Effectiveness of Nupercaine Hydrochloride and Phenobarbital Sodium in the Suppression of Ventricular Tachycardia Associated with Acute Myocardial Infarction

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In 22 dogs with ventricular tachycardia accompanying myocardial infarction, Nupercaine hydrochloride was found to be a potent suppressor of ectopic impulses. When used alone Nupercaine also produced vomiting and convulsive movements. When combined with morphine, vomiting was eliminated, but convulsions still occurred. When combined with phenobarbital sodium or pentobarbital sodium, the ectopic impulse suppressor action of Nupercaine was enhanced and both vomiting and convulsive movements were prevented. The duration of ectopic impulse suppressor action was significantly greater in the phenobarbital-Nupercaine experiments than in any other group. No deaths occurred.

The demonstration by Mautz in 1936 that procaine, Metacaine and cocaine, locally applied, significantly increase the electrical threshold of heart muscle for premature systoles was followed by the widespread application of procaine as a protective agent in cardiac surgery. The studies of Mautz also initiated investigations designed to test the effectiveness of procaine in the prevention or suppression of cardiac arrhythmias of other origins. The experimental arrhythmias usually were produced in animals by the administration of epinephrine after sensitization with chloroform or cyclopropane. Some authors reported that procaine was effective in preventing ventricular tachycardia and fibrillation which commonly resulted from these procedures, but Huggins and co-workers found that the effects of procaine were too fleeting to be of practical value. Zapata-Diaz and co-workers terminated auricular paroxysmal tachycardia and ventricular premature systoles in a few cases by intravenous procaine, but failed in other cases of auricular paroxysmal tachycardia, auricular fibrillation, and ventricular tachycardia.

Recently, procaine amide (Pronestyl), which is removed from the blood slowly, and which therefore has a prolonged duration of action, has been found more effective in preventing epinephrine-induced arrhythmias in animals and in the treatment of certain types of arrhythmias in patients. Procaine amide has been only partially successful in the prophylaxis and therapy of cardiac arrhythmias during thoracic surgery and in the treatment of supraventricular arrhythmias. It has produced distressing toxic reactions including paroxysms of ventricular tachycardia.

The development of a standard technic for producing ventricular tachycardias associated with myocardial infarction in dogs has provided an experimental preparation which reproduces in many important features this grave type of arrhythmia in man. A high frequency ectopic ventricular tachycardia produced by myocardial infarction often has been found difficult to control with drugs most commonly used clinically for this purpose, therefore the use of such an experimental preparation provides a severe test for the drug being studied. In tests of this kind, procaine proved to be practically useless. Procaine amide was effective in reducing high frequency tachycardias to safely low frequencies, but it would not stop all ectopic activity. Furthermore, it was quite ineffective in certain...
other animals with lower frequency tachycardias and scattered ectopic ventricular complexes.\textsuperscript{15}

The effectiveness of procaine amide, though leaving much to be desired, proved that drugs in the local anesthetic group could be of practical value in the suppression of high frequency ectopic rhythms resulting from cardiac pathology. Since only procaine and procaine amide of this series of chemically related compounds had been tested with animal preparations of this kind, it appeared important that the studies be extended to other drugs of the cocaine-like group. Nupercaine hydrochloride* was chosen for testing in a new series of experiments because of its high potency as a local and spinal anesthetic, and its long duration of action.

**TECHNICS**

Myocardial infarction was produced in 22 dogs, and toxicity tests were made in two additional unoperated dogs. For surgery the animals were anesthetized with pentobarbital sodium, 30 mg. per kilogram. Using artificial respiration and aseptic surgical methods, the heart was exposed via an incision in the fourth intercostal space. The anterior descending artery was dissected free from adjacent structures just enough to allow the passage of ligatures at the level of the free edge of the left auricular appendage. The artery was occluded in two stages. The first ligature was tied snugly but not tightly around the artery together with a 20 gauge hypodermic needle, and the needle was withdrawn immediately. After 30 minutes of partial occlusion the second ligature was tied tightly, producing a complete and permanent occlusion. The wound was closed, and the dog was given careful postoperative attention, including fluids and morphine if needed.

On the morning of the following day, 16 to 24 hours after occlusion, a ventricular tachycardia with only slight variations in frequency from hour to hour was present in almost all animals. After four or five control electrocardiograms were recorded, testing was begun.

In the first four experiments Nupercaine† was administered by intravenous injection, 0.5 to 2.0 mg. per kilogram being diluted to 10 or 20 cc. with Locke's solution and injected via a plastic catheter during a period of 10 or 20 minutes. In the remaining 18 animals the Nupercaine was administered by constant venolysis from a 50 cc. burette for periods from one to four and one-half hours at a rate of 50 cc. of fluid in 30 minutes. The fluid was Locke's solution containing Nupercaine in concentrations of 1 to 2 mg. per kilogram (weight of dog) per 50 cc. In a majority of experiments the concentration was 1 mg. per kilogram per 50 cc.

There were four groups of experiments: (a) animals that received Nupercaine alone; (b) Nupercaine after morphine, 3 or 5 mg. per kilogram; (c) Nupercaine after phenobarbital sodium, 25 or 40 mg. per kilogram; and (d) Nupercaine after pentobarbital sodium, 10 or 15 mg. per kilogram.

Blood pressure and the electrocardiogram were recorded simultaneously on a Sanborn Twin-Viso cardiette. A Statham gage and SIE Transducler were employed in the pressure channel.

The arbitrary criterion of success which has been applied to tests with other drugs\textsuperscript{14,15} has been used in judging the results with Nupercaine. A successful test, according to the criterion is one in which the ectopic rate is reduced by the treatment to zero for some period of time, and maintained at a level less than one half of the pretreatment control rate for four hours or longer without toxic manifestations sufficiently severe to endanger the life of the animal. An effort was made to administer the minimal quantity of Nupercaine necessary to achieve this result.

**RESULTS**

**Nupercaine Alone**

The intravenous administration of Nupercaine to four unanesthetized animals with ventricular tachycardia on the first day after occlusion and to 18 on the second day produced ectopic impulse suppressor action in every case. In all of the four first postocclusion-day tests and some of the second postocclusion-day tests with Nupercaine alone the reduction of frequency of ectopic complexes was accompanied by toxic reactions. The toxic manifestations were retching, vomiting, and convulsive movements. Retching and vomiting occurred in all first day tests with Nupercaine alone. Convulsive movements occurred in two of the four animals.

Figure 1, the chart of the first experiment with Nupercaine, illustrates both the ectopic suppressor action and the incidence of vomiting in a dog with a moderately high frequency ventricular tachycardia. More complete suppression of the arrhythmia undoubtedly could

* The Nupercaine hydrochloride used in these studies was generously supplied by Ciba Pharmaceuticals, Inc.

† The shortened names Nupercaine, phenobarbital, and pentobarbital will be used in the remainder of the paper to mean Nupercaine hydrochloride, phenobarbital sodium, and pentobarbital sodium, respectively.
have been achieved if the rate of administration of the drug had not been slowed because of the vomiting. The doses and periods of administration are indicated in the figure. Nupercaine, 1 mg. per kilogram in 20 cc. of Locke's solution, was injected in 20 minutes at the times designated by 1, and 0.5 mg. per kilogram in 10 cc. Locke's solution was injected in 10 minutes at the times designated by 0.5.

According to the criterion of success, previously defined, all of the first postocclusion-day tests with Nupercaine alone could be classified as just barely successful. The ectopic frequencies could be maintained at levels about one half of the pretreatment ectopic rates or slightly less for periods up to four hours, but the toxic reactions were distressing. The

second postocclusion-day results will be further analyzed in succeeding sections.

**Nupercaine Following Morphine**

The effects of Nupercaine were tested following administration of morphine in five dogs with ventricular tachycardia. Four dogs received morphine, 5 mg. per kilogram, and one dog received 3 mg. per kilogram. The morphine was injected subcutaneously 30 to 75 minutes prior to the beginning of the administration of Nupercaine. Blood pressure was recorded during the main testing periods in all of these experiments.

Figure 2A is a chart of one of the experiments, and it may be regarded as portraying a typical result. During the control period, 19 to 20 hours after occlusion the ventricular ectopic rate was 190 to 210 per minute. After the beginning of the infusion of Nupercaine-

Locke's solution the ectopic rate began to decline almost immediately, though it did not reach zero until 100 minutes later. At this time Nupercaine, 4.5 mg. per kilogram, had been infused. A total infusion of 9 mg. per kilogram was given during the first day. Tests in four of the five animals in this group fulfilled the criterion, but convulsive movements occurred in all of them. There was no vomiting.

Figure 2B illustrates the results of two infusions of Nupercaine in the same animal in which the test shown in 2A was made. This later test was performed without morphine on the second postocclusion day. It can be seen that vomiting occurred during the first infusion. Prompt and highly effective ectopic suppressor action was recorded during each infusion.

![Chart of effects of administration of Nupercaine to dog with ventricular tachycardia.](image1)

**Fig. 1.** Chart of effects of administration of Nupercaine to dog with ventricular tachycardia. Ordinate, frequency in beats per minute. Abscissa, hours after occlusion. Squares, total heart rate. Circles, ectopic rate; triangles, sinus rate. Doses described in text.

![Chart of experiment in which Nupercaine was infused after morphine.](image2)

**Fig. 2(A).** Chart of experiment in which Nupercaine was infused after morphine, 5 mg. per kilogram subcutaneously. (B) Second postoperative day, Nupercaine without morphine.

In summary, morphine did not appreciably change the ectopic impulse suppressor action of Nupercaine, nor prevent convulsions. It did protect against nausea and vomiting.

**Nupercaine after Phenobarbital**

Nupercaine was administered to seven animals following sedation with phenobarbital, 25 mg. per kilogram and two dogs received 40 mg. per kilogram. The results in the tests with the different dosages of phenobarbital were similar except that the animals that received 40 mg. per kilogram slept more soundly during the tests and showed more residual effect on the following day. For these reasons the smaller dose of phenobarbital is regarded as preferable.

Figure 3 illustrates the effects of Nupercaine infusion following phenobarbital, 25 mg. per kilogram, to a dog with an ectopic ventricular tachycardia with a frequency of 210 to 220
per minute before the test. Infusion of Nupercaine, 4 mg. per kilogram in two hours, reduced the ectopic rate to zero. After this infusion had been finished for about one and one-half hours there was some return of ectopic activity. An additional infusion of Nupercaine, 3 mg. per kilogram, practically eliminated all ectopic beats for the remainder of the day. On the morning of the next day some ectopic activity had returned (rate 90 to 150). An infusion of Nupercaine, 2 mg. per kilogram, sufficed to restore a completely normal rhythm.

During this experiment, both days of testing, there was neither vomiting nor convulsive movements. In all of the eight experiments with Nupercaine after phenobarbital excellent control of the arrhythmia was achieved. There was no sign of nausea or vomiting in any experiment, and only brief, doubtful, tonic extensor movement was noted in two animals. The ectopic activity was so well controlled that a much more stringent criterion than that adopted on a basis of experience with other ectopic suppressor drugs could have been fulfilled with 100 per cent success. The administration of Nupercaine on the second postocclusion day without additional phenobarbital to five of the dogs that had been treated on the first postocclusion day with phenobarbital and Nupercaine yielded good ectopic suppressor action without toxic manifestations. Phenobarbital, 25 mg. per kilogram, therefore exerts some protective effect for as long as 24 hours or more. From a therapeutic point of view the results are regarded as definitely superior to those in the experiments with Nupercaine alone or Nupercaine after morphine.

**Nupercaine Following Pentobarbital**

Nupercaine was administered to four dogs following sedation with pentobarbital sodium. In three dogs the dose of pentobarbital was 15 mg. and in the other one 10 mg. per kilogram. All of these dogs had high frequency tachycardias, the control rates in the different animals ranging from 200 to 310 per minute. Such tachycardias have usually been found more difficult to control than those with lower frequencies. In the first postocclusion-day tests in all four of these dogs the ectopic rates were reduced to zero within a short time after the beginning of infusion of Nupercaine and good control was maintained over a period of four to six hours without toxic manifestations. The electrocardiograms in figure 4 are from the animal which exhibited the highest ectopic frequency prior to treatment in this series of experiments. The chart in figure 5 presents in detail the data from this experiment.

The record in figure 4A was taken just prior
to the beginning of the Nupercaine infusion. The ectopic rate at this time was 310 to 320.
Figure 4B, made 45 minutes after the infusion was begun, shows complete restoration of sinus rhythm (fig. 5A, 19 hr. 45 min.). At this time Nupercaine, 1.5 mg. per kilogram, had been infused. To maintain good control throughout the day a total of 6 mg. per kilogram was administered.

On the following day (fig. 5B) Nupercaine was administered without the prior injection of pentobarbital and vomiting occurred repeatedly. In this second postoperative day test a total of 7 mg. per kilogram of Nupercaine was required to suppress the relatively mild tachycardia that had redeveloped overnight. The pentobarbital protection against toxic side reactions had disappeared.

![Figure 5](chart.png)

Fig. 5. Chart of experiment from which figure 4 was made. (A) First postocclusion day, Nupercaine after pentobarbital. (B) Second postocclusion day, Nupercaine alone.

The results in the other experiments with Nupercaine following pentobarbital sodium were similar to those represented by this experiment. Both barbiturates, phenobarbital sodium and pentobarbital sodium, increased the completeness of the ectopic impulse suppressor action of effective doses of Nupercaine, and counteracted the nausea and convulsive effects. The duration of the protection against Nupercaine toxic side reactions following phenobarbital is greater than that of the protection following pentobarbital.

Comparison of Durations of Ectopic Suppressor Effects of Just Adequate Total Doses of Nupercaine in the Four Groups of Experiments

The data on duration of control by the smallest quantities of Nupercaine which were found necessary to reduce the ectopic rate to zero and suppress the tendency of ectopic impulses to return for a period of four hours are summarized in table 1. The listed mean duration of control, 8.3 hours for phenobarbital-Nupercaine and about four hours for Nupercaine alone or in other combinations, do not show the full degree of superiority of phenobarbital and Nupercaine in this category. Only the hours of actually observed control were tabulated. In the phenobarbital-Nupercaine experiments suppression of ectopic activity exceeded the period of observations in every case. This was not true in the other three series.

Both series with barbiturates were superior to the other two in that toxic side reactions were almost totally eliminated by the barbiturates used. Morphine eliminated vomiting but not convulsions.

Toxicity Tests with Rapid Administration of Nupercaine in Unoperated Dogs

Two dogs without coronary occlusion were infused with Nupercaine at a rate of 8 mg. per
kilogram per hour, a rate four times as fast as that used in almost all of the dogs with ventricular tachycardia. These unoperated dogs received pentobarbital sodium, 15 mg. per kilogram, for sedation prior to the Nupercaine tests. With continuous infusion, these animals received Nupercaine, 24.5 and 22 mg. per kilogram, before the heart and circulation failed.

During the Nupercaine infusion electrocardiograms and blood pressures were recorded and the significant measurements are presented in table 2. At the fast rate of administration used significant prolongation of P-R and QRS intervals occurred after the animals received 4 to 8 mg. per kilogram. In animal 26, A-V dissociation began at 12 mg. per kilogram. In animal 27 A-V block and nodal rhythm began after 18 mg. per kilogram. The duration of QRS increased irregularly as the administration continued.

In animal 26 mean blood pressure decreased only from 120 to 100 with the administration of the first 16 mg. per kilogram of Nupercaine and was 75 mm. after 20 mg. per kilogram had been administered. Cardiac arrest occurred after 25 mg. per kilogram. In animal 27 the blood pressure declined from 125 to 100 mm. Hg with the administration of the first 16 mg. per kilogram. A severe degree of intraventricular block began after the administration of

Table 2.—Infusion of Nupercaine at a Rate of 8 mg. per Kilogram per hour. Electrocardiographic and Blood Pressure Effects. Sedation with Pentobarbital Sodium, 16 mg. per Kilogram

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Nupercaine mg./Kg</th>
<th>Duration P-R</th>
<th>Duration QRS</th>
<th>Mean B.P.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nu 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>.08 sec.</td>
<td>.035 sec.</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>.08 sec.</td>
<td>.055 sec.</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>.14 sec.</td>
<td>.06 sec.</td>
<td>110</td>
<td>Irreg. nodal rhythm</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>A-V disso.</td>
<td>.07 sec.</td>
<td>110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>A-V disso.</td>
<td>.10 sec.</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>A-V disso.</td>
<td>.10 sec.</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>18 sec.*</td>
<td>.10 sec.</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>18 sec.*</td>
<td>.10 sec.</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.5</td>
<td>.18 sec.</td>
<td>.18 sec.</td>
<td>10</td>
<td>Corneal reflex pres.</td>
<td></td>
</tr>
<tr>
<td>25.0</td>
<td>Cardiac arrest</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Nu 27     |                   |              |              |           |         |
| 0         | .10 sec.          | .035 sec.    | 125          | Tonic convulsions |
| 4         | .16 sec.          | .14 sec.     | 135          |         |
| 8         | .16 sec.          | .16 sec.     | 115          |         |
| 12        | .16 sec.          | .16 sec.     | 105          | Vent. extra. and conv. |
| 16        | .18 sec.          | .19-.11 sec. | 100          |         |
| 18        | .19 sec.          | .20 sec.     | 75           | Intrav. block |
| 20        | .18 sec.          | .18 sec.     | 35           | Vent. extra. and conv. |
| 22        | 16-.18 sec.       |              | 20-0         |         |

* Occasional association P-QRST

Electrocardiographic and Blood Pressure Observations during Slow Administration of Nupercaine in Tests upon Control of Ectopic Rhythms.

At the slower rates of administration used in the majority of tests of ectopic impulse suppressor action (2 mg. per kilogram per hour) only minor changes in the duration of P-R and QRS were observed. Data from two experiments are reproduced in table 3. The two experiments were chosen for publication because relatively large amounts of Nupercaine were used in them. The durations of P-R and of normally initiated QRS complexes could not be measured during the control period prior to the beginning of administration of
Nupercaine because no normal complexes existed. In experiment 22 after some normal cycles were restored by Nupercaine, 1 mg. per kilogram, the duration of P-R was 0.10 second and that of QRS was 0.05. At the end of the infusion of the total amount of Nupercaine required for control of the ectopic activity, 8 mg. per kilogram, P-R was 0.12 and QRS was 0.06 second. These small decreases are only slightly greater than the range of spontaneous variations and are not indicative of dangerous effects. The data for experiment 17 show no prolongation of P-R and the increase in QRS is similar to that in experiment 22.

Table 3.—Durations of P-R Intervals and of QRS Complexes in Dogs Undergoing Nupercaine Treatment for Ventricular Tachycardia. Rate of Nupercaine Infusion 2 mg. per Kilogram per Hour

<table>
<thead>
<tr>
<th>Hrs. after occ.</th>
<th>Rate Total</th>
<th>Rate Ectopic</th>
<th>Nupercaine mg./Kg.</th>
<th>P-R sec.</th>
<th>QRS sec.</th>
<th>Mean BP mm.Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 hrs.</td>
<td>175</td>
<td>80</td>
<td>1</td>
<td>0.10</td>
<td>0.05</td>
<td>120</td>
</tr>
<tr>
<td>19 hrs. 30 min.</td>
<td>180</td>
<td>10</td>
<td>2</td>
<td>0.10</td>
<td>0.05</td>
<td>145</td>
</tr>
<tr>
<td>20 hrs. 30 min.</td>
<td>185</td>
<td>0</td>
<td>4</td>
<td>0.11</td>
<td>0.05</td>
<td>160</td>
</tr>
<tr>
<td>21 hrs. 30 min.</td>
<td>170</td>
<td>0</td>
<td>6</td>
<td>0.11</td>
<td>0.055</td>
<td>160</td>
</tr>
<tr>
<td>22 hrs. 30 min.</td>
<td>155</td>
<td>5</td>
<td>8</td>
<td>0.12</td>
<td>0.06</td>
<td>140</td>
</tr>
</tbody>
</table>

Experiment 17 with Phenobarbital 25 mg./Kg.

<table>
<thead>
<tr>
<th>Hrs. after occ.</th>
<th>Rate Total</th>
<th>Rate Ectopic</th>
<th>Nupercaine mg./Kg.</th>
<th>P-R sec.</th>
<th>QRS sec.</th>
<th>Mean BP mm.Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 hrs. 15 min.</td>
<td>180</td>
<td>110</td>
<td>1</td>
<td>0.09</td>
<td>0.05</td>
<td>90</td>
</tr>
<tr>
<td>21 hrs. 15 min.</td>
<td>180</td>
<td>40</td>
<td>3</td>
<td>0.10</td>
<td>0.06</td>
<td>95</td>
</tr>
<tr>
<td>22 hrs. 15 min.</td>
<td>175</td>
<td>25</td>
<td>5</td>
<td>0.10</td>
<td>0.065</td>
<td>90</td>
</tr>
<tr>
<td>23 hrs. 15 min.</td>
<td>190</td>
<td>30</td>
<td>7</td>
<td>0.10</td>
<td>0.065</td>
<td>90</td>
</tr>
<tr>
<td>24 hrs. 15 min.</td>
<td>185</td>
<td>10-60*</td>
<td>9</td>
<td>0.085</td>
<td>0.06</td>
<td>85</td>
</tr>
</tbody>
</table>

* Forty-five minutes after the completion of the 9 mg. per kilogram, all complexes were normal. There was no return of ectopic activity.

Blood pressure tended to rise somewhat during a number of the tests, and to remain relatively unchanged in others. There was never a tendency toward a development of hypotension during slow administration of Nupercaine. The pressures listed in the two experiments in table 3 and those charted in figures 2A, 3 and 5A are illustrative of the series.

During some ventricular tachycardia tests in which Nupercaine administration was faster than usual, some brief periods of wide slurred QRS complexes (intraventricular block) accompanied by declining blood pressure were observed. Figure 6B illustrates one such episode. The onset of the broad complexes and pressure decline occurred after the infusion of Nupercaine, 7 mg. per kilogram at a rate of 4 mg. per kilogram per hour. Recovery of normal duration of QRS complexes and of mean blood pressure to a level higher than the control occurred promptly upon suspending the infusion (fig. 6C, 30 seconds after B).

No deaths occurred in the 22 dogs with ventricular tachycardia accompanying myocardial infarction during tests with Nupercaine alone or in combination with morphine, phenobarbital, or pentobarbital.

Discussion

The foregoing experiments have shown that Nupercaine and phenobarbital, used as described, constitute a relatively safe and highly effective combination for the treatment of ventricular tachycardia accompanying myocardial infarction in dogs. No fatalities have occurred during or soon after testing with Nupercaine in 21 animals. Using essentially similar methods, similar guides to effectiveness and dosage, and similar warnings of danger, fatalities did occur in the previously reported series of tests with quinidine lactate and gluconate, procaine amide (Pronestyl),
magnesium sulfate and chloride\textsuperscript{16} and diphenylhydantoin sodium and phenobarbital.\textsuperscript{17} These observations may be regarded as evidence that drugs mentioned. In addition, the phenobarbital-Nupercaine treatment ranks high in terms of freedom from toxic side reactions. These results should lead to early clinical trials under carefully controlled conditions.

It should be emphasized that safety in the treatment of a severe ventricular tachycardia by any potent intravenously administered drug requires continuous observation with frequent records on a direct-writing electrocardiograph. These records then serve as guides to the adequacy of dosage and to degree of approach to detrimental overdosage as indicated by prolongation of P-R and QRS intervals, especially the latter.\textsuperscript{14} Frequent blood pressure determinations should be a requirement also. Pronounced hypotensive effect should be regarded as a danger sign, even when the electrocardiogram fails to show impairment of conduction.\textsuperscript{14}

The finding that phenobarbital or pentobarbital prevents toxic side reactions of Nupercaine in therapeutically effective doses might logically have been anticipated from reports of Tatum and co-workers\textsuperscript{15-20} that barbital sodium alone or in combination with paraldehyde completely prevented cocaine convulsions in dogs and monkeys, and increased the lethal dose of cocaine by 300 to 400 per cent. Tatum and co-workers reported that morphine is ineffective as an antidote to cocaine. Other drugs found ineffective or deleterious in cocaine antidote tests were atropine, chloral hydrate and ether.

Although phenobarbital significantly increased the effectiveness and usefulness of Nupercaine and of dilantin sodium\textsuperscript{17} as ectopic impulse suppressor compounds, generalizations concerning its possible usefulness in combination with other ectopic impulse suppressor substances are not justified in the absence of specific tests. Tests of quinidine compounds in combination with phenobarbital and pentobarbital are in progress. Barbiturates markedly increased the mortality in experiments with magnesium sulfate and chloride.\textsuperscript{16} Knowledge of the nature of the processes by which ectopic impulses are produced, and of the mechanisms of action of suppressor drugs is far too insufficiently advanced to supply a

\textbf{FIG. 6.} Electrocardiograms showing durations of complexes, and blood pressures in experiment with development of intraventricular block due to rapid administration of Nupercaine. (A) After rapid infusion of Nupercaine, 6.5 mg. per kilogram. (B) Wide irregular QRS complexes after 7 mg. per kilogram. Note moderately well sustained blood pressure and large pulse pressures, even in the presence of wide electrocardiogram complexes. (C) Thirty seconds after stopping infusion. Recovery of normal electrocardiogram durations, and of mean blood pressure.

in effective dosage and with adequate electrocardiographic observation, treatment with phenobarbital and Nupercaine is safer than is effective treatment with any of the other
rational basis for predicting the efficacy of drug combinations in this field.

Summary

Nupercaine hydrochloride administered intravenously by slow injection or constant venoectomy to dogs with ventricular tachycardia accompanying myocardial infarction exhibited ectopic impulse suppressor effects in each of 22 animals divided into four groups:

A. Nupercaine alone was effective in suppressing ectopic activity, but vomiting and convulsive movements commonly occurred and interfered with administration in some animals.

B. Morphine before Nupercaine prevented Nupercaine vomiting but did not prevent convulsive movements. Morphine did not enhance nor prolong ectopic impulse suppressor action.

C. Phenobarbital sodium before Nupercaine eliminated vomiting. Mild stretching of doubtful cause occurred in two of nine dogs during tests. Ectopic impulse suppressor effect was enhanced and markedly prolonged by the phenobarbital.

D. Pentobarbital sodium before Nupercaine eliminated vomiting and convulsive activity, and enhanced the ectopic suppressor effect, but did not prolong it.

Statistical evaluation of the reliability of the comparison of mean durations of ectopic suppressor action shows that the duration of control in the phenobarbital-Nupercaine experiments was significantly greater than in any other group.

No fatalities occurred in any group.

Blood pressure tended to rise or remain constant in all slow administration tests. P-R and QRS durations showed only minor alterations in such tests.

In some rapid administration tests, periods of prolonged QRS deflections and hypotension occurred. Upon stopping the fast infusion all signs returned to normal within 30 seconds.

The phenobarbital-Nupercaine combination is regarded as an effective and relatively safe combination for the treatment of ventricular tachycardia accompanying myocardial infarction when suitable precautions are observed.

Sumario Español

En 22 perros con taquicardia ventricular acompañada de infarto del miocardio, hidrocloruro de Nupercaina se encontró ser un supresor potente de impulsos ectópicos. Cuando la Nupercaina se usa sola también produce vómitos y movimientos convulsivos. Cuando se combinó con morfina, los vómitos se eliminaron pero las convulsiones no. Cuando se combinó con fenobarbital sódico o pentobarbital sódico, la acción de suprimir impulsos ectópicos fue aumentada y los vómitos y convulsiones suprimidos. La duración de la acción de suprimir los impulsos ectópicos fue significativamente mayor en el experimento con fенobarbital y Nupercaina que en ningún otro grupo. Ninguna muerte ocurrió en los 22 perros.

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