Quinidine Lactate and Gluconate in the Suppression of Ectopic Ventricular Tachycardias Associated with Myocardial Infarction

Control of Toxicity by Morphine

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In dogs with myocardial infarction, produced by a standard technic, rapid persistent ectopic ventricular tachycardia develops. Intravenous quinidine lactate and quinidine gluconate effectively control the arrhythmia in 56 to 60 per cent of the animals, but produce toxic reactions in many of them. Morphone sulfate prevents vomiting and diarrhea from quinidine, but does not prevent convulsive movements. The most effective treatment of the arrhythmia was by use of morphine followed by quinidine gluconate. This combination was successful in 89 to 100 per cent of the cases. Principles for guidance in the treatment of severe ventricular arrhythmias have been drawn from these studies.

Quinidine has long been known to be effective in terminating ventricular tachycardias.\(^1\)\(^-\)\(^4\) In some cases, however, it has failed,\(^5\)\(^-\)\(^6\) and ventricular tachycardias have been produced by its administration.\(^1\)\(^-\)\(^2\)\(^7\) Fatal ventricular fibrillation has occurred during slow intravenous administration of quinidine to a patient with ventricular tachycardia which developed following myocardial infarction.\(^8\) Ventricular premature beats, brief paroxysms of ventricular tachycardia and transient ventricular fibrillation have been precipitated by quinidine in patients who were subject to spontaneous episodes of this kind.\(^9\) Toxic manifestations of other kinds, especially nausea and vomiting, are of frequent occurrence upon intravenous administration of quinidine even when it succeeds in the abolition of abnormal cardiac rhythms.\(^2\)\(^-\)\(^4\)

Quinidine is widely regarded as the drug of choice for the treatment of ventricular tachycardias in spite of the untoward occurrences.\(^2\)\(^-\)\(^5\)

It is apparent, therefore, that there is need for carefully controlled experiments to determine and analyze the conditions under which success, failure, and exacerbation of the arrhythmia result from its use. In the past, controlled study of the effectiveness of drugs and procedures in the suppression of dangerous cardiac arrhythmias of kinds similar to those which occur in patients (except arrhythmias induced by drugs) has been severely limited by the lack of a method by which such arrhythmias could be produced in experimental animals.

A technic for the production in dogs of a high frequency ectopic ventricular tachycardia associated with myocardial infarction has recently been developed.\(^10\) Ninety per cent or more of the animals prepared by the standardized technic develop ectopic ventricular tachycardias with rates of 160 per minute or higher and rates of 200 to 260 were developed in 53 per cent of a recently tabulated series of 32 consecutive dogs. In an occasional dog the maximal ectopic rate reaches 300. The delayed ventricular tachycardia has its onset four and one-half to eight hours after occlusion of the artery, that is, after a period of occlusion that approximates the minimal duration of ischemia that is required to produce microscopically visible evidence of necrosis.\(^10\)\(^-\)\(^12\) After the onset of the

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tachycardia the rate increases rapidly to a maximum which is reached within 10 to 20 hours after occlusion. The tachycardia, if untreated, typically lasts two to four days, and there may be some ectopic beats on the fifth day.

The availability of dogs with rapid ectopic ventricular tachycardia associated with myocardial infarction has provided an opportunity for controlled evaluations of the effects of drugs upon this serious arrhythmia. Using these animals after the development of a rapid and persistent tachycardia, the effects of quinidine lactate and quinidine gluconate have been studied to determine their effectiveness in the suppression of ventricular ectopic rhythms, and their toxicity. The effects of morphine in conjunction with quinidine have been studied also, and this developed into an important part of the investigation.

**MATERIALS AND TECHNICS**

Fifty dogs were used in the study of ectopic impulse suppressor effects of quinidine lactate and gluconate. In addition four dogs were used in preliminary experiments in which quinidine sulfate was administered.

For surgery, the dogs were anesthetized with pentobarbital sodium, 30 mg. per Kg. Using artificial respiration and aseptic surgical techniques, the anterior descending artery was ligated via a small incision in the left fourth intercostal space. The artery was dissected free at a level between 0 and 5 mm. distal to the free edge of the left auricular appendage. A doubled ligature was passed beneath the artery and cut to provide two ligatures. One of the ligatures was then tied snugly but not tightly around the artery together with a 20 gage hypodermic needle. The needle was withdrawn, leaving the artery constricted but passing some blood. The second ligature was tightened 30 minutes later, occluding the artery. The chest was closed in layers, the lungs inflated and natural respiration restored.

Electrocardiographic observations and records were made at frequent intervals. Ventricular ectopic rates and total heart rates were measured from electrocardiograms and plotted on charts.

Drug tests were begun during the morning of the first postoperative day, that is, 15 to 20 hours after occlusion. In almost all animals the ectopic ventricular rate at that time was between 180 and 250 beats per minute. In a number of animals additional tests were performed on the second and third postoperative days when the frequency of the returned or persisting ectopic ventricular tachycardia usually was lower than that which existed prior to treatment on the first postoperative day.

All drug tests were performed without anesthesia except in those trials in which morphine was used as sedation for blood pressure measurements, and to test the combined effects of morphine and quinidine upon the ectopic ventricular tachycardia, and upon the toxic manifestations.

The quinidine preparations were administered intravenously. To facilitate the injections and to insure complete control over them, a small plastic catheter was inserted into the femoral vein and kept there throughout the one, two, or more days of testing in a majority of experiments. A flexible wire was kept in the lumen of the catheter except during injections.

*Dosage and Rate of Administration.* A dose of 10 mg. per Kg. of the quinidine compound under test was adopted as a standard and used in all experiments except three of the early ones. The duration of an injection (governing rate of administration) was standardized at five minutes. The dose was diluted with saline to 20 cc.

Multiple control records were made at 15 to 30 minute intervals during a period of one to two hours just prior to the administration of the first dose of quinidine in each test. The term “test” is used to designate all of the repeated doses, procedures, and observations made upon an animal in any day of testing.

**RESULTS**

**Quinidine Lactate.** Thirty-nine tests of the effects of quinidine lactate alone were made upon 26 dogs while fully unanesthetized and exhibiting a persistent ectopic ventricular tachycardia.

The results were strikingly variable. In 16 tests, or 41 per cent of the total number, the arbitrarily established criterion of “therapeutic success” was attained. The criterion required that the ectopic rate be reduced to zero and maintained during a period of four hours or longer at a frequency lower than one-half of that which existed during the control period just prior to the beginning of treatment. These 16 tests with most favorable results were performed upon 14, or 54 per cent, of the dogs.

Toxic signs, i.e., vomiting, diarrhea, or convulsive movements, occurred during eight of these 16 tests in which the ventricular tachycardia was most successfully controlled. In a

*The quinidine lactate and quinidine gluconate used in these studies were generously supplied by Eli Lilly and Company.*
number of other tests adequate administration of the drug was interfered with by severe toxic reactions. In later experiments it was learned that the vomiting and diarrhea produced by quinidine could be totally eliminated by morphine (see sections on toxicity and on quinidine compounds after morphine). In view of these findings, the percentage of favorable results in this first series should be regarded as conservative.

Graphic and detailed representations of the results of administration of quinidine compounds are contained in the charts. Figure 1 shows the usual effects upon ectopic activity of the initial doses of quinidine lactate injected at 30 minute intervals. This was found to be the optimally effective spacing of doses for cumulative suppressor effect upon the ectopic rhythms. In this animal with an ectopic rate (total heart rate) of 230 per minute, each dose resulted in a quick but moderate diminution of the ectopic rate, and the effects were cumulative with succeeding doses. The administration was interrupted because of the advent of convulsive movements before ectopic complexes were eliminated, but the ectopic rate remained within a safely low range. The animal survived and, except for a period of convulsive move-

ments, appeared to be in good condition at all times.

An experiment showing unusually effective suppressor action is represented in figure 2. The first dose, 10 mg. per Kg., restored an entirely normal rhythm for a few minutes, and the rate of ectopic discharging was kept at a level below one-half the control rate for an hour, though ectopic complexes were returning rapidly at the end of the hour. The addition of a second dose eliminated all ectopic activity for about two and one-half hours, after which there was a rapid increase. Following the third dose few ectopic beats were recorded during the remaining four hours of observations on that day. On the following day some ectopic activity (40 to 90 per minute) was present. A single dose sufficed practically to eliminate it. In general the higher ectopic rates (200 and above) were more difficult to control than the lower ones. Ventricular tachycardias with rates of 220 or above were distinctly more resistant to treatment than those with rates below 180. However, there were marked variations in response which could not be accounted for on a basis of ectopic rate.

Quinidine Gluconate. The effects of quinidine gluconate alone upon ectopic ventricular tachy-
cardias were recorded during 12 tests in 10 dogs. In six, or 50 per cent, of the tests, the ectopic frequency was reduced to zero and

ments interfered more seriously in the experiments with quinidine lactate. It is probable that no significant difference in ectopic impulse

maintained at less than one-half of the pre-treatment rate for more than four hours. These most favorable therapeutic results were found in six dogs or 60 per cent of the total number of animals. These percentages are slightly higher than the corresponding ones obtained with quinidine lactate, but convulsive move-
suppressor action is to be found between the two quinidine compounds.

A chart of one of the experiments with quinidine gluconate is reproduced in figure 3. This animal had a ventricular tachycardia with a rate of 240 to 250 on the morning of the first postoperative day prior to the first injection

![Figure 2](http://circ.ahajournals.org/)

**FIG. 2.** Effects of quinidine lactate in animal with moderately rapid ectopic ventricular tachycardia. Keys to chart same as for figure 1.

![Figure 3](http://circ.ahajournals.org/)

**FIG. 3.** Effects of quinidine gluconate in animal with rapid ectopic ventricular tachycardia. Keys to chart same as for figure 1.
of quinidine gluconate. Each dose lowered the ectopic rate immediately, and following each reduction there was a prompt rise toward the preceding high level. However, cumulative action was shown in the fact that after each additional dose the ectopic rate reached a new low level, and following the fifth dose the rise was much slower than the rises following earlier doses. After the sixth dose there was yet another rise and spontaneous fall after which no further doses were needed. Thirteen hours after the last dose the ectopic rate was only 30 per minute. This experiment is an example of successful control of a severe ventricular tachycardia by a sufficient number of doses more widely spaced than the 30 minute intervals which were found to be optimal for relatively quick suppressor effects.

Quinidine Lactate following Morphine in Strongly Analgesic Doses. Six tests of the ectopic suppressor effects of quinidine lactate following morphine were carried out in five dogs. In four of the six tests ectopic activity was abolished for a time and maintained at a frequency less than one-half of the control rate for more than four hours. The two failures were first and second postoperative day tests in the same resistant animal. Effective suppression of ectopic impulses was achieved in four of five animals, but one of them died in standstill one hour after the last dose. In three of the tests, all in the successfully controlled group, there was a significant diminution in ectopic frequency, though not a large one, between the injection of morphine and the first dose of quinidine lactate.

Quinidine Gluconate following Morphine. Nine tests of the effects of quinidine gluconate following morphine upon ventricular tachycardia were performed in nine dogs. All ectopic activity was eliminated temporarily in each of the animals and the ectopic rate was below one-half of the control rate longer than four hours (six hours to permanent) in eight of them and possibly the other one also. Unfortunately records from one animal were discontinued two and one-half hours after ectopic activity was brought under control. At least 89 per cent, and possibly 100 per cent, of the morphine-quinidine gluconate animals belong in the well-controlled group. Between the administration of morphine and the first dose of quinidine gluconate the ectopic frequency declined significantly in six of the nine dogs. This observation together with a similar one in the morphine-quinidine lactate experiments may indicate that morphine alone has a minor ectopic impulse suppressor effect, but it appears more probable that the ineffectual reductions in frequency resulted from general sedation.

Toxic Reactions. Vomiting, diarrhea, and convulsive movements figured prominently in the results of both quinidine compounds, gluconate and lactate. Since the experiments were performed for the study of the suppressor effects of these drugs upon ectopic impulses, the number of 10 mg. per Kg. doses administered was determined by the persistence, disappearance, and recurrence of ectopic activity, except that in some experiments the administration of quinidine had to be interrupted or postponed because of the severe toxic reactions.

In the 39 tests with quinidine lactate alone vomiting occurred in 10, or 26 per cent, and convulsive movements in nine, or 23 per cent. Diarrhea accompanied the vomiting in a few experiments, and in one test defecation without vomiting occurred after each dose. Quinidine gluconate alone produced vomiting in three of 13 tests, or 23 per cent, and convulsive movements in one, or 8 per cent. The incidence of vomiting was about equal with the two quinidine compounds, but convulsions occurred in a significantly higher percentage of cases and were more prolonged in the experiments with quinidine lactate.

In the 15 tests in which morphine was given one to three and one-half hours prior to the first dose of quinidine (six with lactate, nine with gluconate), no vomiting or diarrhea occurred. Convulsions occurred in three. Morphine was administered subcutaneously in all trials. The doses in milligrams per kilogram were 5 in nine trials, 4.5 in two trials, 2 in two trials, 7 in one trial, and 7.5 in one trial.

The administration of morphine to a dog commonly induces vomiting. When repeated doses of morphine were injected, however, only the first one induced vomiting. Morphine gave complete protection against the induction of
vomiting by additional morphine (see Leake\textsuperscript{40}) just as it protected against the induction of vomiting and diarrhea by quinidine.

**Blood Pressure.** Systolic, diastolic, and mean blood pressures were recorded from the femoral artery in a number of experiments via a small plastic catheter connected with a Statham gage transducer modified for use with a carrier-frequency amplifier.\textsuperscript{*} A Sanborn Poly-Viso Cardiette recorded the pressure tracing and electrocardiogram simultaneously (fig. 4). The recording was changed from mean to systolic-diastolic pressures for a few beats in a majority of trials, thus permitting mean pressure and pulse pressures to be measured. This change could be made instantaneously by turning a valve.

Mean pressure measurements just before and immediately after injections of quinidine lactate, 10 mg. per Kg., injected slowly during a period of five minutes, revealed that the pressure dropped during 17 injections and remained unchanged in one. The range of the diminutions was 0 to 45 mm. Hg. The average decline was 18 mm. Hg. Recovery of the mean pressure was 50 to 80 per cent complete in 15 minutes and 75 to 100 per cent complete in 30 minutes. The one injection that produced a 45 mm. drop was given to an animal that died shortly afterward.

Upon administration of quinidine gluconate in the same dosage by the same technic, the mean blood pressure fell during 15 injections, rose during two (both in the same animal) and was unchanged in one. The range of modification was +40 to −45 mm. Hg. The average change was a drop of 16 mm. Hg, which is almost identical with the average result obtained with quinidine lactate. The rate of recovery from the diminutions in pressure following injections of the two quinidine compounds were equal also.

Charts showing the mean blood pressure reactions together with the ectopic impulse suppressor effects of quinidine gluconate are reproduced in figures 5 and 6. The blood pressure reactions of these two animals were very different. Each animal had received morphine, 5 mg.

\textsuperscript{*} Made by Southwestern Industrial Electronics Co., Houston, Texas.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{Electrocardiograms and systolic-diastolic and mean arterial pressure records in dog with ectopic ventricular tachycardia while under test with morphine and quinidine gluconate. \textit{Control}, one and one-half hours after morphine sulfate, 5 mg. per Kg., but before first dose of quinidine gluconate. Prior to morphine, ectopic rate was 230. At time of control, ectopic rate averaged 180 in a longer record. \textit{1st inj.}, immediately after first dose of quinidine gluconate, normal rhythm and somewhat reduced blood pressure. \textit{1 hr.}, record made 1 hour after first dose of quinidine gluconate and 30 minutes after second dose, showing recurrence of ectopic rhythm and status of the arterial pressures. \textit{5 hr.}, record made 5 hours after first dose of quinidine gluconate and 1 hour after the fifth and last dose, showing a lasting normal rhythm and normal arterial pressures (115/60).}
\end{figure}

per Kg., for analgesia more than three hours before the first dose of quinidine. The experiment illustrated in figure 5 was unique in that

the only rises in mean pressure during quinidine injections that were recorded during the whole series of experiments occurred in this animal.

The fact that the rises in pressure occurred only after the third dose and during the fourth
and fifth may perhaps be correlated with the observation that convulsions usually occurred after three or more doses if they occurred at all. Convulsions are indicative of central nervous system excitation, and the increases in blood pressure could have resulted from nervous excitation on a subconvulsive level. Impulses output due to improvement in pumping, and (b) that they might have resulted from an increased blood volume due to additions of saline were judged to be improbable or relatively unimportant factors. Otherwise, rises in pressure should have occurred in all animals, not in one alone.

![Fig. 5. Effects of morphine and quinidine gluconate upon rapid ectopic ventricular tachycardia and mean blood pressure.](image)

![Fig. 6. Effects of morphine and quinidine gluconate upon rapid ectopic ventricular tachycardia and blood pressure in an unusual animal in which some of the quinidine injections produced rises in the mean blood pressure.](image)

could radiate from cranial nuclei to the heart and vasoconstrictor effectors via sympathetic pathways. The increase in heart rate following the third, fifth, and seventh doses may tend to confirm this interpretation though the rises in pressure and in rate could logically be explained as results of vagal paresis. Other suggestions (a) that the rises in blood pressure might have resulted from increased cardiac output due to improvement in pumping, and (b) that they might have resulted from an increased blood volume due to additions of saline were judged to be improbable or relatively unimportant factors. Otherwise, rises in pressure should have occurred in all animals, not in one alone.

The diminutions in pressure could, conceivably, be due to more than one effect of quinidine also. There is evidence that it produces vasodilation and weakens the contraction of cardiac muscle, although in some experiments small doses have increased the shortening of auricular and ventricular muscle with no change in rate, or even an increase. In one study in which increased excursion of the ven-
tricular myograph was reported, an increase in the dose of quinidine resulted in weakening of the ventricular muscle.\(^{19}\)

Pulse pressures were significantly reduced during the dip in mean pressures in a number of trials in our series. This suggests that the systolic discharge was reduced, but does not prove it because the femoral pulse pressure is greatly influenced by superimposed waves which are subject to reduction by a lowering of the peripheral resistance. Experiments with skeletal muscle and perfused hearts, summarized by Sollmann,\(^{20}\) support the view that quinidine weakens contraction.

Vasodilatation appears to be a very sensitive reaction to quinidine, and it is probable that this is the chief cause of the decline in mean blood pressure that follows the injection of a small or moderate dose. Following a very large dose or a succession of doses within a brief period, weakening of the myocardium and vasodilatation both probably contribute to the production of hypotension.

Production or Exacerbation of Ectopic Ventricular Tachycardia by Quinidine. This response was observed in three experiments. In two of them paroxysms of ventricular tachycardia accompanied convulsive movements.

The association of the production of ventricular ectopic activity with the occurrence of convulsions in some cases following the administration of quinidine may be regarded as circumstantial evidence that these increases in ectopic activity may have been induced by increased nervous activity. It is well known that sympathetic nerve excitation and injected epinephrine can produce or facilitate the production of ectopic ventricular beats.\(^{21-23}\)

Although recent studies have shown that sympathetic impulses to the heart constitute only a relatively minor factor in the production of the ectopic ventricular tachycardia which develops with myocardial infarction in the dog,\(^{24}\) a large increase in the discharge of cardiac sympathetic impulses and of epinephrine, induced by quinidine excitation of the nervous system, could be the excitatory mechanism which produces the ectopic activity in these exceptional cases. This concept places the ectopic impulse production by quinidine upon the same basis as the blood pressure raising effect. Both are relatively infrequent reactions to the administration of quinidine.

Fatalities: Danger Signs. A total of six deaths occurred during or soon after testing procedures. Three animals died during tests with quinidine lactate alone, two died during tests with quinidine lactate and morphine, and one died during the night following a test in which quinidine gluconate and morphine were used. Certain observations from the records of these animals may contribute to better recognition and evaluation of signs of danger during treatment with quinidine, especially via the intravenous route.

Since widening of the QRS deflection has long been recognized as a sign of quinidine action and since lengthening beyond certain limits has become a sign of overdosage, the durations of QRS at various stages of these six experiments with fatalities have been measured carefully.

Four of the six animals that expired exhibited widening of the QRS deflection by 75 to 100 per cent or more before death, but one of these four developed the widening and died after only one dose (10 mg. per Kg.) of quinidine. This animal and two others that did not develop significant widening of QRS constitute 50 per cent of the fatality cases. In one-half of these cases, therefore, no warning could have been obtained from the duration of the QRS deflection prior to the final dose. Furthermore, a number of animals among the 44 survivors developed prolongation of QRS by as much as 100 per cent. Such a prolongation cannot be regarded as a sure sign that death is imminent. Nevertheless, a great prolongation should be heeded as a warning. The practice of withholding quinidine after the QRS is prolonged by 50 per cent\(^{2} \text{ appears to be conservative and desirable. Since significant prolongation does not occur in all quinidine fatalities, other signs are needed.}\)

Two of the six animals that died during testing exhibited intense dyspnea. One of them had only a moderate dyspnea before the first dose of quinidine, but the degree of dyspnea became more severe after each dose. This animal died five minutes after the injection of the
third dose. The other fatality case with intense dyspnea exhibited the dyspnea prior to the administration of quinidine and died after only one dose, 10 mg. per Kg. In certain other animals, some increase in respiratory movements followed the administration of quinidine, but these increases were moderate and lasted for only a few minutes, coinciding with the brief period of reduced blood pressure that was commonly observed. Dyspnea was produced by quinidine in only the one animal cited.

Dyspnea was rare in the 50 dogs with myocardial infarction used in this study. In addition to the two fatality cases, this sign was noted in the protocol of only one other dog, and that observation was on the third postocclusion day when the dog had a normal heart rhythm with a rate of 90. The dog had received no treatment since the first postocclusion day when a rapid ventricular tachycardia was brought under control by three doses of quinidine gluconate.

Blood pressure was recorded continuously during the quinidine tests in 11 of the 50 animals. Two of the fatalities were from these 11 cases. The mean pressures prior to the first quinidine injections were distributed as follows: two dogs, 105 mm. Hg; one dog, 100 mm.; two dogs, 90 mm.; two dogs, 85 mm.; four dogs, 70 mm. Both of the dogs that died were from the 70 mm. group.

With so few cases of marked dyspnea and hypotension as a basis, perhaps no conclusions should be reached, but the observations upon these fatalities suggest that in the presence of either of these conditions quinidine and other depressant drugs should be used only with great care.

**DISCUSSION**

*Comparison of Results Obtained in Dogs with Data in Clinical Reports.* The ventricular tachycardias which are being studied in the dog preparations begin after a period of four and one-half to eight hours following occlusion. The severity of the ventricular tachycardia increases rapidly during the next few hours as the infarction develops.

Numerous authors have reported clinical ventricular tachycardias that were associated with myocardial infarction. The collection of human cases that can be correlated most definitely with the observations on dogs are those of Armbrust and Levine. In their series of 107 patients with paroxysmal ventricular tachycardia, 79 cases, or 74 per cent of the series, had coronary disease as the underlying cause of the tachycardia. In 44 cases, the attack was associated with acute myocardial infarction. The onset of the ventricular tachycardia occurred *most often on the first day of the infarction*, though the incidence was high on each day of the first two weeks. The finding of most frequent onset on the first day conforms to the observations in the dog with a large infarct. The onset of tachycardia in some patients after a delay of a number of days differs from the dog with its maximal delay of eight hours. It is possible, however, that in some patients the initial symptoms resulted from obstruction of a relatively small artery which did not produce ectopic activity, and that the ventricular tachycardia was produced some days later as a result of additional occlusions or extension of the thrombosis with enlargement of the necrotizing mass of muscle. The differences in time of onset of the tachycardia with respect to time of occlusion may be apparent differences only.

In the cases of Armbrust and Levine the attacks of tachycardia were of two kinds, intermittent and persistent. The intermittent attacks were short paroxysms, lasting seconds or minutes, which ceased spontaneously or were readily controlled by therapy. The persistent type of attack was more difficult to control. In 31 persistent episodes of ventricular tachycardia, intravenous quinidine was successful in controlling the attacks in 20 cases or 65 per cent of them. This percentage of favorable results in patients with severe arrhythmias lies within the range of percentages of successful results in the dogs with the persistent high frequency tachycardias.

In the dog experiments also there were a few animals with intermittent ventricular ectopic rhythms which ceased spontaneously or were easily suppressed by drugs, and a larger number of animals with persistent high frequency tachycardias which required larger amounts of quinidine for control, and some of these severe
arrhythmias could not be controlled by quinidine.

Recent studies upon blood quinidine concentrations in patients have shown that in order to raise the blood level to the 4 to 9 mg. per liter range found necessary to restore sinus rhythm, the required dosage was 0.4 to 0.6 Gm. of quinidine every two hours for five doses. The highest concentration was required in a case of paroxysmal ventricular tachycardia. A dose of 0.6 Gm. to a 70 Kg. man would be 8.6 mg. per Kg., closely approaching the 10 mg. per Kg. doses used in the dog experiments. Five doses also approximate the average number of doses required during the several hours of a test in severe ventricular tachycardia in the dog. It should be remembered that our studies with dogs have been concerned with only the ectopic ventricular tachycardias that arise in association with acute myocardial infarction. No comparisons with arrhythmias arising from other causes are as yet attempted.

Nature of the Arrhythmia and Mechanism of Its Suppression. Critical examination of the electrocardiograms (see fig. 4) reveals evidence that the abnormal complexes must be due to discrete ectopic ventricular impulses, and not to re-entrant conduction. Re-entrant conduction would be continuous conduction within intraventricular circuits. Intraventricular conduction is represented in the electrocardiogram by the QRS deflection. Therefore re-entrant conduction in the ventricles, if it existed, would produce continuous QRS complexes, that is, each QRS would be joined to the next one before and after. This is clearly not to be found in a great majority of records. In the ventricular tachycardia record reproduced in the control electrocardiogram of figure 4 the QRS deflections are widely separated from each other, occupying no more than about one-fifth of the total time in the record instead of the entire time as continuous intraventricular conduction would require. As the frequency of abnormal complexes is reduced by treatment, the separations become wider. In extremely fast ventricular tachycardias, 300 per minute and above, the wide QRS deflections that commonly are found in such frequencies often appear to be joined or nearly so. Under these conditions there is grave danger of a change from ventricular tachycardia to ventricular fibrillation, a condition that is characterized by continuous conduction. In view of the universally branching syncytium that makes up the musculature of the ventricles, it is highly improbable that re-entrant conduction could occur in a cyclic manner in the ventricles for more than one or two beats before conduction would become disorganized into fibrillation. It is concluded that the ventricular tachycardia results from ectopic impulses arising in ventricular muscle. In previous papers evidence that these impulses arise in the boundary of the infarct has been presented and the probable excitatory factors discussed. The reduction of the ventricular tachycardia by quinidine therefore is attributed to its suppressor action upon ectopic pacemakers in agreement with Gold.

Clinical Implications. The similarities in the reactions of dogs with persistent high frequency ventricular tachycardias accompanying myocardial infarction to the reported reactions of patients with similar tachycardias, following intravenously administered quinidine compounds, suggest that observations made upon this kind of animal preparation may be of value in deriving principles for the improvement of treatment of this kind of severe ventricular arrhythmia.

The main conclusions of a practical nature which can be drawn from the present series of experiments are the following: (a) In order to eliminate a high frequency ectopic ventricular tachycardia, or to produce a lasting reduction of the ectopic frequency to a safe level, it usually is necessary to administer large and relatively frequent doses of quinidine (as compared with the usual regime) during the first few hours. (b) A large dose of morphine sulfate, administered subcutaneously, has been found effective in stopping or preventing all vomiting and diarrhea which might result from quinidine administration. (c) In exceptional cases one or two standard doses of quinidine (10 mg. per Kg., slowly infused) are sufficient to control the arrhythmia. Administration should be stopped when this point is reached. (d) In other exceptional cases even one or two standard doses can be fatally toxic. In this series, the
animals that died after only a small amount of quinidine exhibited intense dyspnea, hypotension, or prolongation of the normally initiated QRS complex by as much as 75 to 100 per cent of the control. These are regarded as important warning signs that quinidine should be withheld or that caution must be used in administering any further doses. The four fatal cases reported by Armbrust and Levine\textsuperscript{5} were described as having pulmonary edema, congestive heart failure, and shock. (e) It is not necessary to eliminate all ventricular ectopic beats, and in some cases it is dangerous to attempt to do so. A reduction of the rate of an ectopic ventricular tachycardia from 200 to 250 per minute to 100 will abolish danger of ventricular fibrillation\textsuperscript{7} and may be calculated to improve pumping action enough to markedly reduce the danger of cardiac and circulatory failure.\textsuperscript{8} (f) During the treatment of a persistent high frequency ventricular tachycardia with quinidine, and other ectopic suppressor drugs as well, the constant presence and frequent use of an electrocardiograph should be required. This is necessary in order to make use of the principles summarized in c, d, and e.

**SUMMARY**

A method of producing animal preparations with rapid, persistent, ectopic ventricular tachycardia associated with myocardial infarction has been developed. These animals duplicate some of the major features exhibited by patients with myocardial infarction in whom a severe ventricular arrhythmia arises, including types of arrhythmia and reactions to quinidine.

Four series of experiments were performed with these animal preparations. The tests made in the four groups were as follows: (1) tests with quinidine lactate alone, (2) tests with quinidine gluconate alone, (3) tests with morphine sulfate followed by quinidine lactate, and (4) tests with morphine sulfate followed by quinidine gluconate.

In series 1, 2, and 3 the percentages of animals in which successful control of the arrhythmia was achieved in one or more tests were 54, 60, and 60, respectively. No significant difference appears in these results. In series 4, in which morphine sulfate was followed by quinidine gluconate successful control was achieved in 89 to 100 per cent of the animals. These results are regarded as therapeutically superior to those of the other three groups.

Vomiting, diarrhea, and convulsions complicated a number of the experiments. The incidence of vomiting was about equal following quinidine gluconate and lactate. The incidence of convulsions was greater following quinidine lactate.

Morphine sulfate, 5 mg. per Kg., stopped or completely prevented vomiting and diarrhea from both quinidine preparations. Morphine did not stop or prevent convulsions.

During injections the blood pressure declined somewhat in almost all cases. In one animal the pressure rose following some injections.

Paroxysms of ectopic ventricular tachycardia were induced by quinidine injections in three of the 50 animals. Convulsive movements accompanied the paroxysms in two animals. The unusual paroxysms are attributed to increased excitation of the central nervous system and consequent sympathoadrenal stimulation of the heart.

Study of the six fatalities indicates that quinidine administration may be especially dangerous in the presence of marked dyspnea or pronounced hypotension. Prolongation of QRS is not present to serve as a warning sign in all cases, but when it does exist in marked degree, administration of quinidine should be stopped.

Evidence is presented to show that the abnormal rhythm is due to ectopic impulses and not to re-entrant conduction. The reduction in abnormal activity by quinidine is due to suppression of ectopic pacemakers.

From the observations a list of principles which should be of value in the treatment of severe ventricular tachycardias has been formulated.

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