Transient Ventricular Fibrillation

IV. The Effects of Procaine Amide on Patients with Transient Ventricular Fibrillation during Established Auriculoventricular Dissociation

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Procaine amide was given intravenously to three patients with transient ventricular fibrillation during established auriculoventricular dissociation at a time when they were free from symptoms as well as during the attacks. It was determined that this drug has a transitory slowing effect upon the auricles. It depresses rhythmicity in the auriculoventricular node, prolongs the refractory period of the ventricles, results in intraventricular conduction disturbance and the development of premature beats of the ventricles followed by the various forms of ventricular acceleration leading to ventricular fibrillation. Because of these alterations in heart rhythms, procaine amide is contraindicated in the treatment of such patients.

The purpose of this study was to determine the effects of procaine amide on patients with transient ventricular fibrillation during established auriculoventricular dissociation. It is apparent from various reports that this drug has been found useful in the abolition of various forms of premature beats of the ventricles and in the control of ventricular tachycardias. More recent observations have revealed its beneficial effects on some of the supraventricular types of arrhythmias such as auricular fibrillation and nodal tachycardias.

Mautz was under the impression that when procaine was applied locally to the heart, it reduced cardiac irritability as indicated by the added intensity of stimulation necessary to induce premature beats of the ventricles or ventricular fibrillation. Other observers found it difficult to produce ventricular fibrillation by faradic stimulation after animals had received procaine. Stutzman and his co-workers, however, doubt the ability of procaine products to prevent adrenalin-induced ventricular fibrillation in dogs. Nevertheless, because of its beneficial action in some patients with ventricular tachycardia, it has been suggested that procaine amide would appear to be indicated in the various forms of ventricular acceleration and ventricular fibrillation that may form the basis of Adams-Stokes seizures during heart block.

Yet, on the basis of experimental observations on the turtle heart and clinical experiences in a patient with auricular fibrillation who developed heart block and intraventricular conduction disturbance following procaine amide, Wedd and his co-workers sound a warning that procaine amide may be particularly dangerous when there is disease of junctional tissues. With these points in view the following experiments were made.

Method of Study

Three patients who were subject to recurrent attacks of transient ventricular fibrillation during established A-V dissociation form the basis of this study. One of these has been under observation at the Montefiore Hospital for over 10 years and has been found to respond favorably to atropine sulfate. Another male patient had his attacks for over two years and likewise responded to atropine sulfate. A third patient was seen at a time when he had numerous seizures of transient ventricular fibrillation and was given procaine amide for their relief.

The natural course of the development of their seizures and the successive alterations in the rhythm of their hearts leading to these attacks, as well as the changes following the revival of the heart from transient ventricular fibrillation were studied carefully prior to the experiments.

The patients were kept in the electrocardiographic circuit or under personal supervision throughout the
entire day of the experiments so as to be certain of the nature of the cardiac mechanism present at any one time. Continuous electrocardiograms were obtained prior to, during and subsequent to the injection of the drug and whenever it was found of interest after that.

No other drugs were used for one week prior to the experiments except atropine sulfate as indicated in the specific protocols. We wished to determine the direct effects of procaine amide on the sinoauricular and auriculoventricular nodes in the absence of vagal influences.

These studies were concerned only with the intravenous effects of procaine amide. In many preliminary experiments, the minimal dosage of the drug sufficient to yield a response with changes in the rhythm of the heart during A-V dissociation was found to be 200 mg. diluted with 3 cc. of physiologic saline. This amount was given intravenously over a period of five minutes. For control purposes, similar amounts of physiologic saline were injected on the alternate days of the experiments.

In one instance, peripheral pressure changes were recorded with a manometer inserted in the left femoral artery and records were obtained simultaneously with the electrocardiograms, prior to, during and subsequent to the injection of procaine amide.

The changes which were induced by procaine amide may be best exemplified by a description of the following experiments each one of which depicts a particular action of the drug.

RESULTS OF EXPERIMENTS

In one patient, the intravenous injection of procaine amide in doses of 200 mg. each, yielded no changes on three separate occasions. In the fourth experiment, there developed short runs of bigeminal rhythm due to alternate premature beats of the ventricle, that lasted for 37 minutes after the injection. However, since he had shown such premature beats on the morning of this day, it was likely that their appearance was fortuitous and not the result of the drug.

In another patient the sequence of events was of unusual interest. On one occasion the basic ventricular rate averaged 34 beats per minute and the auricular rate 107 beats. The rhythm was regular. Immediately following the injection of 200 mg. of procaine amide diluted with 3 cc. of distilled water within five minutes, and before the needle was out of the vein, the ventricles slowed to 25 beats per minute and the auricles to 83.6 beats (fig. 1A-1). In less than a few seconds there appeared premature beats of the ventricles at first singly (fig. 1A-2) and then in groups of two (fig. 1A-3). The returning cycle following these premature beats was of the same duration as the cycles of the basic ventricular complexes, which were downwardly directed and were of the same shape, size and form from beat to beat. The T waves accompanying these were likewise directed downwardly.

Thirty seconds after the end of the injection, there was a sudden stoppage of ventricular activity lasting about six seconds (fig. 1B-1) before the basic ventricular rhythm returned. Now the T waves of the ventricular complexes were large and negative with a prolonged RS-T segment and they presented on their ascending limbs, portions of premature beats of the ventricles resulting in the development of so called “deformed ventricular complexes.” Such abnormalities in the ventricular complexes have been previously described as important preliminary events in the onset of ventricular fibrillation during established A-V dissociation.13

Now, the returning cycles following the premature beats of the ventricles increased progressively (fig. 1B-2, 3 and 4, 5) averaging 6.4 to 8.4 seconds in duration whereas usually they were only 2.0 seconds. For the next half minute, the patient became pale, perspired profusely, shut his eyes momentarily and could not respond to questions. No heart sounds were audible and no pulses were palpable during this episode.

In the next 15 seconds he became rigid and had a slight convulsive seizure. Apnea with cyanosis supervened and the cardiac mechanism registered for the next 27 seconds was one of ventricular fibrillation ended by a premature beat of the ventricles. This was followed by ventricular standstill of seven seconds duration with persistent auricular activity and then the return of a basic ventricular beat (fig. 1C).

Ten minutes after the injection, the respirations which were of the Cheyne-Stokes variety returned to normal and the basic ventricular rhythm was restored. The idioventricular rate however, waxed and waned for a time with an
average ventricular rate varying between 20.2 and 31.2 beats per minute (fig. 1D), finally returning to its basic normal, 14 minutes after the injection.

On another occasion, in the same patient, the basic ventricular rate averaged 31.2 beats per minute and the rhythm was regular without the interposition of any premature beats of the ventricles (fig. 2A–1). For the previous seven days the patient had received intramuscular injections of atropine sulfate (2.0 ng.) each day so as to regularize his cardiac mechanism and prevent a fluctuation in the rate of the idioventricular pacemaker.

Immediately following the injection of 200 mg. of procaine amide diluted with 3 cc. of saline, there ensued a standstill of the ventricles of 7.52 seconds duration with 13 auricular beats being present to each ventricular contraction (fig. 2A–2).

Following this period of standstill, the pacemaker of the ventricles was assumed by another focus either in the A-V node itself or one of its bundles as may be judged by the presence of upwardly directed ventricular complexes accompanied by large negative T wave and a prolonged RS-T segment (fig. 2A–3). The T waves accompanying this new ventricul-
lар complex became progressively deeper from beat to beat (fig. 2A–3, 4, 5). Soon this deformity was enhanced by the superposition of fractions of premature beats of the ventricles on the ascending limbs of the T waves, forming bizarre deflections. These “deformed ventricular complexes” are identical to those previously described as premonitory to the abrupt onset of ventricular fibrillation.

The returning cycles following the premature beats of the ventricles increased in duration very early (fig. 2A–5, 6 and 6, 7).

![Figure 3](image)

**Fig. 3.** *A.* In control record normal ventricular complexes alternate with aberrant deflections. *B.* (1, 2) Procaine amide causes abrupt increase in returning ventricular cycles following premature beats. *C*, *D.* Alternate periods of standstill and ventricular fibrillation with final return to basic rhythm, five minutes after injection.

Fifteen seconds after the injection, the direction and form of the ventricular complexes changed abruptly and after a series of alternate premature beats of the ventricles had disrupted the basic rhythm, there was ushered in a period ventricular fibrillation lasting 14.4 seconds (fig. 2B–1). A pause of 2.6 seconds ended this period and the idioventricular pacemaker reasserted itself.

For the next 20 seconds, the basic ventricular rate slowed to 20 beats per minute and the rhythm was regular only to be interrupted (fig. 2C–1) by another period ventricular fibrillation of 8.6 seconds duration (fig. 2D–1). Premature beats of the ventricles and “deformed ventricular complexes” alternated for two and one-half minutes when the patient suddenly lost consciousness. He became very pale, apnea was followed by intense cyanosis lasting about 20 seconds. There was a drop in blood pressure and pulsations were absent at the radial artery. No heart sounds were audible at the apical region of the heart. The return of the basic rhythm was heralded abruptly by a sudden

flush of the face but the speech remained incoherent for some time thereafter.

From then on, for the next four hours, his rhythm was that of short runs of ventricular fibrillation alternating with a bigeminal rhythm as a result of the persistent presence of premature beats of the ventricles during established A-V dissociation. All of these abnormalities disappeared by the next morning.

In a third experiment procaine amide was given to a patient at a time when the idioventricular rhythm was labile (fig. 3A–1). It
consisted of downwardly directed ventricular complexes with upwardly directed T waves, and with a cycle measuring 2.08 seconds in duration. This rhythm alternated with one consisting of aberrant ventricular complexes with downwardly directed large T waves and a slower cycle of 1.84 seconds duration (fig. 3A–2).

Three seconds after the injection of the drug, there was an abrupt increase in the duration of the returning cycle following the premature beat of the ventricles (fig. 3B–1) from 2.08 seconds to 3.60 seconds. Each succeeding returning cycle following a premature beat of the ventricles became progressively longer (fig. 3B–2) and varied between 5.8 seconds and 6.4 seconds in duration. At such times, the patient became pale, perspired profusely and shut his eyes momentarily. He complained of nausea and pain in the chest.

Three minutes after the injection, when the basic heart rate averaged only 10 beats per minute as a result of depression of impulse formation in the A-V node, there appeared markedly negative T waves. Deformed ventricular complexes now resulted from the superposition of fractions of premature beats of the ventricles on the ascending limbs of the T waves. In less than a few seconds after their appearance, there developed a short run of ventricular fibrillation of 4.0 seconds duration followed by a standstill of the ventricles of 6.0 seconds duration (fig. 3C–1).

For the next minute (fig. 3D–1) longer periods of ventricular fibrillation were followed by periods of standstill of the ventricles, so that no heart sounds were audible and no pulses would be felt for 18 seconds at a time. With this episode, the patient lost consciousness and had a short convulsive seizure. After two and one-half minutes of recurrent periods of ventricular fibrillation and standstill of the ventricles (fig. 3E–1) there was an abrupt return to the basic cardiac mechanism five and three-fourths minutes after the injection.

The return of the basic rhythm was associated with a waxing and waning of the impulse pacemaker in the A-V node so that the ventricular cycles were at times shorter (fig. 3E–2) and at times longer (fig. 3E–3) until a uniform cycle prevailed for the rest of the day, four and one-half hours after the beginning of the experiment.

Procaine amide was given to two patients at a time when they were both experiencing recurrent Adams-Stokes seizures due to long periods of ventricular fibrillation in the preceding 24 hours. In both instances, immediately after the injection, the seizures increased in duration and persistence. One patient died 24 hours after the injection without regaining consciousness following one such long seizure. The other, after repeated attacks of all forms of ventricular acceleration and ventricular standstill, remained cyanotic with irregular breathing and in a semistuporous state for the next five days. The attacks subsided gradually after he had been using oxygen to overcome the profound anoxemia present continuously during that period.

**Discussion**

These observations reveal that in patients with transient ventricular fibrillation during established A-V dissociation, the action of procaine amide may differ from day to day in the same patient and may act variably in different patients. It has been noted that the A-V pacemaker of the heart may at times be in a "labile" state when it responds to drugs very readily with a change in the rate and rhythm of the ventricles and at other times it may remain in a relatively "fixed" state when it may not respond at all. This is very likely in part due to the state of the extrinsic nervous mechanism of the heart and in part to physicochemical factors inherent in the A-V pacemaker itself.

The sinoauricular pacemaker of the heart which is usually under nervous influences may be depressed very early after the use of procaine amide. Such transitory slowing in well atropinized patients with A-V dissociation must then be considered to be the result of the direct depressing effect of the drug upon the sinoauricular node itself.

Of greater clinical significance was the early and marked depressing effects of procaine amide upon the A-V pacemaker itself. This specialized junctional tissue may be so sensitive that it responds with long pauses of ventricular in-
activity with impulse formation in the A-V node displaced to another part of the heart, such as in one of the bundles or the ventricles themselves. This is reflected in the electrocardiogram by an aberrant ventricular complex different from that present usually and with a change in rhythm. It would appear that conduction within the ventricles themselves is likewise disturbed at the same time that the A-V pacemaker is affected.

Another index of the depressing action of procaine amide on the ventricles may be gained from the constant changes noted in the prolongation of the returning cycles following the presence of premature beats of the ventricles after these have appeared.

Usually the returning cycles of the premature beats of the ventricles during A-V dissociation are approximately the same length as the cycles of the idioventricular rhythm of the heart. Indeed sometimes the returning cycles are shorter. However, if repeated attacks of ventricular fibrillation recur with increasing frequency, the duration of the returning cycles in the presence of premature beats of the ventricles may be prolonged.

It is important to bear this in mind when studying the effects of drugs in such patients with heart block. If any depression of rhythmicity or conduction takes place, this portion of the heart cycle may be the earliest to show changes.

Again, in studying the mode of revival of the heart from ventricular fibrillation, it was pointed out that shorter runs may be ended abruptly either by a premature beat of the ventricles or by the last of the fibrillatory waves. A postundulatory pause follows with the return of the basic rhythm immediately after. The longer runs of ventricular fibrillation may end in a period of standstill of the ventricles while the auricles continue their contractions.¹⁴

This postfibrillatory standstill of the ventricles was found to be longest in duration when the heart had been the seat of repeated bouts of ventricular fibrillation, recurrent short fibrillary periods or even numerous premature beats of the ventricles. The prolongation of ventricular inactivity after the cessation of ventricular fibrillation appeared to be dependent more on these factors than on the duration of any one attack of fibrillation itself.

For example, fibrillary periods lasting one and one-half minutes appearing early in the course of the syndrome would return to a basic rhythm of A-V dissociation without the intervening periods of standstill of the ventricles. On the other hand, shorter periods of fibrillation lasting only a few seconds have been known to be followed by a prolonged period of standstill after the presence of numerous attacks of ventricular fibrillation or prefibrillary periods preceding them.

Cushny¹⁶ noted that when the ventricle was beating automatically and its usual slow rhythm was accelerated by a series of shocks at a more rapid rate, it did not resume its original rhythm when the artificial stimulus was withdrawn. As a general rule the ventricles remained quiescent for some time and then recommenced beating very slowly and irregularly, accelerating their rhythm until they resumed their original rate before stimulation.

The factors determining the appearance of these pauses were attributed in part to the duration of stimulation but primarily to fatigue increasing for some time after the acceleration had ceased.

This type of retarded rhythmicity following rapid beating of the dissociated ventricles has its counterpart in the postfibrillatory periods of the human heart in patients with transient ventricular fibrillation during established A-V dissociation. By prolonging this period in further depressing its action, procaine amide retards rhythmicity in the A-V node.

These transitory but profound changes in the depression of rhythmicity in the A-V node and conduction disturbances within the ventricles would in themselves be of little importance in such patients were it not for the fact that simultaneously with their appearance, there may arise from the ventricles multiple ectopic foci, which always appear after the basic ventricular deflections.

The ease with which premature beats of the ventricles and the various forms of ventricular acceleration develop during heart block, more than with any other abnormal cardiac mechanism, is well known. The possibility sug-
suggests itself that in certain patients with A-V dissociation stimuli formation in ectopic foci of the ventricles is conditioned by the state of the A-V pacemaker of the heart. It has been repeatedly observed that variations in the rate and rhythm of the A-V pacemaker invariably precede the development of premature beats of the ventricles in such patients even though they may last only a few seconds at a time. Since these premature beats of the ventricles are a necessary preliminary event in the development of transient ventricular fibrillation, such a drug as procaine amide which provokes their appearance is distinctly contraindicated in them. No changes in blood pressure were observed to have followed the use of procaine amide in any of the patients during the presence of A-V dissociation when the basic rhythm was present either before or after the development of transient ventricular arrhythmias. Pressure changes however were found to be associated with the abnormal rhythms themselves.

Conclusions

A study was made of the effects of procaine amide on three patients with transient ventricular fibrillation during established A-V dissociation.

It was determined that the action of this drug is variable from patient to patient, and in the same patient it differs in its effects from day to day.

Procaine amide was found to have an early transitory depressing effect upon the sinoauricular node since it slowed the auricular rate even in the well atropinized patient.

Procaine amide depressed impulse formation in the A-V node as evidenced by (a) temporary cessation of ventricular activity with a profound slowing of the heart rate during already existing heart block, (b) increase in duration of returning cycles following the appearance of premature beats of the ventricles, (c) undue prolongation of ventricular standstill in the presence of persistent auricular activity following revival of the heart from ventricular fibrillation, (d) displacement of the A-V pacemaker to a lower portion in the ventricles such as in one of the bundles as evidenced by the appearance of new ventricular complexes different in shape, size and form from those present before the use of the drug, and finally (e) by a waxing and waning of rhythmicity in the A-V node when the effects of the drug began to wear off as may be judged by the variability in the rate and rhythm of the heart from moment to moment with the return of the basic complexes.

This action of procaine amide on the junctional tissues was independent of the influence of the nervous mechanism on the A-V node in these patients.

Procaine amide depressed conduction within the ventricles as evidenced by (a) a change in the shape, size and form of the ventricular complexes to one with marked aberration previously not present, (b) unusual prolongation of the RS-T or Q-T segments and (c) the appearance of large negative T waves. These changes favored the development of deformed ventricular complexes similar to those observed to be the forerunner of ventricular fibrillation in the natural course of this syndrome during heart block.

Procaine amide favored the development of ectopic beats of the ventricles resulting in the various forms of ventricular acceleration ending in transient seizures of ventricular fibrillation. All of these changes appeared much earlier and lasted longer when procaine amide was given in the presence of intraventricular conduction disturbance, premature beats of the ventricles or when recurring seizures of ventricular fibrillation were present.

It was found that the effects of procaine amide in such patients appeared and disappeared earlier than the effects of quinidine when administered under similar conditions.

Procaine amide is contraindicated in patients with the various forms of ventricular acceleration leading to ventricular fibrillation during established A-V dissociation.

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