Quinidine Syncope

Paroxysmal Ventricular Fibrillation Occurring during Treatment of Chronic Atrial Arrhythmias

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Quinidine occupies an almost unique place in the therapy of cardiac arrhythmias. In the 45-odd years of its clinical use only very few drugs possessing similar pharmacologic properties have been found, but none could match quinidine in its broad therapeutic applications. Consequently, the knowledge concerning its clinical use and toxicity is of considerable importance, for patients who tolerate this drug poorly or are hypersensitive to it may face the prospect of inability to have normal cardiac rhythm restored or maintained. The pharmacology and toxicology of quinidine have been the subject of several reviews, but certain aspects of it are still poorly understood. The purpose of this communication is to focus attention on syncopal attacks occurring during quinidine therapy and apparently related to paroxysms of ventricular flutter or fibrillation. Until very recently such ventricular arrhythmias have been considered a very rare manifestation of quinidine toxicity, yet they may well be occurring quite frequently, unrecognized, in the course of quinidine therapy.

Material and Methods

The report is based on eight cases with repetitive ventricular arrhythmias occurring during conversion of chronic atrial arrhythmias with quinidine, or after conversion of such arrhythmias by electric atrial defibrillation. These cases were observed during a 4-year period in this unit. While the exact number of courses of quinidine administered to patients with atrial arrhythmias is not known, it is estimated that the figure is between 200 and 300.

Quinidine therapy has been administered with slight modifications, as follows: A priming dose of 0.2 Gm. of quinidine sulfate every 4 hours was frequently given for 1 or 2 days. As a rule, the rapid method of administration of quinidine was then used, namely, five doses every 2 hours were administered orally, beginning at 5:00 or 6:00 a.m. The initial dosage varied from 1.0 to 2.0 Gm. per day and was increased, usually every other day, by increments of 0.6 or 1.0 Gm. per day. The total daily dose rarely exceeded 4.0 Gm. During the past 2 years blood quinidine levels were determined daily, usually at 3:00 p.m., or more often, if indicated. Quinidine blood level determinations were performed by the fluorometric method of Brodie and Udenfriend, but the simplified method was used, not requiring extraction. Consequently, blood quinidine levels were appreciably higher than those reported by Sokolow and Edgar, roughly twice their corresponding levels. Thus, average conversion of atrial fibrillation occurred with quinidine blood levels between 10 and 20 mg. per liter, usually under 15 mg. per liter. Quinidine blood levels were considered excessive when they reached or exceeded 25 mg. per liter.

Quinidine therapy was terminated in unsuccessful cases when quinidine blood levels reached toxic proportions; when electrocardiograms showed significant myocardial toxicity (prolonged QRS complexes, by more than 25 per cent, multiple premature contractions); or when side effects of quinidine became truly intolerable. Lesser degrees of gastrointestinal upsets were controlled as long as possible by appropriate medication. In many instances with unsuccessful quinidine therapy another course was administered with the use of combined quinidine and procaine amide. Quinidine gluconate, administered orally every 6 to 8 hours was also occasionally used in those patients who had gastrointestinal upsets after modest doses of quinidine sulfate. After March 1963 most patients with chronic atrial flutter or fibrillation underwent electric defibrillation with the direct-current shock triggered by the R wave of the electrocardiogram. Such patients were started on quinidine maintenance therapy the day before
defibrillation, usually by the administration of 1.6 Gm. of quinidine sulfate per day in divided doses.

**Case Reports**

**Case 1**

M. S., a 54-year-old woman, was well until March 1958, when she first developed dyspnea and palpitations. She was found to have mitral stenosis with atrial fibrillation, apparently of recent onset. She was controlled by digitalis, but in spite of good medical management developed progressive disability and in October 1959 entered the hospital for mitral valvotomy. The operation was performed on October 12 and the patient was making a satisfactory recovery. On October 16 quinidine therapy was started by the administration of 0.2 Gm. of quinidine sulfate every 4 hours. On October 20 the mode of administration of the drug was changed to the 2-hour method: The patient was given doses of 0.4 Gm. at 6:00, 8:00, and 10:00 a.m. and at 12:00 noon. At 1:00 p.m. the patient complained of feeling “numb.” The 2:00 p.m. dose of the drug was cancelled. At 2:30 p.m. she vomited. At 3:30 p.m. she developed a convulsive seizure, without warning. The patient appeared deeply cyanotic, her respiration stopped. Within about 2 minutes her thorax was opened and cardiac massage instituted, followed by termination of ventricular fibrillation by the electric defibrillator. The patient persisted in atrial fibrillation but her cardiac status gradually deteriorated and she died on October 24. Permission for autopsy was not granted.

**Case 2**

E. D., a 55-year-old woman, was known to have rheumatic heart disease with mitral stenosis. In 1957 she developed atrial fibrillation and, coincidentally, progressive symptomatology leading to moderate disability. Mitral valvotomy was performed in October 1958 with satisfactory results, and the patient left the hospital in good condition. No attempt to restore sinus rhythm at that time was made, but the patient re-entered the hospital in June 1959 for quinidine therapy. On June 21 and 22 she received 0.2 Gm. of quinidine sulfate every 4 hours. On June 23 the 2-hour schedule was first used and she received five doses of 0.4 Gm. of the drug between 6:00 a.m. and 2:00 p.m. The patient felt well all day. During afternoon rounds the cardiac rhythm was found to be regular and an electrocardiogram

![Figure 1](image-url)

*Figure 1*

Electrocardiographic tracing of lead II in case 1 during postsyncopal stage of ventricular irritability.
showed that normal sinus rhythm had been re-established. Markedly prolonged Q-T interval was noted and interpreted as quinidine effect. At 8:30 p.m. the patient complained of "feeling funny." A few minutes later, while a physician was examining her she had a sudden convulsive seizure with fecal and urinary incontinence. The attack lasted about 2 minutes during which time mouth-to-mouth resuscitation was instituted, but no other measures were necessary as the attack terminated spontaneously. During the attack no cardiac action could be heard. Following the attack sinus rhythm was restored. The patient felt well and no ectopic beats were recorded.

The following morning the contemplated maintenance therapy was started and a dose of 0.4 Gm. of quinidine sulfate was given at 8:00 a.m. At 11:30 a.m. the patient had a convulsive seizure without any warning which lasted 1½ minutes and terminated spontaneously. During the following 2 hours the electrocardiogram revealed evidence of ventricular irritability with multiple premature contractions, runs of ventricular tachycardia, and short bouts of ventricular fibrillation (fig. 1). The patient remained conscious during this time and had no important symptoms. She made a satisfactory recovery and left the hospital in sinus rhythm without antiarrhythmic drugs. Regular rhythm persisted for the next 3 years.

Case 3
M. D., a 50-year-old woman, was known to have a heart murmur since her early twenties. At one time the diagnosis of congenital heart disease was entertained, but later it was thought that the correct diagnosis was mitral regurgitation due to rheumatic disease. The patient's only symptomatology was frequent bouts of palpitations, which were shown to be due to multiple ectopic beats and paroxysmal tachycardias. In February 1962 a more persistent attack of palpitations developed, which was shown to represent atrial fibrillation. The patient was hospitalized for treatment of this arrhythmia. After slowing of the ventricular rate by the administration of digitalis a test dose of quinidine (0.1 Gm.) was administered on February 26. The following day she was started on a 2-hourly schedule of quinidine, receiving a dose of 0.2 Gm. at 5:00, 7:00, 9:00 and 11:00 a.m. After the fourth dose, sinus rhythm was restored but the patient became nauseated. Electrocardiogram revealed sinus rhythm alternating with atrial fibrillation and periods of bigeminal rhythm. At 2:30 p.m. the patient had a sudden syncopal attack. Electrocardiographic diagnosis of ventricular fibrillation was made. The patient was treated by external cardiac massage but ventricular fibrillation continued until electric defibrillation with an alternating-current defibrillator restored normal sinus rhythm. The patient made an uneventful recovery and remained in sinus rhythm during the next 12 months.

Case 4
F. C., a 46-year-old woman, had an attack of rheumatic fever at age 7 and had known of valvular heart disease thereafter. At the age of 29 she had a transient hemiplegia from which she recovered completely and led an active life. In 1959 cardiac failure first developed coincidentally with the onset of atrial fibrillation. She had shown marked limitation of activities and persisted in cardiac failure. Clinical examination and hemodynamic studies established the diagnosis of mitral stenosis and aortic regurgitation. Surgical repair of both valves was performed on July 24, 1962, with use of extracorporeal circulation. Her postoperative course was satisfactory and on August 3 quinidine therapy for the restoration of sinus rhythm was begun. Initially 0.66 Gm. of quinidine gluconate was administered every 6 hours. On August 5 she was given five 2-hourly doses of 0.4 Gm. of quinidine sulfate beginning at 5:00 a.m. The following day, the same dose and mode of administration of the drug were repeated. At 2:00 p.m., 1 hour after the last dose, the patient suddenly had a seizure, consisting of twitching of the right face, loss of consciousness, cessation of respiration, and deep cyanosis. No heart beat could be heard during the seizure. The attack lasted over 1 minute and the recovery was spontaneous and immediate. During the following 6 hours the patient had 10 more attacks of 30 to 60 seconds' duration, each one reverting without intervention. Electrocardiogram showed ventricular fibrillation with spontaneous recovery and resumption of sinus rhythm (fig. 2). The patient was somewhat drowsy between attacks but showed otherwise normal responses. After 8:00 p.m. she began to feel better, attacks were no longer present but atrial fibrillation recurred. The patient made a good recovery and left the hospital in satisfactory condition except for atrial fibrillation.

Case 5
M. S., a 41-year-old woman, was known to have rheumatic heart disease with mitral valve involvement for many years. Significant clinical symptomatology with progressive disability developed for about 2 years until June 1962, when clinical and hemodynamic studies established the diagnosis of predominant mitral regurgitation and led to cardiac surgery. On September 6, 1962, repair of the mitral valve under direct vision was performed. The patient's postoperative recovery was uneventful. Prior to discharge from the hos-
hospital a 3-day course of quinidine was administered but the patient developed severe gastrointestinal symptomatology which necessitated the cessation of treatment before sinus rhythm could be restored. She was readmitted on November 26 for further therapy. On November 26 she was given 0.2 Gm. of quinidine sulfate every 6 hours and the following day was started on a combination of 0.4 Gm. of quinidine and 0.25 Gm. of procaine amide every 6 hours. On December 2, at 8:30 p.m., 2½ hours after the last dose of the drugs she had a grand mal type of convulsive seizure with spontaneous recovery. During the next 6 hours she had nine more such episodes lasting from 30 seconds to 3 minutes. Electrocardiograms revealed rapid ventricular tachycardia or flutter. In an attack lasting more than 1 minute external resuscitation was instituted, which each time terminated the attack without necessity of electric defibrillation. After 2:00 a.m. attacks ceased; the patient remained in atrial fibrillation. Quinidine blood level the following morning was 2.8 mg. per liter. Further recovery was uneventful.

**Case 6**

T. G., a 57-year-old man, was first found to have valvular heart disease in 1960. He developed dyspnea and evidence of cardiac failure coincidentally with attacks of atrial fibrillation, which at first could be terminated by quinidine therapy. However, in January 1962 sinus rhythm could no longer be restored and the patient was left with marked limitation of activities. A diagnostic study performed in April 1962 revealed that the patient had combined mitral stenosis and regurgitation, the latter predominating. Marked hemodynamic abnormalities were found. Open-heart surgery was done on May 15, 1962, when moderately successful plastic operation upon the mitral valve was performed. On May 21 quinidine therapy was started with quinidine sulfate in increasing doses. Because of gastrointestinal symptomatology sinus rhythm could not be restored.
and quinidine was discontinued on May 28. The patient left the hospital and was readmitted in November 1962. On November 20 he was started on a regimen of quinidine sulfate 0.4 Gm. and procaine amide 0.5 Gm. every 6 hours. This treatment was continued and on November 23 blood quinidine level was 6.8 mg. per liter. On November 24, while on the same regimen, the patient had four seizures consisting of loss of consciousness without warning, associated with clonic-tonic convulsions lasting less than 1 minute each, with spontaneous recovery. The treatment was abandoned, and the patient remained in atrial fibrillation.

**Case 7**

A. H., a 49-year-old woman, had an attack of rheumatic fever in childhood but was free from significant symptoms until the age of 34, when she suffered a hemiplegia, presumably due to cerebral embolism from atrial fibrillation. The patient had a partial recovery and led a sheltered, relatively inactive life with few cardiac symptoms until mid-1960 when she developed progressive dyspnea and orthopnea. She was found to have pure mitral stenosis and atrial fibrillation. Mitral valvuloplasty was performed under direct vision on December 5, 1962, and satisfactory relief of valvular obstruction was accomplished. The patient was progressing satisfactorily and on December 18 quinidine treatment was started by the slow method: 0.4 Gm. of quinidine sulfate every 6 hours for 8 days. On December 27 she was given 0.4 Gm. of quinidine sulfate every 2 hours for five doses. This schedule was repeated daily, between 2.0 and 2.4 Gm. of the drug being given per day, until January 2, when she was administered 0.6 Gm. at 5:00, 7:00, 9:00, and 11:00 a.m. Shortly after the fourth dose she was found to be regular and the electrocardiogram revealed sinus rhythm. Quinidine level at 12:00 noon was 20.5 mg. per liter. At 3:00 p.m. a routine electrocardiogram revealed the return of atrial flutter with atrial rate of 260 and ventricular rate of 130. The patient was feeling well, but a few minutes later she suddenly developed a convulsive seizure with deep cyanosis, which lasted about 90 seconds. The house officer was summoned but before resuscitative measures were started the patient recovered spontaneously. Blood quinidine level reported at 4:00 p.m. was 18.8 mg. per liter. The patient had no further seizures, her vital signs remained stable. She lapsed into atrial fibrillation and left the hospital on January 12.

On March 24, 1963, the patient re-entered the hospital for further treatment of atrial fibrillation. It was then thought that the single syncopal attack in January was caused by too high a dosage of quinidine and did not constitute contraindication for quinidine therapy. The patient received three doses of quinidine, namely, 0.4 Gm. at midnight March 24 and at 6:00 a.m. and 12:00 noon March 25. At 2:00 p.m. on that day she was given general anesthesia, and four direct-current shocks of 100 watt-seconds each were administered to the precordial region of the thorax. The fourth shock restored sinus rhythm. The patient was awake at 3:00 p.m., and electrocardiograms revealed sinus rhythm with many multifocal ventricular ectopic beats. At 3:30 p.m. the patient suddenly became cyanotic and pulseless and had a generalized convulsive seizure. Closed-chest massage was promptly instituted and restored normal heart action and respirations within less than 2 minutes. Blood quinidine level taken shortly afterwards showed a value of 6.3 mg. per liter. At 4:00 p.m. atrial fibrillation recurred. Further attempts to restore sinus rhythm were abandoned and the patient was discharged in satisfactory condition on March 28.

**Case 8**

A. D., a 42-year-old woman, was found to have heart disease at the age of 30. A diagnostic study performed in November 1961 established the diagnosis of congenital heart disease with atrial septal defect and pulmonary hypertension. The patient at that time showed severe disability and was in chronic cardiac failure. Operative closure of the defect with the use of extracorporeal circulation was performed in December 1961. The patient made satisfactory progress until the twelfth postoperative day, when atrial flutter with 2 to 1 block developed. Treatment with digitalis and quinidine was unsuccessful in re-establishing sinus rhythm and the patient remained in chronic atrial flutter with a rapid ventricular rate. The patient nevertheless made a fairly satisfactory recovery and was able to lead a moderately active life, presenting a considerable improvement from her preoperative status. During 1962 three more courses of quinidine therapy were given, each unsuccessful because of uncontrollable nausea and diarrhea, which invariably developed when quinidine dosage reached the level of 2.0 to 3.0 Gm. per day. One more course of treatment with quinidine-procaineamide combination was equally unsuccessful. The patient re-entered the hospital on March 26, 1963, for electric defibrillation. She was given 0.33 Gm. of quinidine gluconate at midnight March 26; this dose was repeated at 6:00 a.m. and at noon on March 27. At 3:00 p.m. on that day sinus rhythm was restored by a single electric shock of 100 watt-seconds administered under general anesthesia. The patient was given 0.3
Gm. of quinidine gluconate every 6 hours. The patient was very well after the procedure. Quinidine blood level in the afternoon of March 27 was 2.5 mg. per liter and on March 28 it was 4.0 Gm. per liter. The following day (March 28) at 5:00 p.m. she first complained of nausea. Examination then revealed the presence of multiple ventricular ectopic beats and short runs of ventricular tachycardia. The severity of arrhythmia had been increasing and at 5:30 p.m. she was given 7.5 mg. of isoproterenol sublingually. No apparent improvement occurred, and at 6:00 p.m. she suddenly lapsed into coma with deep cyanosis and had generalized convulsions lasting for about 1 minute. Electrocardiogram revealed ventricular flutter (fig. 3). External cardiac massage promptly restored effective heart beat and respiration and electrocardiogram then showed sinus rhythm with ventricular ectopic beats. During the next 20 minutes she had four more identical seizures terminated by similar measures. At 6:30 p.m. regular sinus rhythm was present and the patient’s condition remained satisfactory. At 12:30 a.m. on March 29 multiple ventricular arrhythmias developed, resembling those preceding the first syncopal attack. Infusion of 5 per cent dextrose containing 0.2 mg. of isoproterenol\(^9\) was started immediately and within a few minutes evidence of ventricular irritability disappeared. The patient made an uneventful recovery and remained in sinus rhythm without maintenance therapy (follow-up up to 6 months).

**Comments**

The 10 reactions occurring in the eight patients reported here are assumed to represent a specific toxic effect of quinidine. In five patients ventricular fibrillation or flutter has been electrocardiographically documented. The similarity of the clinical feature in the other reactions suggests very strongly that the same mechanism was operating in them as well. These reactions represent typical examples of cardiac syncope, hence the term “quinidine syncope” is used. Various factors related to quinidine syncope are presented in table 1. All patients were adequately digitalized, since the arrhythmia under treatment was atrial fibrillation or flutter, where ventricular rate provides a convenient index of digitalis dosage. In none was there evidence of digitalis overdose. Both the slow and rap-
### Table 1

**Summary of 10 Quinidine Reactions**

| Cases | Previous use of quinidine | Known drug allergy | Other background information | Cumulative dosage of quinidine this course, Gm. | Total dosage day of syncope, Gm. | Quinidine blood level, mg./L | Syncope hours after last dose | Number of attacks | ECG during attack | ECG quinidine effect | ECG quinidine toxicity | Rhythm after recovery | Digitalis maintenance |
|-------|--------------------------|-------------------|-----------------------------|----------------------------------------|----------------------------|-----------------------------|----------------------------|------------------|----------------|-----------------|-----------------|------------------|-----------------|---------------------|
| 1 M.S. | None known | Sulfa-mides | History of syncopal attacks | 3.8 | 1.6 | 3½ | 1 | Ventricular fibrillation | 0 | 0 | - | + |
| 2 E.D. | None known | None | - | 4.4 | 2.0 | 6½ | 1 | Ventricular fibrillation | + | Premature ventricular contractions | Sinus rhythm |
| 3 M.D. | None known | None | Ventricular irritability for years | 0.9 | 0.8 | 3½ | 1 | Ventricular fibrillation | 0 | 0 | - | + |
| 4 F.C. | None known | None | History of epilepsy; on Dilantin | 7.4 | 2.0 | 16.2 | 11 | Ventricular fibrillation | 0 | 0 | Atrial fibrillation |
| 5 M.S. | 1 course | None | - | 6.0 + 4.0 procaine amide | 1.2 + 0.75 procaine amide | 2.8 | 2½ | 10 | Ventricular flutter | 0 | 0 | - | + |
| 6 T.G. | 4 or 5 courses | Ephedrine | - | 5.8 + 6.0 procaine amide | 0.8 + 1.0 procaine amide | 6.8 | 3 | 4 | - | + | 0 | Sinus rhythm |
| 7 A.H. | None known | Penicillin | - | 22.2 | 2.4 | 20.5 | 2 | 1 | - | + | 0 | Atrial fibrillation |
| 7 A.H. | 1 course | Penicillin | - | 1.2 | 0.8 | 6.3 | 3 | 1 | - | 0 | 0 | Atrial fibrillation |
| 8 A.D. | 4 courses | None | - | 2.4 quinidine gluconate | 0.9 quinidine gluconate | 4.0 | 2 | 5 | Ventricular flutter | + | Premature ventricular contractions | Sinus rhythm |
id quinidine administration methods were used in the patients. Quinidine sulfate alone was used in five patients, quinidine-procaine amide combination in two, and quinidine gluconate in one, prior to the syncopal reactions. Half of the patients had previously been taking quinidine and in none unusual evidence of intolerance to the drug was observed, although in one patient moderate dosages repeatedly caused gastrointestinal upsets. In none of the patients could the dose of quinidine be considered excessive and in only one were even moderately high doses used. In three of the five patients in whom quinidine blood levels were determined on the day of the syncopal reactions, they were found to be below the usual conversion level. In the other two, moderately high levels were found, but merely at the upper end of the usual conversion spectrum, below toxic levels. The most uniform finding was the time after the last quinidine dose, namely, with one exception, within the range of 1 to 3½ hours. The significant background information included a history of marked ventricular irritability (unrelated to quinidine) in one patient and a history of drug allergy in three, but none for agents related to quinidine.

The 36 attacks occurring in eight patients showed considerable similarity to each other. Typically, the attack occurred without premonitory symptoms or after rather vague complaints: nausea, faintness, ill feeling, etc. Most attacks were associated with almost immediate loss of consciousness, intense pallor, or pallor associated with cyanosis, muscular twitching with frequent convulsions, but only occasionally generalized “grand mal” type of seizure. Involuntary micturition and defecation occurred rarely. Most attacks lasted between 30 seconds and 3 minutes, terminated spontaneously, and were associated with immediate return of consciousness. In some, of course, resuscitative measures had to be performed, since their spontaneous termination was uncertain. The repetitive nature of such attacks is characteristic, as is the relatively short duration of the critical ventricular hypersensitivity, usually less than 6 hours. In cases where resuscitation was performed, simpler measures, such as pounding upon the chest wall, mouth-to-mouth respiration, and short periods of external massage restored cardiac action in most. In one, open-chest cardiac massage was performed. Electric defibrillation was found necessary in only two cases. The most interesting observation was the occurrence of a second reaction in two patients in whom the role of quinidine in the first reaction was not recognized: in both, second reactions occurred after very much smaller doses of the drug than the first one.

As already mentioned, the exact number of courses of quinidine therapy is not known, but, based on our estimate, the incidence of quinidine syncope is between 3 and 5 per cent. It should be emphasized that none of these reactions occurred in patients whose treatment was stopped because of electrocardiographic evidence of myocardial toxicity.

Discussion

The mortality of quinidine treatment of chronic atrial arrhythmias has been quoted as 3 to 4 per cent. Fatalities occurring in the course of quinidine therapy have been thought to be due in part to systemic embolization and in part to myocardial toxicity. The recent collected data by Thomson concerning quinidine fatalities suggest “quinidine shock,” possibly due to toxic effect of quinidine upon the central nervous system, as the probable cause of sudden death during quinidine therapy. The rarity of documented systemic embolization during such treatment has been stressed recently.5, 6 Direct myocardial toxicity due to quinidine involves most frequently the appearance of various atrioventricular and intraventricular conduction defects and of ectopic rhythms. However, ventricular fibrillation has always been considered rare and only a few documented cases have been reported.11-14 Only recently 15, 16 has this arrhythmia received more attention as a possible toxic manifestation of quinidine. The series of cases reported here leaves little doubt that ventricular fibrillation is a common manifestation of quinidine toxicity. It strongly
suggests that it is the principal cause of quinidine deaths, rather than the vague and unproven "quinidine shock." It is obvious that many such attacks are not recognized. Some reasons for this are suggested by the analysis of our findings.

The most characteristic feature of the attacks of ventricular fibrillation is their paroxysmal and repetitive nature. Most attacks terminated spontaneously; others required simple resuscitative measures for their termination so that electric defibrillation was seldom necessary. Attacks occurred more frequently as a series than as a single reaction, but the attacks were always separated by periods of recovery and orderly cardiac action lasting at least 10 minutes. Another feature of the attacks was their rare association with usual toxic effects of quinidine. Dosages and quinidine blood levels varied widely and were more often low in relation to usual conversion methods. Electrocardiographic changes were absent in half of the cases, and in those present, showed quinidine effects and not quinidine toxicity. Conversely, syncopal attacks have never been observed in those cases in the series where quinidine had been discontinued because of excessive quinidine blood levels, electrocardiographic evidence of myocardial toxicity, hypotension, or severe cinchonism. Furthermore, quinidine syncope appeared unrelated to hypersensitivity to this drug: none of the patients exhibited fever or skin reaction; gastrointestinal intolerance in cases reported here was not different from that expected in eight random patients undergoing quinidine therapy. Finally, in two cases repetition of quinidine administration after quinidine syncope produced further syncopal attacks with much smaller dosages, suggesting the possibility of progressive sensitization of the myocardium.

Thus it would appear that quinidine produces in certain individuals a specific sensitization of the myocardium by reducing the fibrillation threshold. Quinidine syncope probably represents attacks triggered by some as yet unrecognized precipitating factor. No clues as to the nature of the triggering factor could be found in this series: the contributory effects of such possible additive factors as digitalis, procaine amide, electric defibrillation, or cardiac failure are not clear. Since the myocardial action of quinidine is related to potassium flux and membrane permeability—processes also influenced by the other drugs—summation appears to be a good possibility, but individual sensitivity obviously comes into play here.

Certain practical considerations are clear and worthy of emphasis. In the first place, paroxysmal nature of quinidine syncope suggests that all cases are salvageable. Fatal attacks unquestionably represent instances in which a long paroxysm becomes self-perpetuating by way of myocardial ischemia. Modern monitoring technics make it easy now to discover ventricular fibrillation in time to prevent such a disaster. Furthermore, if our contention that most quinidine deaths are due to this mechanism is correct, then it should be possible to reduce the risk of quinidine therapy to a negligible one. Yet, in order to accomplish this objective, it would have to be necessary to consider every patient undergoing quinidine therapy a subject for quinidine syncope and to institute a complete safeguard system, for the occurrence of such attacks early in the course of therapy and in the presence of low quinidine levels appears well documented. In selecting patients for therapy it is also well to remember that meticulous attention should be paid to the history of "fainting," "dizzy attack," and other symptoms suggestive of shorter episodes of ventricular fibrillation. A positive history may justify the complete omission of quinidine as a therapeutic agent in such a patient in order to eliminate the possibility of a reaction during later quinidine maintenance therapy.

Summary and Conclusions

Thirty-six syncopal attacks occurring in eight patients undergoing quinidine therapy for chronic atrial arrhythmias have been observed and in the majority ventricular fibrillation was demonstrated as their cause. They are believed to represent specific sensitization
of the myocardium by quinidine, hence the term "quinidine syncope" is used.

These attacks are characteristically sudden, seldom preceded by warning prodromes, and consist of immediate loss of consciousness, cessation of respiration, and involuntary muscular contraction, occasionally grand mal type of seizures. They are paroxysmal in nature, usually well within the time limit permitting instant and complete recovery. Attacks of longer duration can be terminated by simpler resuscitative measures, so that electric defibrillation is seldom necessary. They usually occur within 1 to 3 hours after the last dose of quinidine and have a tendency to periodic recurrence, suggesting that myocardial hypersensitivity persists for a period of a few hours after the first syncopal attack.

Quinidine syncope has not been found to be associated with toxic myocardial action occurring after administration of high doses of the drug, for in most cases syncope occurred after modest doses of quinidine and in the presence of relatively low quinidine blood levels. Furthermore, such attacks have never been observed in patients in whom quinidine had to be discontinued because of fall in blood pressure or electrocardiographic evidence of quinidine toxicity.

Clinical implications of these observations are discussed and the view is expressed that paroxysmal ventricular fibrillation is a common, frequently unrecognized, complication of quinidine therapy and the usual mechanism of sudden quinidine death. The paroxysmal, temporary, and reversible nature of this myocardial reaction to quinidine, on the one hand, and the availability of satisfactory monitoring and resuscitative techniques, on the other hand, suggest the possibility that the risk of quinidine therapy can be materially, perhaps dramatically, reduced.

References
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