Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arrhythmias

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Blood quinidine determinations by the photofluorometric method were made in 30 patients with auricular fibrillation or flutter in whom conversion to sinus rhythm was attempted. Successful conversion occurred in 82 per cent of the patients, with a mean blood level of 5.9 mg./liter. Vomiting and, in one case, ventricular tachycardia were the most important toxic manifestations. Doses of 0.4 to 0.6 Gm. every two hours for five doses daily were usually adequate to obtain the average conversion blood level. The importance of the quantitative aspects of quinidine therapy and the relation of time, dose and concentration of quinidine in the blood are discussed.

THE desirability of quantitative studies of blood concentration in relation to dose and therapeutic effect of a drug has been emphasized in recent years. Experiences with penicillin, the sulfonamides, and the salicylates have demonstrated that more rational therapeutics result from such studies. There exists a diversity of opinion in the literature regarding the indications and methods of the administration of quinidine.[1–13] The fact that quinidine has variously been used in an empiric manner accounts in part for this lack of uniform experience and opinion. The recent study by McMillan and Welfare[12] has demonstrated the excellent results that can be obtained with quinidine in the treatment of auricular fibrillation, and has emphasized the need for a re-evaluation of quinidine therapy.

The development during the war of more satisfactory analytic methods for study of various basic organic compounds, including quinidine, afforded opportunity for more detailed investigation than in the past. Several papers have appeared recently[14–17] which utilize quantitative measurements, but the data are incomplete. The present study was undertaken to determine the effective blood quinidine levels required for conversion of cardiac arrhythmias in individual patients, to determine whether or not such levels are comparable in different individuals, to determine the most satisfactory dose schedule to achieve such levels, and to learn something further about the absorption and excretion of quinidine.

From the Division of Medicine of the University of California School of Medicine, San Francisco.

Supported in part by cooperative agreement between the National Heart Institute and the University of California, and by the Schwabacher Fund.

Presented in part before the Second Annual Meeting of the Western Society for Clinical Research, November, 1948 in Los Angeles, California, and before the National Meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, May, 1949.

METHOD

A number of technics for measuring the concentration of quinidine in biologic samples have been described. Referring to basic organic compounds in general, Brodie states that "the simplicity and speed of fluorometric assay recommend it as the method of choice when possible."[18] Quinidine and allied cinchona derivatives exhibit a natural fluorescence in acid media and are therefore well suited to this method of analysis. Two fluorometric procedures have been described by Brodie and his co-workers.[19, 20] One involves the direct measurement of fluorescence in protein-free plasma filtrates, the other the extraction of the biologic samples with suitable solvents to remove degradation products before the final determination of fluorescence is made. Referring to the first of these methods, Brodie states that ". . . it has the advantage of speed and simplicity, but it lacks specificity, since interfering metabolic derivatives of the compound (quinine or quinidine) are not removed."[18] From Brodie's work, and from our own in a separate study, it is clear that this simpler method gives consistently higher levels than does the more specific extraction procedure.[20, 26]

In the present study the extraction method of analysis was used, the actual procedure followed being based on Linenthal's adaptation[15, 21] of the Brodie method. Briefly, it is carried out as follows:

A sample of urine or serum is added to distilled commercial ethylene dichloride, the mixture alkalinized with 10 per cent sodium hydroxide, and shaken for ten minutes in a mechanical agitator.

The aqueous phase is separated by centrifugation and removed by aspiration. With serum, no further extraction is required, but two additional washings with sodium hydroxide are necessary to assure removal of quinidine degradation products from urine. An aliquot of the urine or serum extract is diluted with ethylene dichloride and acidified with trichloracetic acid. Absolute ethanol is added to minimize adsorption. The fluorescence is then measured in the Coleman photofluorometer. The extraction in an identical manner of a blank specimen of serum or urine containing no quinidine permits determination of the net fluorescence of quinidine contained in the unknown sample. This is then compared with the net fluorescence of two standards containing known amounts of quinidine. With slight modifications in the technic, tissue and fecal samples may also be analyzed for their quinidine content.

Further details of our experience with the technical aspects of the method will be the subject of a separate communication.[26] The method has proved accurate in known dilutions within 8 per cent; the accuracy was considerably less with blood concentrations below 2 mg. per liter, unless twice the usual serum sample was used. The specificity of the method has been investigated by Linenthal and his associates,[15, 12] and no interference found from such commonly used drugs as aspirin, codeine, morphine, Demerol, phenobarbital, Seconal, pentobarbital, thiamine hydrochloride, ascorbic acid, menadione, sulfonamides, penicillin, digitalis, insulin and stilbestrol.

Subjects and Methods

The present study includes 72 patients in whom measurements of quinidine concentration in blood or urine were made. The data on conversion of auricular flutter and fibrillation are based on results in 3 patients with auricular flutter and 27 with auricular fibrillation* in whom it was thought that conversion to sinus rhythm was indicated according to the criteria outlined by the National Research Council.[22] The remaining 42 patients were receiving quinidine for a variety of reasons (prevention of paroxysmal arrhythmias, after myocardial infarction, or after chest surgery). In 4 of the 27 patients with auricular fibrillation, the arrhythmia was of less than one week duration and was considered acute. Table 1 summarizes the causes of the auricular arrhythmia in the cases studied. The patients were first fully digitalized in order to produce a slow ventricular rate, and maintenance doses of digitalis were then continued. If cardiac failure was present, rigid restriction of sodium and use of mercurial diuretics were employed as required to improve the cardiac failure as much as possible before attempted conversion. All patients were hospitalized and frequent clinical observations, electrocardiograms, and simple hemodynamic studies, such as vital capacity, circulation time, venous pressure, and exercise tolerance were studied before and after conversion in most instances. Patients were kept at bed rest while quinidine was being given. After preliminary studies, and in the light of previous clinical experience, two different schedules were used, more commonly the first: (1) quinidine was given every two hours for five to six doses, and (2) quinidine was given every four hours day and night. Frequent blood levels of quinidine were determined throughout the day and in most cases blood levels were obtained at the time of conversion. If relapse occurred, levels were determined at the time of relapse. If conversion to sinus rhythm was not accomplished, the peak blood level obtained by the dose schedule employed was noted. In many cases, total urine quinidine excretions were obtained and the relationship of dose given and quinidine excreted studied.

* This includes 2 cases of auricular fibrillation who were given quinidine in small doses to control ventricular premature beats. Both converted to sinus rhythm unexpectedly (Cases J. L. and A. O.).

Results

Of the 72 patients in whom pharmacologic data was obtained, attempts at conversion to sinus rhythm were made thirty-four times in 30 patients with auricular fibrillation and flutter. Sinus rhythm was re-established twenty-eight times in 24 patients, while six attempts in 6 patients failed. This represents a conversion rate of 82 per cent. Table 2 summarizes the details of total dose of quinidine, peak blood levels, and evidences of toxicity.

Figure 1 illustrates the blood levels obtained in the cases converted to sinus rhythm as well as in those who did not. The mean peak blood level in the cases in whom sinus rhythm was restored was 5.9 mg. per liter. In 75 per cent (twenty-one of twenty-eight attempts) the peak levels were between 4 and 9 mg. per liter. In only two of the twenty-eight attempts were levels above 10 mg. per liter successful in restoring sinus rhythm. Levels above 9 mg. per liter were reached in 6 patients, but resulted in only two conversions to sinus rhythm. Of the six failures, levels of 7 mg. per liter or above were obtained in all, and four did not convert despite levels of 10 mg. per liter or above. In contrast, in 71 per cent of the successful conversions (twenty in twenty-eight attempts), the peak level was below 7 mg. per liter.

In 5 cases, conversion occurred with peak levels of less than 4 mg. per liter. In one of

these (H. M.), auricular fibrillation had been present for a year following thyroidectomy for Graves' disease. Conversion occurred after five doses of 0.4 Gm. of quinidine every four hours rhythm occurred with only two doses of 0.2 Gm. of quinidine two hours apart at a level of 2 mg. per liter. In another similar case (L. C.) auricular fibrillation had been present for only

TABLE 1.—*Data on the Conversion of Arrhythmias with Quinidine: Summary of Thirty Cases (Thirty-four Attempts)*

	Converted	Failed	Relapsed	Time of Relapse	Reconverted	Remarks
I. Auricular Fibrillation (27 Cases) *Acute* (4)						
1 after pneumonectomy (E.F.)	1	0	1	1 day	1	
2 after auricular flutter (M.G., L.C.)	2	0	0		0	
1 associated with H.T.C.V.D. (R.B.)	1	0	0		0	
Chronic (23)						
11 with R.H.D.*	7	4†	2	2 wk. (C.G.)	1 (C.G.)	(C.G.) Reconversion not included in data since done elsewhere and no blood levels available
				12 hr. (V.H.)		(V.H.) No attempt to reconvert
3 with coronary disease (M.G., J.L., L.S.)	3	0	2	1 wk. (M.G.) 3 da. (L.S.)	No attempt	(J.L.) Converted unexpectedly while treating P.M.B.‡ Follow-up now 5 mos.
4 with thyrotoxicosis (T.B., H.M., F.B., A.O.)	3	1 (F.B.)	1	10 mo. (T.B.)	1	(T.B.) Relapsed again 1 wk. after 2nd conversion, not reconverted. (H.M.), followed 1 yr. (A.O.), Converted during treatment P.M.B.‡
1 with calcified pericardium (V.O.)	0	1	0		0	Early case; probably would use larger dose now.
4 with undetermined cause (C.N., W.Y., M.D., A.T.)	4	0	3	1 wk. (C.N.) 6 mo. (A.T.) 10 da. (W.Y.)	2 (W.Y., A.T.)	(C.N.) No attempt to reconvert
II. Auricular Flutter (3 Cases)						
1 with R.H.D. (L.G.)	1	0	0		0	
2 undetermined cause (F.D., F.W.)	2	0	1	6 mo. (F.W.)	1 c̄ dig, 1 c̄ quin.	(F.W.) Regular 2 mos. after relapse
Totals	24	6	10			
Summary	28 conversions in 34 attempts (82 per cent)					

* Patients: B.A., T.G., C.G., L.H., J.M., M.C., D.C., M.L., L.W., D.R., V.H.
† Patients: J.M., T.G., M.L., D.R.
‡ Premature beats.

at a blood level of approximately 3.1 mg. per liter. In the second (F. G.), a patient in whom auricular flutter had been converted to auricular fibrillation with digitoxin five days before quinidine was begun, conversion to sinus twenty-four hours following conversion of auricular flutter with digitalis and responded to 0.6 Gm. quinidine in four hours at an approximate serum level of 2.3 mg. per liter. The fourth case (A. O.) was under treatment for Graves'

TABLE 2.—*Summary of the Data on Twenty-four Patients Converted to Sinus Rhythm with Quinidine (Twenty-eight Conversions)*

Case	Age	Sex	Etiology and Duration of Arrhythmia	Dose of Quinidine (Gm.)	Peak Level (mg./liter)	Toxicity and Comment
B.A.	44	F	Rheumatic heart disease—3 months	2.6 in 2 days	7.5	None
T.B.	49	F	Post - thyrotoxicosis — 14 months	3.0 in 2 days	5.8	None
			Same 10 months later, 1 month after relapse			
M.C.	45	F	Rheumatic heart disease—12 months	2.6 in 2 days	8.0	None
C.F.	66	M	Chest surgery 2 days before. Still fibrillating 6 days after onset.	1.2 in 1½ days	7.0	None
			Quinidine then started. Relapse 24 hours after conversion at level of 3.8	2.0 in 1½ days	5.5	No toxicity
F.G.	64	F	Coronary heart disease—5 days	0.4 in 4 hours	2.0	Nausea 1–2 hours after conversion
M.G.	63	M	Coronary heart disease—3 months	6.2 in 2½ days	7.0	Nausea, headache, mental confusion, second day
C.G.	39	M	Rheumatic heart disease—2 months	8.2 in 3 days	15.8	Anorexia first day; nausea second day; decreased hearing and weight loss third day
L.H.	42	F	Rheumatic heart disease—3 weeks	4.2 in 2 days	4.8	None
H.M.	56	M	Post-thyrotoxicosis—18 months	2.4 in 1½ days	3.1	None
C.N.	55	F	Unknown etiology—4 months	2.4 in 1 day	5.7	None
L.S.	64	F	Coronary heart disease—2 months	1.8 in 1 day	4.0	None
A.T.	29	M	Unknown etiology—1 month	5.4 in 4 days	6.7	Tinnitus
			Relapse 6 months later—3 weeks	3.0 in 1 day	5.4	Slight tinnitus
D.C.	45	F	Rheumatic heart disease—1½ years	2.0 in 1 day	4.6	Vomiting, headache, tinnitus
W.Y.	62	M	Unknown etiology and duration. Quinidine discontinued 5 days after conversion.	4.0 in 1½ days	6.2*	None
			Relapse 4 days later. Treatment started same day.	1.8 in 16 hours	4.2*	None
M.D.	67	M	Unknown cause—3 months	4 in 3 days	5.8	None
J.L.	69	M	H.T.C.V.D., V.P.M.B.'s	1.6 in 24 hours	3.3*	None
A.O.	44	F	Thyrotoxicosis, V.P.M.B.—3 years	1.7 in 24 hours	1.3*	None
L.W.	42	F	Rheumatic heart disease—6 weeks	9.3 in 3½ days	7.0*	None
L.C.	45	M	Treatment of auricular flutter with Cedilanid, 24 hours	0.6 in 4 hours	2.3*	None
V.H.	43	M	Rheumatic heart disease—prob. 3 years	8.4 in 3 days	8.3	Slight nausea on second day with level of 7.9
R.B.	53	F	H.T.C.V.D.—6 days	2.0 in 24 hours	5.7*	Anorexia, nausea, weakness after second dose, level of 3.3
L.G.	41	F	Rheumatic heart disease—6 days	2.4 in 1 day	6.2	Nausea, vomiting, tinnitus, headache, 2 to 3 hours before conversion
F.W.	66	M	Coronary heart disease—3 weeks	5.8 in 4½ days	10.0*	None
F.D.	58	M	Coronary heart disease—24 hours	4.4 in 3 days	5.4	None

* Approximate level.

disease (sedation, propyl thiouracil) and was given quinidine to suppress ventricular premature beats. Conversion of auricular fibrillation unexpectedly occurred after 1.7 Gm. had been given (0.1 Gm. test dose, followed by 0.4 Gm. four times a day) at an approximate level of 1.3 mg. per liter. In the fifth case (J. L.) auricular fibrillation had been present for an unknown number of months. He had had cardiac failure for the previous seven weeks. The patient responded to 1.6 Gm. of quinidine in twenty-four hours at an approximate level of

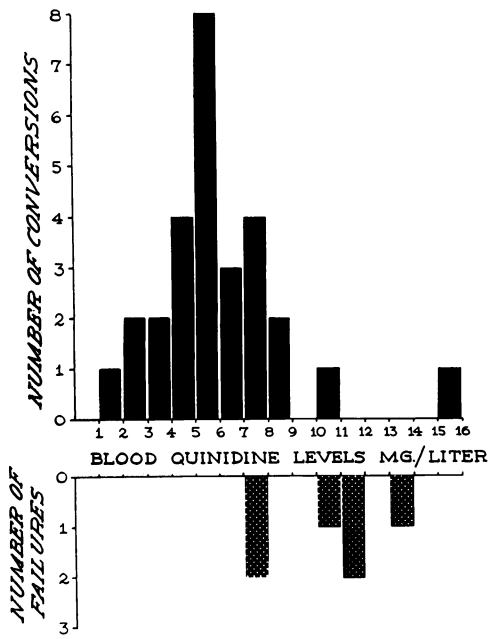

FIG. 1.—Distribution of blood quinidine levels required for conversion of 28 cases of auricular fibrillation (25) and auricular flutter (3) to sinus rhythm. Six failures are illustrated below the line.

3.3+ mg. per liter. The quinidine was given to control premature beats, and conversion to sinus rhythm occurred.

The amount of quinidine required to convert the patients to sinus rhythm was usually 0.4 or 0.6 Gm. every two hours for five doses. In only one instance was the dose of 0.8 Gm. every two hours for five doses employed (fig. 2, C.G.). The commonly advocated dose of 0.2 Gm. every two hours for five doses infrequently produced a blood level of as much as 4 mg. per liter and therefore was usually ineffective.

Clinical Pharmacology

In addition to therapeutic considerations, some data are available on the clinical pharmacology of quinidine. The rise in blood quinidine level with successive doses of the drug bore an inverse relationship to the rate of auricular contractions in both auricular fibrillation and auricular flutter (fig. 3, *a*, *b*). This was particularly true in the first twelve hours and supports the concept that the blood quinidine levels reflect the cardiac effects of the drug.

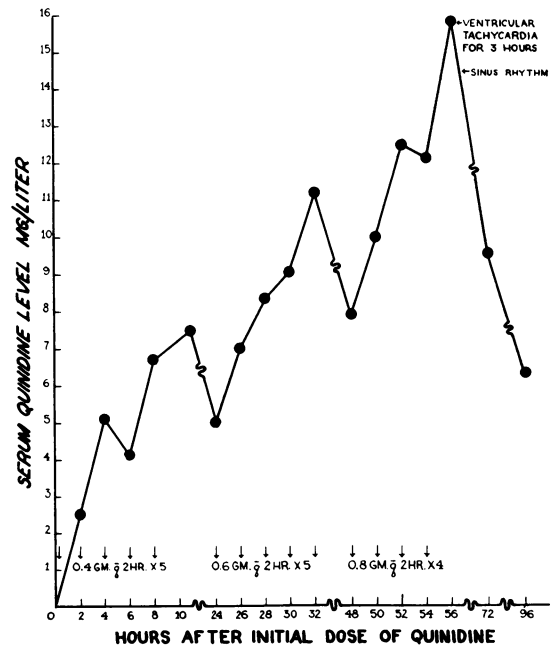

FIG. 2.—(C. G., No. 154628. Age 39. Auricular fibrillation.) A graph illustrating the progressive rise in blood quinidine level that occurs with the five-dose daily schedule when the individual dose is increased from 0.4 to 0.8 Gm. Note the high percentage of quinidine remaining in the blood twelve hours after the peak evening level.

In the patients with auricular flutter or fibrillation, conversion did not always occur when the blood level was at its peak. In 2 cases (T.B. fig. 4, and L.G.,) it followed by approximately two hours, and in 5 others (T.B., C.G., C.N., M.G., M.D.) occurred during the night after the peak level had passed.

After a given dose of quinidine, the maximum blood level was usually reached in approximately two hours; the level at the end of one hour at times was found to be approximately

30 per cent that of the two hour level as shown in the following 3 patients:

Case	Blood Level (mg./liter) Dose (Gm.)	One hour	Two hours
V.T.	0.4	0.8	2.3
J.G.	0.2	0.45	1.1
J.G.	0.4	0.45	1.3

The blood level invariably was lower four hours after a given dose than at the peak two-hour level, the decrement usually being in the neighborhood of 10 to 20 per cent, as indicated in the following cases in which levels two and four hours after a given dose are listed. All patients in this group had been given multiple doses of quinidine.

Case	Blood Level (mg./liter) Two hours after dose	Four hours after dose
A.T.	6.7	5.6
A.T.	5.4 (1½ hrs.)	4.0
C.N.	5.7	4.6
H.M.	2.9	2.7
H.M.	3.9	3.1
M.G.	7.0	6.4
M.G.	4.4	3.7
L.G.	6.2	5.8
E.F.	7.0	5.6
M.C.	8.0	7.3
T.B.	5.5 (3 hrs.)	4.0
L.H.	2.8	2.0
V.	7.0	6.5

In view of textbook statements that quinidine is rapidly excreted and that the effect of a given dose by mouth ceases in four to five hours,[10] it was of interest to find that significant levels remained in the blood for some twelve to twenty-four hours (fig. 5). The average residual blood level twelve to eighteen hours after the last dose was 42 per cent of the previous peak level (20 patients, thirty-six levels). The average residual blood levels the next morning after three commonly used conversions schedules are tabulated below:

0.2 Gm. every two hours for five doses = 1.8 mg./liter (8)*
0.4 Gm. every two hours for five doses = 2.5 mg./liter (14)*
0.6 Gm. every two hours for five doses = 3.9 mg./liter (7)*

* Total number of cases in each group.

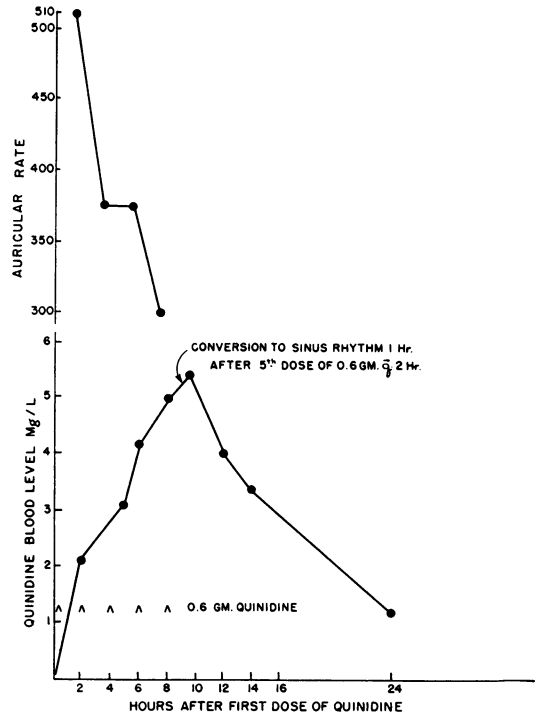

FIG. 3*a*.—The relationship between the decrease in the auricular rate and rise in blood quinidine concentration in a case of auricular fibrillation (A. T., U 120498. Male, age 29).

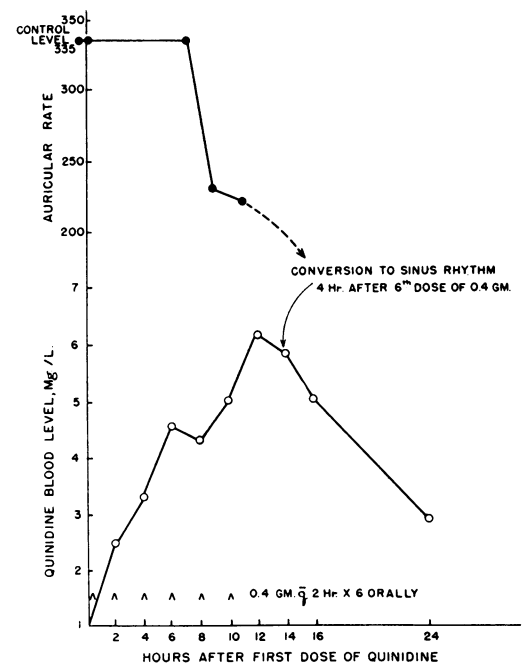

FIG. 3*b*.—The relationship between the decrease in the auricular rate and rise in blood quinidine concentration in a case of auricular flutter (L. G., U 1577699. Female, age 41).

Measurable residual levels were found for as long as seventy-two hours after the last dose of quinidine in one patient, for fifty-six hours in another, and for thirty-three hours in a third. No attempt was made to determine the length of time quinidine remained in the blood in the other patients.

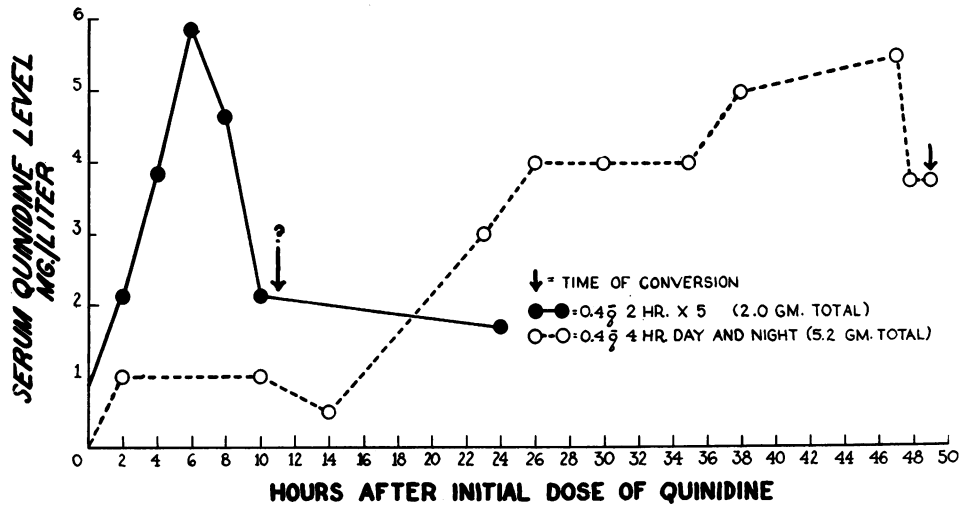

FIG. 4.—Comparison of two- and four-hour dose schedules in a patient with two episodes of auricular fibrillation ten months apart (T. B., No. 134316, age 49).

When quinidine was given every two hours for about five doses (four to six) the net increment in blood level rose as the size of the individual dose was increased. The average net increase in blood level (peak level minus residual level that morning) with several dose schedules was:

0.2 Gm. every two hours for 5 doses = 3.9 mg./liter (8)*
0.4 Gm. every two hours for 5 doses = 4.9 mg./liter (16)*
0.6 Gm. every two hours for 5 doses = 5.7 mg./liter (7)*

When 0.2 Gm. was given, the average net increase (level two hours after last dose minus that morning's residual level) was 3.9 mg. per liter (average of 8 patients). With 0.4 Gm. it was 4.9 mg. per liter (average of 16 patients), and with 0.6 Gm., 5.7 mg. per liter (average of 7 patients). When quinidine was given in this manner, the increment produced by successive doses became less after the first few doses. In 13 patients who were given 0.4 Gm. every two hours, the increment obtained with each of the first two doses was found to be 1.5 mg. per liter, almost double the increment (0.8 mg. per liter) obtained with subsequent doses. When the same dose was repeated every two hours, the level

* Total number of cases in each group.

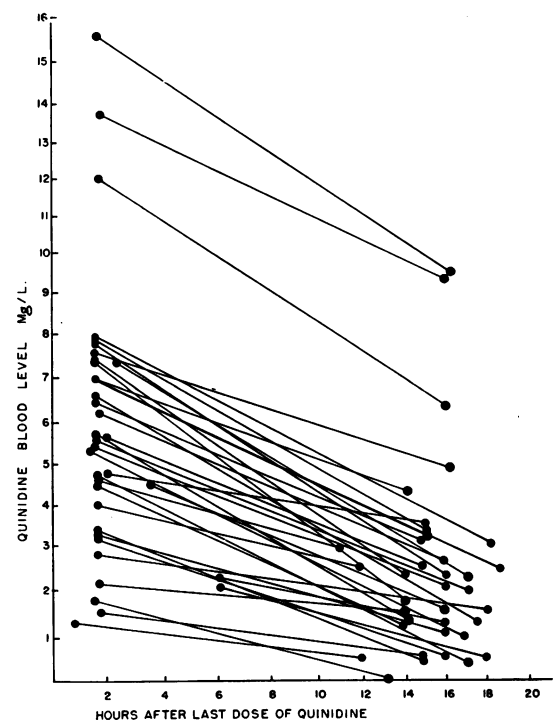

FIG. 5.—The amount of quinidine remaining in the blood ten to twenty hours after the last evening dose is illustrated in the graph showing the relative decrement in blood concentration.

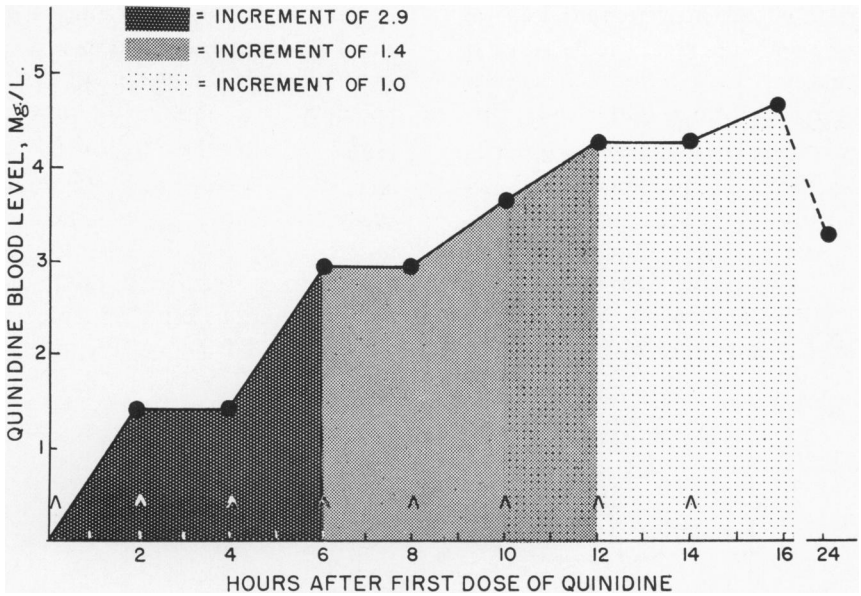

FIG. 6.—Decreasing increment of blood quinidine level with successive doses of 0.4 Gm. each (M. G., U154360. Male, age 63).

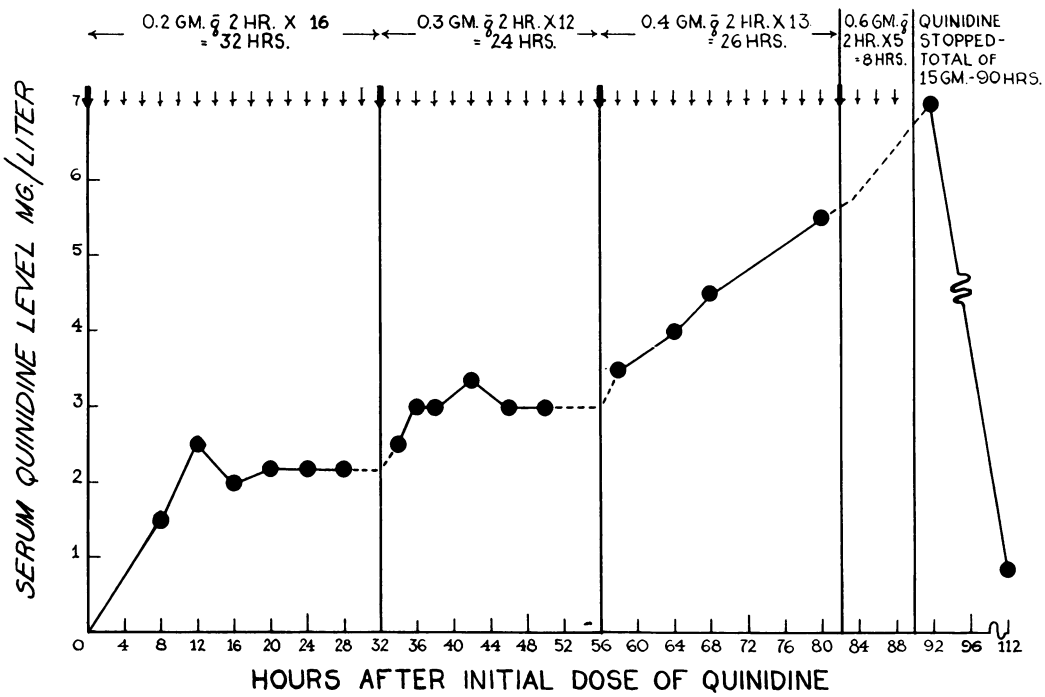

FIG. 7.—The failure of repeated doses of quinidine 0.2 and 0.3 Gm. each to produce further increases in blood concentration after the first four or five doses (F. B., No. 161359, age 57. Auricular fibrillation).

increased more after each of the first two doses than it did after later doses. This tendency is illustrated in figures 6 and 7. This same decreasing effect following multiple doses of the same size may be shown in another way by comparing the increase in level resulting from the first two doses together with that resulting from all the remaining doses together (usually

two to four more, but in some cases, five or six more). With 0.4 Gm. given every two hours, the first two doses resulted in an average increase of 3.1 mg. per liter in 13 patients, while the subsequent three or four doses resulted in an increase of only 2.3 mg. per liter. It is therefore apparent that the initial two doses produced greater effect than did subsequent doses, even if four or five more were given.

This "adaptation" mechanism was similarly observed when patients were given quinidine every four hours day and night or were given the same dose of quinidine at any fixed interval (fig. 8). It was observed when the four-hour interval was used that the peak blood level reached a maximum on the second and third day, maintained a plateau for several days, and then often fell so that at the end of a week the blood level was approximately equal to that which was obtained at the end of the first day. Further experience with fixed daily doses of quinidine has shown that in some cases the daily maximum blood level falls only slightly or not at all after the peak levels have reached a plateau in two to five days. This may represent equilibration between the tissues and the blood. In rare instances, the peak blood level may not be reached for a week after fixed daily doses. It is apparent that if higher blood levels were desired, increasing the size of the individual dose or the frequency of administration would have been necessary to raise the blood level. When a given dose of quinidine was given every two hours, the increment in blood level became progressively less after the first three or four doses and after the sixth dose, no further rise in blood quinidine level was obtained with 0.2 Gm. and 0.3 Gm. amounts despite six or

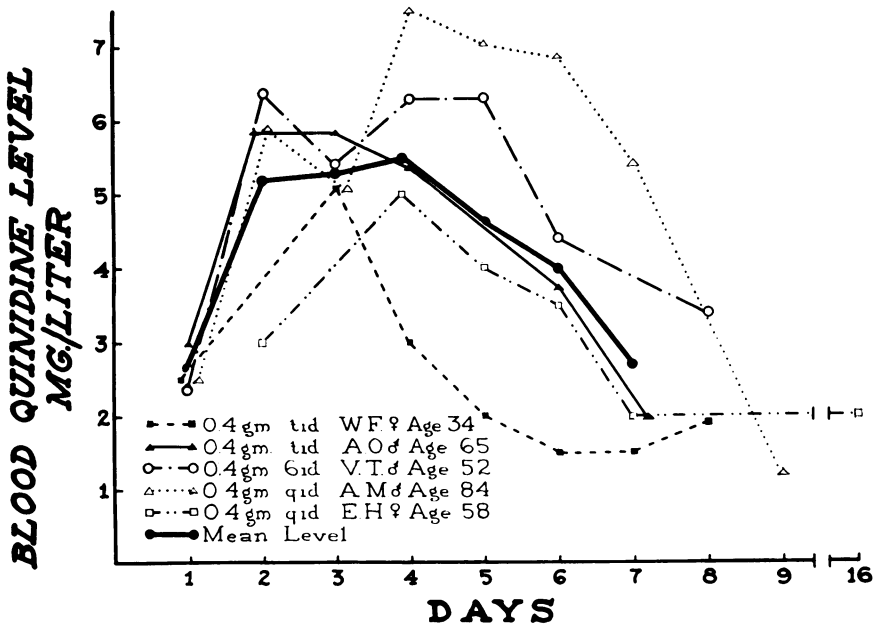

FIG. 8.—The parabolic curve obtained with fixed daily doses of quinidine, illustrating that an "adaptation" mechanism prevents maintenance of the highest blood levels.

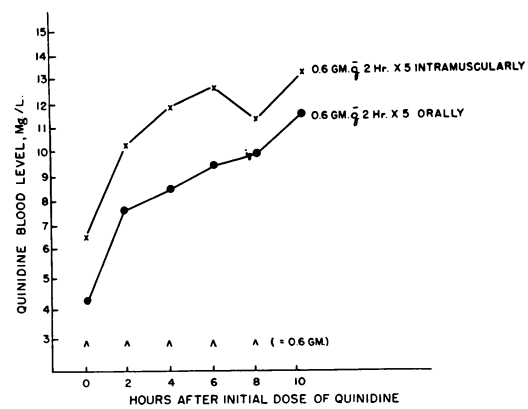

FIG. 9.—Comparison of blood levels obtained with 0.6 Gm. every two hours for five doses orally and intramuscularly in a case of chronic auricular fibrillation. Same patient on successive days. First line represents residual. (J. M., U 59617. Male, age 51.)

seven subsequent doses unless the size of the individual dose was increased (fig. 7).

Two patients with chronic auricular fibrillation were given the same dose schedule of quinidine at separate times orally and intramuscularly (fig. 9), using the urea-antipyrine solution described by Sturnick and his associates.[23] In both patients the time of maximum blood level and the curves of ascending blood level were essentially similar with the two routes of administration. The levels rose at about the same rate, reached the same peak and declined in a similar manner.

Relapses

Ten patients who had been converted to sinus rhythm relapsed to their original arrhythmia at intervals of fourteen hours to seven months (including C.G.). The data is summarized below for each case.

Summary of Six Patients With Auricular Fibrillation in Whom Quinidine Failed to Restore Sinus Rhythm

Case 1. F. B., male, age 57 years: Thyrotoxicosis. Auricular fibrillation of ten years' duration (post-thyroidectomy). Heart moderately enlarged, 35 per cent, especially the left ventricle. A level of 7 mg. per liter was reached without converting the arrhythmia. Quinidine was discontinued although the only evidence of toxicity was mild nausea.

Case 2. T. G., female, age 57 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation of at least five and one-half years' duration. Heart enlarged moderately. Functional Class III despite maximum improvement with digitalis and a low caloric, low salt diet. Quinidine dosage was somewhat irregular but a level of 11 mg. per liter was reached with a dose of 0.6 Gm. every two hours for six doses, at which time the patient noted tinnitus and slight deafness. The rhythm remained irregular and further trial of higher doses was not attempted.

Case 3. M. L., female, age 52 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation for at least two and one-half years, probably for four years. Heart size +35 per cent, moderately enlarged, especially the left auricle and right ventricle. The patient had been on digitalis for four years, since the appearance of symptoms of cardiac failure. She failed to convert at a level of 7.0 mg. per liter after 0.4 Gm. every two hours for five doses on two successive days, followed by 0.6 Gm. every two hours for five doses the third and fourth days. Quinidine was stopped because of repeated vomiting.

Case 4. J. M., male, age 51 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation, probably of at least three years' duration. Slight left auricular and left ventricular enlargement. Onset of failure three years ago, and borderline failure continued despite the use of digitalis and sodium restriction. Two major embolic episodes occurred, the first to the left femoral arteries one year ago necessitating amputation, and the second to the right femoral artery with subsequent claudication, two years ago. The patient failed to convert despite a level of 13.7 mg. per liter after having received 0.4 Gm. every two hours for 5 doses the first day, and 0.6 Gm. every two hours for five doses on each of the two following days (the last course being given intramuscularly). Quinidine was discontinued because of persistent severe nausea and repeated vomiting.

Case 5. V. O., female, age 49 years: Calcific pericarditis of unknown etiology. Auricular fibrillation probably of eighteen months' duration and generalized cardiac enlargement. History of "enlarged" heart twenty years ago with symptoms of weakness and dyspnea. Occasional palpitations for five years with a marked increase in this complaint eighteen months ago. The patient was digitalized three months ago when she was told that she had a "case" around her heart. Symptoms of increasing failure appeared two months ago which responded to mercurials, bed rest, and sodium restriction. She received several courses of quinidine and reached a maximum level of 10 mg. per liter on the fourth day with 0.4 Gm. every four hours day and night. Quinidine was discontinued although no evidence of toxicity was present at the time. (There had been vomiting ten days before, while the patient was receiving 0.4 gm. every two hours for 5 doses.)

Case 6. D. R., female, age 34 years: Rheumatic heart disease with mitral stenosis. Auricular fibrillation of three months' duration. Heart slightly enlarged. The patient received 5.0 Gm. in twenty-four hours (0.6 to 0.8 Gm. every four hours) which resulted in a peak level of 11.3 mg. per liter, but failed to restore sinus rhythm. She then received 0.6 Gm. approximately every four hours, for thirteen doses, but failed to convert despite blood levels of 6.5 to 0.6 mg. per liter during the three-day period. There was no evidence of important toxicity.

Four of the patients were reconverted easily and no attempt was made in the other patients.* Of the ten relapses, seven occurred within two weeks after conversion. Four of the

* One of these 6 patients (C. G.) relapsed and was reconverted with small additional doses of quinidine by an outside physician. He then maintained regular rhythm. He is considered a relapse but not included in our reconversion data because no blood levels are available.

patients who relapsed had received no maintenance quinidine and the maximum maintenance dose in the other 5 patients was 0.2 Gm. four times a day. In the light of subsequent experience in the prevention of paroxysmal arrhythmias, and in the suppression of premature beats,* this amount of quinidine was probably insufficient. It was of interest to note that in the patients reconverted after a lapse of six months, the blood levels required for conversion were essentially the same (A.T., fig. 10, and T. B., fig. 4). When Patient A.T. was first converted, the dose had been gradually raised from an initial regime of 0.2 Gm. every two

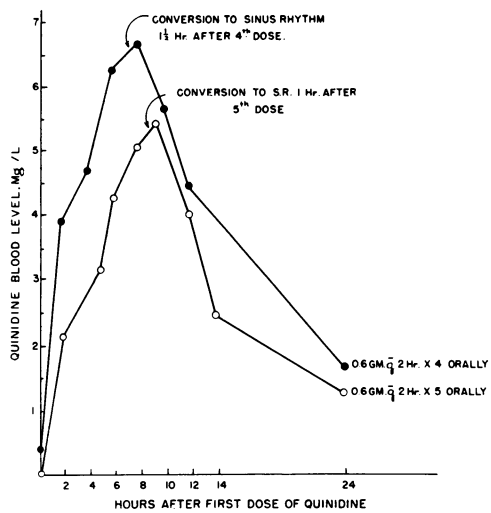

FIG. 10.—Comparison of conversion levels on separate occasions six months apart in a case of auricular fibrillation, with 0.6 Gm. every two hours given both times. (A. T., U 120498. Male, age 29.)

hours for five doses to a final successful schedule of 0.6 Gm. every two hours for five doses on the third day, with a peak blood level of 6.7 mg. per 100 cubic centimeters cent. When the patient relapsed, he was given 0.6 Gm. in five two-hourly doses with successful conversion on the same day, at a peak blood level of 5.4 mg. per cubic centimeters.

One patient (T.B., fig. 4) with chronic auricular fibrillation was treated initially with 0.2 Gm. every two hours for five doses, followed the next day by 0.4 Gm. every two hours for five doses. Sinus rhythm was established during the night after the last 0.4 Gm. dose had been given (total of 2.0 Gm.). Ten months later, the patient again developed auricular fibrillation and this time was given 0.4 Gm. every four hours day and night. Conversion took place after a total of 5.2 Gm. had been given. Figure 4 shows the levels in this patient. It can be seen that peak levels were similar, but the total dose required and the time necessary to achieve the peak levels were much greater when the quinidine was given every four hours.

Urinary Excretion

Studies of urinary excretion of quinidine were carried out in 26 patients. During the first day of quinidine therapy, an average of 4.8 per cent of the first twelve hour dose was excreted in the urine during the same period (average of 14 cases). An average of 10.1 per cent (11, 11, 11.5, 8.5, 8.4, 10.5 and 9.6 per cent) of the first twelve hour dose appeared in the urine during the first twenty-four hours (7 cases). In 12 patients who were receiving fixed maintenance doses of quinidine, the average amount found in the twenty-four hour urine was 15.5 per cent (range of 9 to 24 per cent) of the daily dose, (average of eighteen studies). In 12 of the 18 patients, the amount of the daily dose excreted in twenty-four hours varied between 12 per cent and 16 per cent. In one patient (T.B.) who was taking 0.4 Gm. quinidine every four hours, day and night, the 6 per cent of the first twenty-four hour dose was excreted in the same period; in the second twenty-four hours, the amount rose to 11 per cent, and in the third twenty-four hours, to 20 per cent. In 6 patients in whom serial urine collections were made following discontinuance of quinidine, measurable amounts remained in the urine for fifteen hours in 1, twenty-four hours in 2, thirty hours in 1, and thirty-six hours in 2. (In one of the latter, it was present for thirty-six hours on two different occasions.)

Toxicity

Table 3 summarizes the toxic symptoms noted in our patients converted with quinidine. In 2 patients, vomiting precluded further use of the drug, and one patient underwent a short bout of ventricular tachycardia shortly after conversion. This complication occurred at the

* Report in preparation.

high blood level of 15.8 mg. per liter in a patient who had severe mitral stenosis, marked cardiac enlargement and previous cardiac failure. Conversion had been attempted and quinidine given in large doses because two major arterial emboli had occurred in the previous two months. In the remainder of the cases the toxic symptoms of nausea, diarrhea, tinnitus and headache were of relatively minor degree. Frequent electrocardiograms were taken during conversion and in no case were conduction defects obtained. In a number of patients, auricular flutter occurred as the rapid auricular rate of auricular fibrillation was slowed with quinidine. In only one patient in whom auricular flutter was produced did the ventricular rate rise with a 2:1 block when this occurred just prior to conversion. When quinidine was stopped, the auricular rate rose and auricular fibrillation was again present the next day. In the remaining patients the ventricular rate was essentially unchanged despite the development of auricular flutter. Maintenance doses of digitalis were continued in these patients.

TABLE 3.—*Summary of Toxic Manifestations of Quinidine in the Thirty Patients with Auricular Flutter or Fibrillation in whom Conversion was Attempted*

Case	Symptoms	Degree	Blood Level at Time (mg./liter)	Conversion Level (mg./liter)	Comment
L.G.	Tinnitus, headache, vomiting	+	4.3	5.8	None
M.G.	Nausea, headache, v.p.m.b.'s	+	5.0–7.0	4.4	None
T.B.	Diarrhea, tinnitus, headache	++	4.2	4.0	None
A.T.	(1) Tinnitus	+	5.4	6.7	None
	(2) Tinnitus	+	2.2	5.4	
C.N.	Faintness	++	5.0	4.6–2.1	Pulse 140 with 2:1 flutter just prior to conversion
V.O.	Nausea, vomiting	++	6.3	Failed at 10	None
F.G.	Nausea	+	2.0	2.0	None
T.G.	Tinnitus, slight deafness	+	11.0	Failed at 11	None
J.M.	Diarrhea, vomiting	+++	6.3	Failed at 13	None
F.B.	Nausea	+	7.0	Failed at 7	None
C.G.	Anorexia	+	7.5		None
	Nausea	++	10.0	15.8–9.6	
	Decreased hearing	+	12.5		
	Ventricular tachycardia	3 hrs.	15.8		
M.L.	Vomiting and diarrhea	+	5.0	Failed at 6.9	Vomiting with same blood level obtained by intramuscular quinidine
	Vomiting	++++	6.9		
D.C.	Vomiting	+	2.75		None
	Headache	+		4.6	
	Tinnitus	+	4.6		
V.H.	Slight nausea	+	5.0	8.3	None

The Prevention of Paroxysmal Arrhythmias

Delevett and Poindexter[14] described 2 cases in which critical blood levels could be defined for the prevention of paroxysmal tachycardia. A study of this phase of therapy is in preparation, but one striking case may serve to illustrate the value of blood levels in the prevention of paroxysmal ventricular tachycardia (fig. 11).

The patient was a 63-year-old man with coronary artery disease, in whom ventricular tachycardia of four days' duration was converted to sinus rhythm with 3.4 Gm. quinidine in sixteen hours. The conversion level was 4.1 mg. per liter. During the subsequent two and one-half weeks, while the patient was receiving maintenance doses, he had five recurrences of arrhythmia, and it was possible to establish the approximate effective therapeutic blood

quinidine level necessary to maintain sinus rhythm. Levels taken during four of the paroxysms of tachycardia were 3.3, 3.5, 3.3, and 4.2 mg. per liter. Levels at the time of reconversion of three of the attacks were 4.3, 5.6, and 4.6 mg. per liter. Maintenance doses thereafter were adjusted to keep the level above 4 mg. per liter and no arrhythmia occurred during the remainder of his one-month hospital stay. The patient has since been followed for nine months, and maintained on 3 Gm. (2.8 to 3.2) quinidine daily which produces mid-day blood levels constantly between 5 and 5.5 mg. per liter. Since resuming his normal activities, he has had occasional transient episodes of tachycardia but none have been persistent and only three have required additional quinidine, the longest responding in seven hours to 0.8 Gm. in addition to the maintenance dose. After being free of attacks for several months, while receiving 3 Gm. quinidine daily and maintaining a blood level of 5 mg. per liter, the patient was placed on quinidine "enseals" in the same dosage. His blood level fell to 1.7 mg. per liter and he had a prolonged (twenty-four hour) attack of ventricular tachycardia that responded to oral ordinary quinidine. He was again given ordinary quinidine and has had no further attacks, the blood level again rising to 5 mg. per liter.

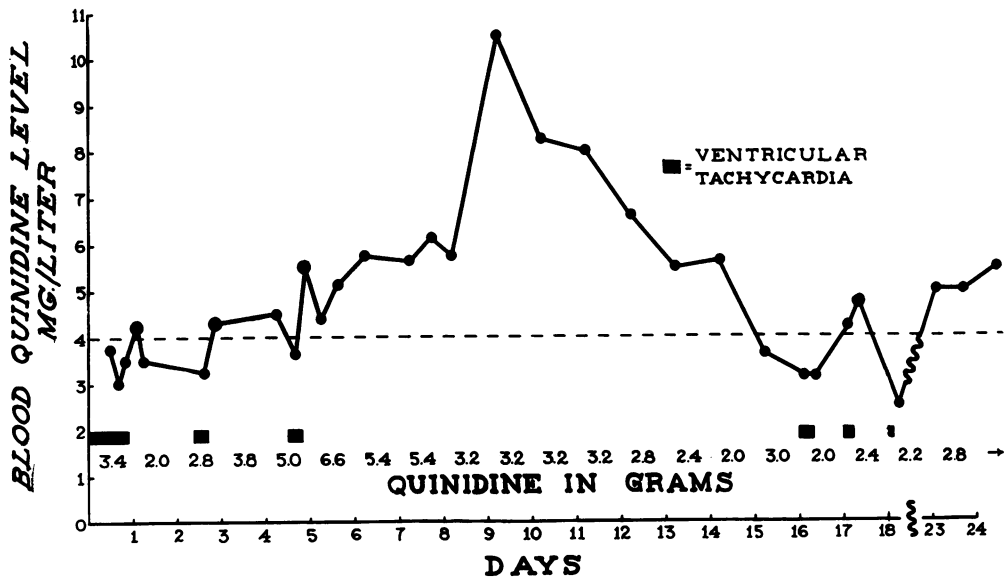

FIG. 11.—The importance of determining the critical blood level required to prevent attacks of paroxysmal ventricular tachycardia. Small additional doses of quinidine increased the blood concentration above the critical level and restored normal rhythm whenever the blood concentration fell below 4 mg. per liter. (W. R., male, age 63. Coronary heart disease. Recurrent ventricular tachycardia for three years.)

Data on Relapses: Auricular Flutter and Fibrillation

Of the 24 patients (twenty-eight instances) converted to sinus rhythm, 10 have relapsed. Five of those who relapsed were reconverted with quinidine. No further quinidine treatment was attempted in the other 5 patients. One was reconverted elsewhere and is not included in our data.

Case 1. E. F., male, age 66 years: Postpneumonectomy, auricular fibrillation. Conversion was accomplished with 6 doses of 0.2 Gm. every four hours at a level of 7.0 mg. per liter. The patient relapsed twenty-four hours later, after receiving three or more doses of 0.2 Gm. (twice on the day of conversion, once the following morning) at a level of 3.8 mg. per liter. He was then reconverted with 0.4 Gm. every four hours for four doses, at a level of 5.5 mg. per liter.

Case 2. M. G., male, age 63 years: Coronary heart disease with chronic auricular fibrillation. Conversion was accomplished with 0.4 Gm. every two hours for eight doses, followed the next day by 0.6 Gm. every two hours for four doses, and the third day by 0.6 Gm. for one dose. The blood level at this time was 4.4 mg. per liter. The patient received 0.4 Gm. four times a day for two days and was discharged home on 0.2 Gm. four times a day. When seen one week later, his rhythm was irregular, but reconversion was not attempted.

Case 3. L. S., female, age 64 years: Coronary heart disease with chronic auricular fibrillation. Conversion was accomplished with 0.4 Gm. every four hours for four doses at a level of 4.0 mg. per liter.

The patient then received 0.3 Gm. every six hours for the next three days and relapsed the morning of the fourth day. No attempt was made to reconvert the rhythm.

Case 4. A. T., male, age 29 years: Auricular fibrillation. This patient gave a history of recurrent prolonged attacks of auricular fibrillation of unknown etiology for ten years The patient had been having two to three attacks a year which were controlled by quinidine in each instance. He was converted to normal rhythm at a time when the blood level was 6.7 mg. per liter. Relapse occurred approximately six months after conversion, but no maintenance doses of quinidine had been taken during that period. He was reconverted with 0.6 Gm. every two hours for 5 doses and the blood level was 5.4 mg. per liter.

Case 5. F. W., male, age 66 years: Auricular flutter. This patient had recurrent auricular flutter of unknown etiology. He had had two previous entries into the University of California Hospital for purposes of conversion. On the third entry, he was converted with 2.8 Gm., given in doses of 0.4 Gm. every four hours, after having had 0.2 Gm. and 0.4 Gm. every two hours for five doses on the two previous days; the blood level at time of conversion was 10 mg. per liter. Six months later, the patient relapsed, having received no maintenance doses of quinidine during this period. The patient was reconverted with digitoxin and three months later, his rhythm was still regular on various doses of quinidine.

Case 6. C. N., female, age 55 years: Auricular fibrillation. This patient had chronic auricular fibrillation of unknown etiology. She was converted with a blood level of 5.7 mg. per liter after 0.4 Gm. every two hours for six doses. She was discharged home on 0.2 Gm. four times a day which she stopped five days later. A few days later, auricular fibrillation reappeared. No further attempt was made to reconvert the arrhythmia.

Case 7. W. S. Y., male, age 62 years: Auricular fibrillation. The duration of the auricular fibrillation is not definite, although it had probably been present for months. The etiology was not definite. The arrhythmia was converted to sinus rhythm with 0.4 Gm. every four hours for five doses, followed the next day by 0.6 Gm. every four hours for four doses, at a blood level of 6.2 mg. per liter. The patient was then given 0.4 gm. four times a day for two days, and 0.2 Gm. four times a day for two days. No quinidine was taken for four days, after which the patient relapsed. The administration of 0.6 Gm. for three doses brought about reconversion. The patient is currently on a schedule of 0.4 Gm. three times a day without relapse.

Case 8. T. B., female, age 49 years: Auricular fibrillation. Auricular fibrillation occurred in the patient following a thyroidectomy, and had been of fourteen months' duration. Conversion resulted at a blood level of 5.8 mg. per liter after 0.4 Gm. every two hours for five doses, and the patient was discharged home on 0.2 Gm. four times a day for five days. One week later, auricular fibrillation was again present, but was converted when the quinidine dosage was increased to 0.4 Gm., 0.4 Gm., 0.2 Gm., and 0.2 Gm. A second relapse occurred two weeks later (the quinidine dose had been reduced by 0.2 Gm.), and conversion was brought about by increasing the daily dose by 0.2 Gm. Thereafter the patient's rhythm remained regular, and the quinidine dosage was gradually reduced. After two and one-half months, the quinidine was stopped, and regular rhythm was maintained without quinidine for four months, after which time another relapse occurred. Conversion at this time was accomplished with 0.4 Gm. every four hours for thirteen doses with a blood level of 5.5 mg. per liter. The patient was discharged home on 0.4 Gm. three times a day, on which dose she relapsed, and did not reconvert with 0.4 Gm. five times a day for three days. No further attempt to reconvert was made.

Case 9. C. G., male, age 39 years: Rheumatic heart disease with mitral stenosis and auricular fibrillation. The auricular fibrillation had been present for two months. The patient had a femoral embolus in June, 1948, which was presumably the result of paroxysmal auricular fibrillation. Sinus rhythm was present during the patient's stay in the hospital. He had a cerebral embolus in the fall of 1948 and at this time, and for the next two months, auricular fibrillation was present. Conversion was accomplished at a peak level of 15.8 mg. per liter. Two weeks later, there was a relapse on a maintenance dose of 0.2 Gm. three times a day. The arrhythmia lasted four days, in spite of increasing the dose to 0.2 Gm. four times a day. A second relapse lasting ten days occurred one week later, while the patient was on a maintenance dose of 0.2 Gm. four times a day. Regular rhythm was restored by increasing the dose to 0.4 Gm. four times a day with a blood level of 7.9 mg. per liter. Since then, the patient's rhythm has remained regular on 0.4 Gm. three times a day and a level of 5.6 mg. per liter.

Case 10. V. H., male, age 43 years: Rheumatic heart disease and auricular fibrillation. Auricular fibrillation had probably been present in this patient for three years. It was converted to normal rhythm after 8.4 Gm. in three days with a peak blood level of 8.3 mg. per liter. The fourth morning, arrhythmia was again present, fourteen hours after conversion, despite doses of 0.6 Gm. two times during the night. No blood level was obtained. No further attempt at reconversion was made.

Discussion

The data presented indicate that the use of quinidine blood levels may provide a more rational basis for the use of quinidine in the treatment of auricular fibrillation and auricular

flutter. The fact that peak levels occur in two hours and that the increase in level becomes progressively less after four to five doses indicates that the total amount of quinidine is not as important as the number of hours over which the quinidine is given and the size of the individual dose. Any given dose schedule, therefore, may fail if these factors are not taken into account.

The value of the blood level of quinidine as a guide in therapeutic conversion of auricular fibrillation and flutter is significant. Most patients were converted to normal rhythm at moderate blood levels. In resistant cases, even when higher blood levels (greater than 9 mg. per liter) were attained, only a small percentage converted (in only 2 of 6 cases). Only 2 patients in whom sinus rhythm was produced required levels exceeding 10 mg. per liter, and in one of them a short bout of ventricular tachycardia resulted. It is of interest that in the 6 patients in whom sinus rhythm was not restored, 4 failed with levels equal to or exceeding 10 mg. per liter. It would appear, therefore, that if successful conversion does not occur with moderate doses and moderate blood levels, forcing the issue with higher doses is only infrequently successful and adds considerably to the possibility of important toxicity. Four of the 6 patients who failed to convert to sinus rhythm had mitral stenosis with hearts that varied in size from but slightly to markedly enlarged.

It was of considerable interest that several patients converted to sinus rhythm at low blood levels with doses of quinidine given not for conversion but for the suppression of premature beats. Since approximately 15 per cent of our patients had normal rhythm restored at blood levels of 4 mg. per liter or less, and since this blood level rarely is attended by any toxicity, one may well wonder if small doses of quinidine might be tried in many cases in which a serious attempt at conversion is not warranted. One may be pleasantly surprised to gain successful results with small doses of quinidine.

The occasional delay in conversion after the peak blood level has passed suggests the possibility of a time element in the action of quinidine on the heart. In this respect, the observations of Weiss and Hatcher[24] are of interest; these workers found that the cat heart may be paralyzed by very high blood stream concentrations of quinidine before much absorption by the myocardium has occurred, whereas with prolonged lower blood concentrations, much higher myocardial levels may be reached without paralysis.

The adaptation of the body to continued administration of quinidine is even more clearly shown in the parabolic curve obtained when the same dose of quinidine is given day and night. The fact that the blood level may rise for the first seventy-two hours with this type of dose schedule only to fall gradually as this same dose schedule is continued makes it clear why some patients may convert on the second or third day of a fixed schedule. However, it also emphasizes the futility of continuing this routine if success is not obtained after the first few days. To increase the blood level of quinidine, the drug must then, after a few days, be given at more frequent intervals or in larger individual doses.

The minor toxicity and high percentage of successful conversions supports the opinion that the dangers of the use of quinidine have been overemphasized. Many of our patients had less dyspnea, less palpitations, were able to do more work, and, in general, were distinctly improved following successful conversion to sinus rhythm. This improvement resulted despite the fact that the ventricular rate when the rhythm was sinus in origin was essentially the same as that obtained in the well-digitalized auricular fibrillation, and despite the fact that often no significant change in vital capacity, circulation time, or venous pressure could be demonstrated.

The successful conversion to sinus rhythm of 2 patients who recently had had serious arterial emboli while fibrillating (C.G. and V.H.) emphasizes the possible benefit to be obtained in sinus rhythm in these patients.[7] The most common cause of arterial embolism in the series of Allen, Barker and Hines[25] occurred in patients with auricular fibrillation. No instances of em-

bolism occurred following conversion in the present series of cases.*

The relatively small percentage of quinidine that is excreted in the urine in relation to the dose given (even when given intramuscularly) indicates that the disappearance of quinidine from the blood is through metabolic processes, the exact nature of which are not known. Similarly, the adaptation phenomena by which the body responds to fixed daily doses of the drug remains unexplained.

Our observations that many patients with auricular fibrillation progress through a stage of auricular flutter under the influence of quinidine as the auricular rate is slowed support the notion that both arrhythmias may be similar in mechanism and differ mainly in the rate of discharge of the ectopic focus.[27] The frequency with which auricular flutter is noted probably depends in part on the frequency with which electrocardiograms are taken as the conversion time approaches. The danger is present of a sudden rise in ventricular rate, as may occur if a 2:1 block develops,[1] but this happens infrequently.

Summary and Conclusions

1. Blood and urine quinidine levels using the photofluorometric method of Brodie, as modified by Linenthal, were obtained in 72 patients, including 30 with auricular fibrillation and auricular flutter in whom conversion was attempted.

2. Successful conversion to sinus rhythm occurred in twenty-eight of thirty-four attempts in 30 patients (82 per cent). The average peak blood level in the cases converted was 5.9 mg. per liter; 75 per cent of the patients converted to normal rhythm at levels between 4 and 9 mg. per liter. These blood levels were obtained with quinidine dose schedules of 0.4 or 0.6 Gm. every two hours for five doses.

3. Blood levels higher than 9 mg. per liter were obtained in 6 patients but resulted in conversion to sinus rhythm in only 2 patients. Of the twenty-eight successful conversions, only 2 patients required levels of 10 mg. per liter or more. Of the 6 patients in whom normal rhythm was not restored, levels of 10 mg. per liter or more were obtained in 4 patients. The likelihood of successful conversion is relatively small if large doses and high blood levels are required.

4. Important toxic manifestations occurred in 3 patients; in 2, vomiting of sufficient degree precluded further treatment, and in one patient a short bout of ventricular tachycardia occurred. In the last patient, a high blood level of 15.8 mg. per liter was required for successful conversion.

5. Data on the clinical pharmacology of the drug have been described and information on the time of peak blood levels, duration of effect, and decrement of blood levels has been noted.

6. The time-dose relationship with fixed dose schedules and the adaptation phenomena have been discussed. The importance of the size of the individual dose and the necessity of being aware of the parabolic blood quinidine curve resulting from fixed daily dose schedules has been emphasized.

7. The inverse relationship in the first twelve hours of the auricular rate as obtained by right precordial electrocardiograms and blood quinidine levels indicates that the blood levels reflect cardiac effects of the drug.

* One patient who converted to sinus rhythm after the present series was completed developed symptoms and signs compatible with a pulmonary embolus coincident with relapse of auricular fibrillation. He did well and no definite diagnosis was made. Another patient, being prepared for conversion, developed a cerebral embolus and died before quinidine therapy was started.

Acknowledgments

We are grateful to Dr. Louis D. Greenberg for his advice in regard to the photofluorometric method, and to Miss Phyllis Waldsmith for valuable technical assistance.

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