions followed injections in two of the animals.

**Procaine following Morphine.** Morphine was combined with procaine in five tests upon four animals. The ectopic suppressor effect of procaine was not improved by the addition of morphine, nor were the convulsive reactions prevented.

The chart reproduced in figure 1 serves to illustrate the effects of procaine alone and in combination with large amounts of morphine. The ectopic suppressor effect of procaine (alone) was more evident in this experiment than was usual in the series. The control ectopic rate during the two hours just preceding the first dose of procaine was 130 to 160 per minute, relatively low frequency ventricular tachycardia. The first two doses of procaine (20 mg. per kilogram) produced a marked reduction in ventricular ectopic rate. Before the third dose was administered, however, the ectopic rate had risen to a level higher than that of the control period. Each of the next two doses also produced significant diminutions of ectopic frequency but they were of short duration. Each dose had produced convulsions.

Morphine, 5 mg. per kilogram, was administered subcutaneously one and one-half hours after the fourth dose of procaine. No significant change in ectopic rate occurred in the first 30 minutes after the morphine. Three additional doses of procaine produced effects that were generally similar to the results of procaine administration before morphine, including convulsions. Another dose of morphine was followed by another dose of procaine, but within 30 minutes after the last dose the ectopic rate had risen again to 170 to 180, the highest level of the day.

On the following morning (45 hours post-occlusion) the ectopic rate was 180. Morphine, 5 mg. per kilogram, was injected. This was followed 30 minutes later by procaine. The ectopic rate fell to 0 at the end of the procaine injection, but after five minutes it had risen again to 150, after which it fluctuated between 170 and 190. Another dose of procaine produced a drop to 100 followed by another quick rise to 150 to 170. Each dose was followed by convulsions as before.

In the other experiments, including those in which convulsions did not occur, the ectopic suppressor effects were as feeble and as fleeting as in the one illustrated. It must be concluded that procaine with or without morphine has no practical value as an agent for the suppression of ectopic ventricular tachycardia produced by myocardial infarction.
**Procaine Amide (Pronestyl)**

The effects of procaine amide alone were determined in 12 tests in eight animals. Morphine was administered prior to the first dose of procaine amide in three tests in three animals.

The electrocardiographic results of the administration of procaine amide to an animal with a very high frequency ectopic ventricular tachycardia is illustrated by figure 2. The control record, made on the morning of the first postocclusion day, 18 hours after the operation, shows a ventricular ectopic rate of 300 per minute. Immediately after completion of the five-minute injection of the first dose (40 mg. per kilogram) many beats of normal origin were present and the ectopic rate was reduced to 80 (second record). The third record, made five and three-quarters hours after the first injection, and four hours after the last injection, shows that some ectopic activity still persisted at a safely low frequency along with many normal complexes. The total amount of procaine amide administered was 120 mg. per kilogram.

More complete data from the same experiment was presented in the chart reproduced in figure 3. The administration of procaine amide, 120 mg. per kilogram, during a period of one and three-quarters hours reduced the ectopic rate from 300 to 0. The complete elimination of ectopic complexes lasted for a few minutes only, but the ectopic frequency remained relatively low (10 to 110) without additional doses during the balance of the day of observations, more than nine hours. By the following morning the ectopic rate had risen to 170 and the rhythm again was totally ectopic. An injection of procaine amide, 40 mg. per kilogram, reduced the ectopic activity to a low level during the next 30 minutes, after which it tended to stabilize at a rate of 70 to 80. A second dose had much less effect than the first, and a large increase in ectopic activity began after about 30 minutes. Two later doses produced restlessness and vomiting, and had relatively little ectopic suppressor action. Vomiting was not observed in any other experiment.

An experiment that showed a somewhat different type of reaction to procaine amide is presented in the chart reproduced in figure 4. The ectopic rate 18 to 19 hours after occlusion was 210 to 230 per minute. The first three doses of procaine amide (each dose 20 mg. per kilogram) at 30-minute intervals reduced the ectopic rate to 0. It remained at 0 to 10 for about 45 minutes, after which there was a quick rise to 140. The second dose reduced the ectopic rate almost to 0 and kept it at a low level for more than an hour after which there was another rising trend. The cycle of increase in ectopic activity and reduction to zero by another dose was repeated two more times at slightly longer intervals.

From the chart in figure 4, it might be expected that additional doses administered at sufficiently short intervals probably would have

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* The procaine amide used in this study was generously supplied by E. R. Squibb and Sons.
completely suppressed all ectopic activity. In other experiments, however, in which the elimination of all ectopic activity by large and frequent doses was attempted, low frequency ventricular ectopic rhythms persisted.

Morphine, 5 mg. per kilogram, was administered prior to the first dose of procaine amide in three experiments. Figure 5 is the chart from one of them. On the morning of the first postoperative day, 17 to 18 hours after occlusion, the ectopic rate was 230 to 240. Following the morphine there was a decrease to 210 to 220. The first dose of procaine amide (30 mg. per kilogram) produced a large reduction in ectopic frequency, lowering it to 130. Further doses of equal size at 30 minute intervals produced only small further reductions, though a total of 10 doses of procaine amide were given within six hours. At no time was the ectopic frequency reduced to 0. On the following day two additional doses again reduced the ectopic rate, but not to 0. The use of morphine prior to procaine amide does not appear to have enhanced or impaired its ectopic suppressor action.

An analysis of the results obtained in all the experiments with procaine amide shows that in every test in which a high frequency ectopic ventricular tachycardia existed prior to procaine amide administration, marked reduction of the ectopic frequency was produced. In each of the five animals with ectopic rates from 200 to 300, the ectopic rate was reduced to a relatively low level and maintained at a rate less than one-half of the pretreatment control rate for four hours or longer without toxic symptoms.

In tests with much lower control ectopic rates, the results were less consistent. In the test on the second postocclusion day of an illustrative experiment with a control ectopic frequency fluctuating between 20 and 90, procaine amide, 60 mg. per kilogram (in 20 mg. per kilogram doses) in one and three-quarter hours, made no detectable change in the ectopic rate or the pattern of the fluctuations. In the test on the third postocclusion day on the same animal with a control ectopic rate of 80 to 90 a single dose, 20 mg. per kilogram, eliminated all ectopic activity. There was no return. Other examples of varying results in the suppression of low frequency ectopic ventricular impulses were found in a number of the experiments.

Blood Pressure. Mean blood pressure records were made during three experiments. The pressures were recorded simultaneously with electrocardiograms on a Sanborn Poly-Viso Cardiette, using a Statham gage and carrier-frequency amplifier. The salient observations of the three experiments were as follows:

Experiment C-279. Five doses of procaine amide, 30 mg. per kilogram, two doses, 40 mg.

![Fig. 4. Procaine amide in another animal. Doses differently distributed.](image)

![Fig. 5. Morphine and procaine amide. Multiple doses of procaine amide administered in futile attempt to eliminate residual low frequency ectopic impulses.](image)
shows that even in a relatively insensitive animal, doses of procaine amide can not be increased indefinitely. In this animal, ectopic activity was never completely eliminated for more than a few minutes at a time.

**Experiment C-282.** Morphine, 5 mg. per kilogram, was followed after an interval of 45 minutes by the first of five 30 mg. per kilogram doses of procaine amide. These were followed by one 40 mg. per kilogram dose. All doses of procaine amide were given at intervals of 30 minutes. Each dose was followed by a decline of mean blood pressure of 5 to 20 mm. Hg. The animal survived and was in good condition until sacrificed some days later. Low frequency (20 to 50 per minute) ectopic complexes returned between doses, but failed to recur after the last one.

**Experiment C-283.** Morphine, 5 mg. per kilogram, was followed after an interval of 45 minutes by the first dose of procaine amide. Five doses of equal size, 30 mg. per kilogram, were administered at 30 to 45 minute intervals. After each of the first three doses of procaine amide there was a sharp drop in mean pressure of 20 to 30 mm. Hg, and the control level was not fully regained between doses. The fourth dose produced a fall of 55 mm., from which there was little recovery during the next 30 minutes. The fifth dose was followed by a fall to 0, intraventricular block, terminal ventricular fibrillation and death. This animal was definitely more sensitive to the depressor effects than were the other two.

Study of the protocols does not reveal the cause of the greater vulnerability of this animal. One of the two less sensitive animals also received morphine, 5 mg. per kilogram. The one dog in the entire series that died after the smallest amount of procaine amide (2 doses, 30 mg. per kilogram each) had received no morphine at all. Unfortunately no blood pressure measurements were made on this animal.

**Duration of QRS Complexes and of P-R Intervals.** In 7 of the 10 dogs, prolongation of the QRS complexes in normally initiated beats was small, remaining below 30 per cent of the control durations throughout the testing procedures. One of these seven dogs with minimal prolongation died after the second 30 mg. per kilogram dose of procaine amide.

Prolongation of QRS by 75 to 100 per cent occurred in three animals. Two of these three animals with a definite prolongation by this amount died.

Variations in the P-R interval bore no relation to dosage or to QRS in seven animals. These included the animal in which failure of the pacemaker and cardiac standstill followed the second dose; the P-R interval was prolonged by no more than 20 per cent (0.10 to 0.12) by the first dose. This is within the limits of spontaneous variation.

There was a significant widening of P-R associated with widening of QRS in the other two fatality cases.

**Fatalities.** There were three deaths during testing. Widening of the QRS complex sufficient to constitute a warning sign existed prior to the last dose in two animals. In the other case, the animal that died soon after the second dose, the greatest width of QRS after the first dose was 0.05 second compared with 0.04 before treatment.

Study of the protocols of these three animals for other observations that might serve as warning signs revealed only that one dog, the animal most sensitive to procaine amide, was quiet and listless prior to the first dose, and its indifference to surroundings became more pronounced after the first dose was given.

**Discussion**

**Procaine.** It has been demonstrated that although intravenous procaine has some ectopic impulse suppressor action, its effective duration is too brief to be of practical value for the treatment of ectopic ventricular tachycardias associated with myocardial infarction. Its tendency to induce convulsions also renders its use in the unanesthetized state objectionable.

**Procaine Amide.** The experiments have shown that procaine amide is very effective in reducing the frequency of rapid ectopic ventricular tachycardias to relatively low frequency ectopic beats mixed with normal complexes. Usually it has not eliminated all ectopic activity although many additional doses and larger doses were administered after the major
reduction in ectopic frequency had been produced. In some experiments with low frequency ectopic activity prior to the beginning of treatment, procaine amide has had little effect on the ectopic activity. In at least one test with a low ectopic frequency, however, one dose permanently restored a completely normal rhythm. These observations probably signify that two or more factors are active in producing the ectopic activity. In high frequency tachycardia the major factor is antagonized by procaine amide; thus, a reduction of the ectopic frequency to low levels is readily effected. Other factors of relatively minor importance in the production of ectopic impulses apparently are not opposed by procaine amide, but continue to cause low frequency ectopic activity after the major exciting factor has been brought under control. Such minor excitatory factors, refractory to procaine amide, could be the sole or major factor in those low frequency ectopic rhythms that are resistant to this drug.

Clinical Significance. It is well known that in the presence of myocardial infarction a high frequency ectopic ventricular tachycardia is a grave complication. The tachycardia may precipitate ventricular fibrillation or lead to circulatory failure. Fortunately, both of these dire sequelae of rapid ventricular tachycardia can be prevented by reduction of the ectopic frequency to low levels, thereby allowing a favorable proportion of sinus impulses to become effective. With the reduced intensity of ectopic excitatory state in the boundary of the infarct, the danger of an ectopic frequency sufficiently great to produce the conditions required to initiate ventricular fibrillation is effectively nullified. Furthermore, with the slowed rate, diastole has a duration long enough to permit a degree of filling of the ventricles sufficient to provide for effective pumping action.

It is not necessary to stop all ectopic activity to prevent death in these severe ventricular tachycardias, and a determined attempt to do so may prove harmful. Although procaine amide is relatively less toxic than quinidine and certain other drugs used for the control of ventricular ectopic rhythms, it should be remembered that one very quiet animal died after only two doses of procaine amide of a size that was well tolerated in the majority of animals though repeated many times. One other dog died after the administration of an amount of procaine amide that may be regarded as being well within the usual therapeutic range of total dosage during a period of a few hours. The third death occurred only after excessive dosage.

The observations upon two of these dogs suggest that, during treatment of severe ventricular tachycardias with procaine amide, some of the principles which were developed from the observations of the reactions of such dogs to the intravenous administration of quinidine lactate and quinidine gluconate should be applied. In those experiments the animals with hypotension and dyspnea tended to be most sensitive to the drug, and to die after administration of relatively small amounts. In all cases of severe ectopic ventricular tachycardia only that amount of drug which is required to reduce the ectopic rate to a safely low range and to maintain it at a low level should be administered. Eventually the harmless low frequency ectopic beats will cease spontaneously. In all cases of severe ectopic ventricular tachycardia, an electrocardiograph machine, preferably a direct-wiring type, should be kept near the patient and used at frequent intervals as a guide to therapy. These experiments indicate that in order to produce equivalent ectopic suppressor effects in ectopic ventricular tachycardias accompanying acute myocardial infarction the dosage of procaine amide should be two to three times that of quinidine lactate or gluconate.

Summary

Procaine, administered intravenously, has a very transient effect in suppressing ectopic impulses in some animals with ectopic ventricular tachycardia, and practically no suppressor effect in others. In some unanesthetized animals, sufficient procaine to exhibit any ectopic suppressor effect induced convulsions. Procaine is of no practical value in such tachycardias. Procaine amide (Pronestyl) is very effective in reducing the frequency of severe ectopic ventricular tachycardia to safely low levels. Usually
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It will not eliminate all ectopic activity, though administered in large and repeated doses. It has yielded variable and unpredictable results in low frequency ectopic rhythms.

It is deduced that in myocardial infarction multiple ectopic excitatory factors probably are active, and that the major factor in high frequency tachycardias is opposed by procaaine amide.

The elimination of danger of ventricular fibrillation and a marked improvement in the effectiveness of pumping are achieved by the reduction of the ectopic frequency to low levels. Since such a reduction can be produced by doses of procaaine amide that usually produce a little or no toxic reaction, it is regarded as a promising suppressor agent for use in severe ectopic ventricular tachycardias.

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