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# THE ACTION OF PROCAINE ON THE HEART *

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PROCAINE, used exclusively as a local anesthetic for many years, has recently found a variety of applications in medicine as a depressant of the nervous and circulatory systems. Certain cardiac effects were early observed but the recent wide usage in chest and cardiac surgery and the recognition of the quinidine-like action of procaine have given new emphasis to the circulatory actions of the drug. The present report is one of a series from this laboratory dealing with the action of drugs on the fundamental properties of heart muscle. The heart of the tortoise *Pseudemys elegans* has been found a suitable test preparation. The effect on rhythmicity has been observed on the spontaneously beating auricle, and this tissue also permits study of action on the autonomic nervous mechanism. The effect on threshold for stimulation and on mechanical contraction has been followed by suspending strips of ventricle in a bath and driving rhythmically by condenser discharges. Refractory period and fiber conduction time have been determined by recording two simultaneous electrograms with small wick electrodes placed on a horizontally suspended ventricular strip, rhythmically stimulated by condenser discharges and permitted to contract isometrically. It has already been shown that the Q-T interval of the electrogram when recorded from a point is a satisfactory measure of the refractory period of the muscle at that place. A wide range of concentrations of procaine has been used, with particular attention to concentrations ranging from 1:40,000 to

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1:50,000 since these appear to approximate concentrations that may safely be used in man. Burstein (1) gave single doses of 150 mg. to dogs under cyclopropane anesthesia with no untoward effects, and gave doses of 30 to 70 mg. to anesthetized patients. One patient of the present study who received 100 mg. rapidly injected showed an increase of 25 per cent in the P-R interval of his electrocardiogram as the only effect of procaine. It is pointed out that although procaine is rapidly broken down in blood, in these experiments chemical examination of the bath by the method of Kisch showed no recognizable destruction of procaine by enzyme liberated from the muscle during the experiment. Because of similarity of certain actions of procaine and quinidine further observations on quinidine have been made with comparable concentrations of each drug. In all experiments only a single observation of the drug was made on each tissue. Brief comments will be added on the response to procaine in a few clinical cases.

*Action on Auricle.*—In general, the response of the auricle to concentrations from 1:90,000 to 1:5000 showed an inconstant effect on rhythmicity; both moderate increases and decreases in rate occurred, and the result did not appear to depend on the particular concentration. Even with high concentrations increases of rate were occasionally seen; with procaine 1:8000 the rate rose from 27 to 40 beats per minute in one instance, and from 16 to 27 in another. When the rate increased there was no significant decline in beat size, which indicates enhanced contractility since normally in these preparations beat size varies inversely with rate. Failure of procaine to increase contraction in rhythmically driven ventricular strips suggests that the increase seen in auricular contraction is the result of removal of vagal tone.

In 1924, Frey (2) demonstrated the power of procaine to "paralyze" extracardiac nerves. This action was confirmed by Schookhoff (3) who also showed a powerful depressant action on conduction in the dog heart. Allen and co-workers (4) found procaine effective against tachycardia produced by cyclopropane-epinephrine anesthesia and attributed the action to myocardial depression. Many studies have been reported on the ability of procaine to antagonize epinephrine and that property has been one basis for the use of procaine in the prophylaxis and treatment of arrhythmias appearing during surgical operations. Recently, however, Smith and Ferguson (5), from experiments on dogs, concluded that procaine gave no protection against epinephrine, and that it did not reduce the frequency of ventricular fibrillation during cyclopropane anesthesia. In their experiments procaine was given five minutes before epinephrine. While epinephrine acts within a few seconds, in the present experiments the time required for procaine to produce definite effects was usually from ten to twenty minutes. The ability of procaine to offset epinephrine could not be shown conclusively by this preparation. Not all auricles

respond to epinephrine, and the response to a second dose is highly uncertain, so that one cannot give epinephrine before and after procaine and assume that failure of a second response was due to procaine. The smallest reliable test dose of epinephrine (synthetic suprarenin was used) proved to be 0.1 cc. of a 1:100,000 solution, which gave concentrations varying from 1:25 to 1:50 million. Procaine concentrations up to 1:20,000 did not prevent increase in rate and force of contraction by epinephrine 1:30 million. Such quantities of epinephrine may be large compared to those released under physiologic conditions. According to D. J. Smith (6), one part epinephrine in 100 million will cause constriction of arterial strips. Procaine concentrations of 1:10,000 did appear to block the action of epinephrine.

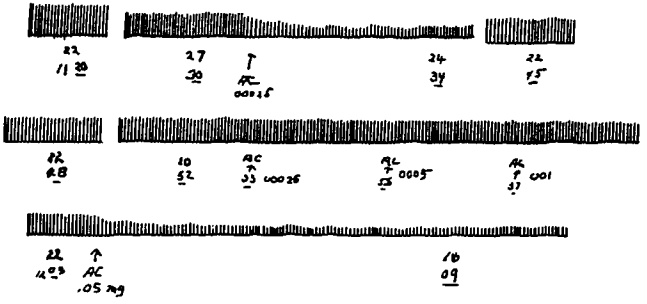


FIG. 1. Spontaneously beating turtle auricle. Response to acetylcholine before and after procaine. Upper figures, beats per minute; lower, time. Top line: 0.00025 mg. of acetylcholine. At time 45 procaine added to concentration of 1:25,000; bath, 25 cc. Middle line: no effect from acetylcholine in doses to 0.001 mg. Bottom line: slowing of rate and decreased beat size following 0.05 mg. of acetylcholine.

The increase in auricular rate that often follows procaine has been attributed to its antivagal action. In all instances in which atropine was first added to the bath, procaine caused slight slowing or no change of rate. In an attempt to study the power of procaine to counteract acetylcholine the same difficulties are met as with epinephrine, owing to variability of initial response and uncertainty of the effect of a second application. From numerous trials, however, it seemed quite certain that procaine can at least reduce the action of acetylcholine. An example of such action is shown in figure 1. In many experiments the subsequent depression of contractility by acetylcholine seemed to be relatively greater than that of rate. The quantity of acetylcholine used may seem large, but it is much less than the concentration required to depress contractility in driven ventricular strips (7). Likewise, Dawes (8) found that procaine reduced the ability of acetyl-

choline to slow the rate and depress the amplitude of contraction of the isolated rabbit's auricle.

*Action on Ventricle.*—For rhythmically driven strips whose beat was recorded mechanically, procaine in concentrations of 1:50,000 or less caused no change in beat size, and often much higher concentrations, up to 1:5000, did not impair contraction.

The refractory period, measured by the Q-T interval of the electrogram, was not influenced by concentrations ranging from 1:100,000 to 1:10,000 (fig. 2). Experiments were terminated by conduction block or alteration in complexes which prevented measurement.

The effect on latent period, the time from the shock to the first response of the proximal electrode, was variable; often it was only slightly increased, although marked increases in threshold and conduction time were produced.

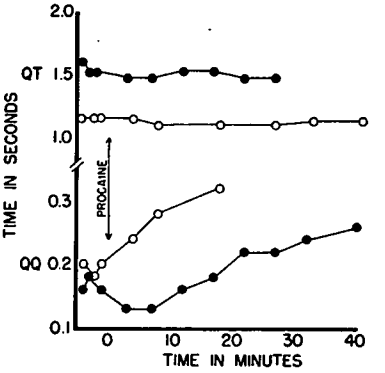


FIG. 2. Effect of procaine on refractory period (Q–T interval) and conduction time (Q–Q interval) in strips of turtle ventricle; solid circles, concentration, 1: 50,000; open circles, concentration, 1: 20,000.

The constant action of procaine on the ventricle was to raise the threshold for stimulation and to prolong fiber conduction time. Threshold measurements made during mechanical recording are more accurate than those obtained when electrical events were recorded, since in the latter technic it is necessary to drain the tissue at the time of recording. Considerable variation in the degree of both threshold and conduction change for a given concentration of procaine was encountered. From earlier observations on the action of quinidine (Wedd, Blair and Gosselin, 9) it was thought that these two effects ran parallel and that prolongation of conduction time could be attributed to raised threshold. While at times in the procaine experiments this parallel

action appeared, in general the magnitude of increase in conduction time was greater than the threshold change. It is quite certain that raising threshold will delay conduction, but these experiments also indicate that these two attributes of heart muscle may vary independently. A preponderant conduction effect may be caused by an increase in chronaxie and is in accord with the finding of Siems (10) who reported increase of chronaxie by procaine in the skeletal muscle of the frog, dog and man. Also significant is the fact that when the procaine solu- was replaced by fresh Ringer solution there was often a more complete return of the threshold toward the initial level than for conduction

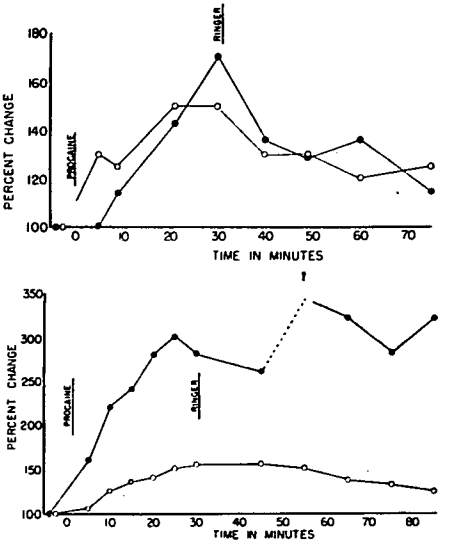


FIG. 3. The effect of procaine on threshold and conduction in strips of turtle ventricle, concentration, 1: 50,000; solid circles, percentage increase in conduction time; open circles, percentage increase in threshold. A. Parallel response. B. Preponderant conduction increase.

values. In general, it may be stated that of the measurable functions of heart muscle, conduction is most easily impaired, and having been altered it is less likely to return to normal during the experiment. These points are illustrated in figure 3. In control experiments the threshold at the end of two hours of stimulation was approximately 120 per cent of the initial value. While recovery was usually quite complete, in an occasional experiment the threshold one hour after the

removal of procaine was 150 per cent of the value before the drug was added.

*Action of Procaine By-products.*—Because of the rapid break down of procaine in the blood, it has been considered that its break-down products, particularly diethylaminoethanol, might be responsible for a continuing procaine-like action (B. Rosenberg et al., 11). This substance produced no consistent effect on either auricle or ventricle of the turtle. Occasionally high concentrations caused diastolic shortening and decreased beat size in the driven ventricular strip and this action was reversed when the bath was changed to fresh Ringer's solution. In other preparations, 1:2000 was without effect. Save for a single experiment in which 1:8000 caused a slight rise, concentrations up to 1:5000 had no influence on the threshold for stimulation. Concentrations up to 1:5000 did not affect the refractory period or conduction time. In the auricle, a concentration of 1:5000 did not prevent the characteristic response to epinephrine. Fewer observations were made, but there was no definite action by para-aminobenzoic acid in concentrations up to 1:5000.

*Comparison of Procaine with Quinidine.*—In his comparative study, using the change in the "effective refractory period" of the rabbit auricle as a measure of activity, Dawes (8) found the activity of procaine to be 0.8 when quinidine was taken as the standard with an activity of 1.0. Individual variation in response makes an exact quantitative comparison difficult, but in the present experiments in most instances the effect of procaine on threshold and on conduction was definitely greater than that of quinidine, not only for equal concentrations but also when considered in terms of molar concentration. Both procaine and quinidine in concentration of 1:100,000 were able to prolong vetricular conduction time; the procaine effect was greater. Comparative action on threshold is illustrated in figure 4. Usually, when the bath containing the drug was replaced by fresh Ringer's solution threshold recovery was more complete after procaine than after quinidine.

It has been stated that procaine had little influence on ventricular contraction. In contrast, quinidine in concentration of 1:50,000 may depress contractility, and will usually do so in higher concentrations. In man quinidine lowers both systolic and diastolic pressure levels. Procaine as it is generally used has no effect on blood pressure.

*Clinical Notes.*—A few patients have been observed and serial electrocardiograms recorded while they received procaine intravenously in 0.1 per cent solution during surgical operation. In 3 instances in which the thorax had been opened ventricular extra systoles ceased shortly after the injection of procaine. In one of these an obliging anesthetist temporarily raised the cyclopropane concentration to 50 per cent; the cycle length increased and premature beats appeared but the P-R interval did not change; following the rapid injec-

tion of 100 mg. of procaine in 5 cc., premature beats ceased and the P-R interval increased from 0.16 second to 0.25 second; seven minutes later it was again 0.16 second, and the cycle length was reduced from 1.16 to 0.56 second. The QRS interval was not affected.

Another patient during an operation with the thorax open received 400 mg. of procaine in one hour. The rhythm continued regular and there was no change in A-V or intraventricular conduction, or in the form of T waves. Blood pressure remained constant.

Early in an exploratory laparotomy rapid nodal paroxysmal tachycardia developed which made it necessary to terminate the procedure. Later the operation was successfully performed; atropine and procaine were given at the start. For a time the infusion containing procaine inadvertently flowed at an excessive rate; a total of 750 mg. was given in fifty minutes, including 500 mg. in twenty-four minutes. There was a slight increase in cycle length, but no change in conduction time. Blood pressure remained constant at 90 mm. systolic and 60 mm. diastolic, and the skin was warm and dry at all times.

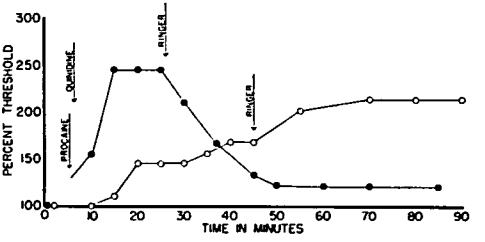


FIG. 4. Comparison of effect on threshold of procaine and quinidine in strips of turtle ventricle; solid circles, procaine, 1: 30,000; open circles, quinidine, 1: 15,000.

An unanesthetized patient who suffered a painful hand injury was given 275 mg. of procaine in eighteen minutes. There were no changes in the electrocardiogram or blood pressure. Subjective relief was doubtful.

Procaine has been considered dangerous in the presence of impaired conduction and the heart block produced. A man with complete heart block of five weeks' duration was brought to the hospital because of recurring syncopal attacks. Three different mechanisms were responsible for syncope, paroxysmal ventricular tachycardia, ventricular standstill and ventricular fibrillation. Since quinidine had given no relief, 250 mg. of procaine was infused in twenty minutes. Before the infusion was begun the atrial rate was 145, and the ventricular, 38.5 per minute. During a paroxysm of ventricular tachycardia the rate was 218. These paroxysms continued during the administration of procaine; during the last paroxysm the rate was 195. (Slowing of

ventricular rate and failure to terminate were observed in another instance of ventricular tachycardia.) During periods of ventricular standstill, the atrial rate fell as low as 50 per minute. Following procaine, ventricular tachycardia seemed to occur less frequently but the therapeutic effect was considered negligible. Ten minutes after administration of procaine, however, there was a long period of uninterrupted idioventricular rhythm during which consciousness returned and blood pressure was measurable; the atrial rate was then 138 and the ventricular rate 37.5, indicating no long-lasting depression from that quantity of procaine. Death occurred five hours later from failure to establish a ventricular pacemaker.

A final case is cited because of speculative interested in the action of procaine. A right carotid sinus, bound in scar tissue that had formed after operation and radiation for malignant disease of the thyroid gland, was denervated because of hypersensitivity. Atropine was given intravenously and procaine injected locally and infused before the skin incision was made. There was an unexplained rise in blood pressure following administration of the atropine, but the procedure was well borne and the patient returned home the next day. Six months later because of a return of symptoms and the appearance of hypersensitivity of the left carotid sinus, it was decided to denervate that side. On this occasion atropine was given but procaine was not injected locally or given intravenously at the beginning of the operation. Again, the blood pressure rose after atropine (to 200 mm. systolic and 140 mm. diastolic) and remained elevated, and there was a sinus tachycardia with a rate of 190. About forty-five minutes after the atropine was given, highly sanguineous edema fluid began to well from the lungs. Procaine infusion was then begun. During the next hour there were marked fluctuations in blood pressure, from 160 mm. systolic and 100 mm. diastolic to zero. After two hours the circulation became stable, bloody fluid ceased to pour from the lungs, and the patient's condition improved, but he died forty-eight hours later from extensive myocardial infarction caused by ischemia, without coronary thrombosis. Postmortem examination revealed a wholly unsuspected pheochromocytoma. The possible role of procaine in preventing disaster during the first operation and in combating epinephrine intoxication during the second procedure cannot be known, but is certainly of interest in a consideration of the action of procaine.

## SUMMARY

The effect of procaine on the turtle heart has been studied. Its constant actions were to raise the threshold for stimulation and to prolong conduction time in the ventricle, with a relatively greater effect on conductivity.

In the spontaneously beating auricle, procaine was able to limit the activity of acetylcholine. The response to epinephrine was blocked

by high concentrations, but not by amounts that could be used in clinical practice.

Diethylaminoethanol and para-aminobenzoic acid in high concentrations were without significant effect on the turtle heart.

Procaine caused a greater rise in threshold and greater prolongation of conduction time than did quinidine, and without the decrease in contraction strength that occurs with comparable concentrations of quinidine. Threshold recovery occurred more promptly after procaine than after quinidine.

Certain clinical experiences with procaine are cited. The blood pressure levels were not lowered. Extra systoles occurring during open chest operations ceased following infusion of procaine. In two instances ventricular tachycardia was slowed but not terminated. The value of procaine in preventing cardiac arrhythmias during operations may be related to raised threshold for stimulation.

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