Factors Influencing Conversion of Chronic Atrial Fibrillation with Special Reference to Serum Quinidine Concentration

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Opinion differs greatly about the value and risk of quinidine. The present communication attempts to demonstrate that more rational use of quinidine is possible by emphasis on serum quinidine concentration rather than on dose alone. Conversion of chronic atrial fibrillation and the appearance of myocardial toxicity are related more closely to the concentration of quinidine in the blood than to the dose. The serum concentration achieved with equal doses of the drug varied strikingly in different individuals; myocardial toxicity was infrequent at levels less than 6.0 μg./ml. and increased proportionately as this level was exceeded. These levels could not always be predicted from the dose given.

The problem of conversion of chronic atrial fibrillation to sinus rhythm with quinidine has concerned physicians for 30 years. Many statements in the literature are based on few cases or were made before the current awareness of the importance (a) of treating cardiac failure prior to the attempted conversion and (b) of quinidine serum concentrations as a guide to therapy. The individualization of dosage on the basis of the concentration of quinidine in the blood has made attempts at conversion less empirical and safer.

It was thought desirable to document our experience with over 200 attempts at conversion with quinidine of patients with chronic atrial fibrillation or flutter, and to clarify the relationship between serum concentration of quinidine and proper dosage, effective therapy, and toxicity.

Material and Methods

Conversion with quinidine was attempted 214 times in 177 patients with chronic atrial fibrillation or flutter; in some patients relapses occurred when maintenance doses of quinidine were inadequate (see below).

The patients selected for conversion fell into the following groups:

1. Those in whom the appearance of atrial fibrillation resulted in abrupt worsening of the cardiac status and clinical condition despite a completely adequate cardiac regimen.

2. Chronic cardiac "invalids" despite full cardiac therapy in whom it was thought that increased cardiac output associated with sinus rhythm might improve cardiac function.

3. Those with atrial fibrillation and episodes of arterial emboli, in whom it was thought that restoration to sinus rhythm might decrease the likelihood of atrial thrombus formation.

4. Those with chronic atrial fibrillation who had undergone a technically successful mitral valvulotomy.

5. Those in whom atrial fibrillation persisted after successful treatment of hyperthyroidism.

6. Those with atrial fibrillation of relatively recent origin (less than 6 months), regardless of symptoms and of the underlying disease.

7. Those in whom disturbing palpitations and awareness of cardiac irregularity persisted despite full digitalization and a slow ventricular rate.

As a general rule, conversion to sinus rhythm was not attempted in middle-aged or elderly patients with chronic atrial fibrillation who were entirely asymptomatic, who had been doing well on digitalis alone, and who had not experienced any cardiac difficulties or emboli over a period of months or years despite the arrhythmia.

Patients with paroxysmal atrial fibrillation are not considered in the present paper.

Etiology

The etiology of the atrial arrhythmia in the 177 patients was as follows: rheumatic heart disease, 94 cases; coronary heart disease, 38 cases; hypertensive cardiovascular disease, 20 cases; thyrotoxic heart disease, 10 cases; congenital heart disease, 1 case; miscellaneous, 14 cases. Approximately half the
patients had rheumatic heart disease; these cases are discussed independently in a separate section.

Technic

The patients were observed closely in the hospital. In all cases saturation doses and satisfactory maintenance doses of digitalis were administered prior to the attempt at conversion. If cardiac failure was present, sodium restriction and mercurial diuresis were employed as required for maximum amelioration of cardiac failure before attempted conversion. Electrolyte and metabolic disturbances and dietary deficiencies also were corrected so far as possible. The attempt at conversion was usually delayed if infection, rheumatic activity, active thyrotoxicosis, pulmonary infarction, or other acute condition was present.

The quinidine was administered in progressively increasing doses by one of two technics. Almost all patients were given a test dose of 0.2 Gm. to determine sensitivity. If no sensitivity was manifested during a 4-hour interval, 0.4 Gm. was administered every 2 hours for 5 doses. If conversion did not occur and if no myocardial toxicity resulted, the doses were increased to 0.6 Gm. given every 2 hours for 5 doses, and on occasion to 0.8, 1.0, or 1.2 Gm. every 2 hours for 5 doses. If minimal gastrointestinal symptoms or minimal electrocardiographic changes occurred, the daily dose (for example, 2 or 3 Gm.) was sometimes repeated for 2 or 3 days before a larger dose was used. No case was considered a failure unless the patient had received at least 2 Gm. of quinidine over a 16-hour period.

The patients were examined prior to each dose of quinidine. An electrocardiogram was taken preceding the fifth dose as a rule, unless the total daily dose had exceeded 3 Gm. a day and the atrial rate had fallen below 200/min. Under these circumstances electrocardiograms were taken 2 or 3 times during the day. Serum for determination of quinidine concentration was taken frequently throughout the day in some cases; in others, as close as possible to the time of conversion or at the time of peak concentration (i.e., 2 hours after the last dose). On examination, the presence of ventricular premature beats or hypotension was particularly noted, and the patients were closely questioned concerning the occurrence of nausea, vomiting, tinnitus, or diarrhea. The electrocardiograms were studied with particular reference to the appearance of runs of ventricular premature beats, slowing of the atrial rate, and widening of the QRS complex. Quinidine was stopped if severe vomiting occurred, if the QRS duration exceeded 50 per cent of the control QRS duration, or if frequent ventricular premature beats (1 or more every 6 beats), not previously present, were noted. If conversion was attempted in patients with incomplete or complete bundle-branch block, quinidine was stopped when the QRS duration exceeded 25 per cent more than the control QRS duration. Tinnitus, nausea, and mild diarrhea were not as a rule considered indications to discontinue quinidine, but were treated with sedatives, paregoric, and at times with antihistaminic agents or morphine derivatives.

If conversion did not occur and toxicity, either gastrointestinal or myocardial, forced cessation of the attempt, a second method of administering quinidine was sometimes used: namely, progressive doses 4 times a day, beginning with 0.4 Gm. and building up to a maximum of 1.2 Gm./dose. Some patients who experienced gastrointestinal symptoms with the 2-hour schedule were able to tolerate the 4-hour one.

In general, anticoagulant therapy was not used prior to attempted conversion, except in a few instances in which recent arterial emboli had occurred.

Serum quinidine determinations were done by Linenthal’s modification of Brodie’s method. Quinidine is determined by a technic in which quinidine is added to distilled commercial ethylene dichloride. The mixture is alkalinized with 10 per cent sodium hydroxide and shaken for 10 min. in a mechanical agitator. The aqueous phase is separated by centrifugation and removed by aspiration. With serum, no further extraction is required; with urine, 2 additional washings with sodium hydroxide are necessary to assure removal of quinidine degradation products. An aliquot of the urine or serum extract is diluted with ethylene dichloride and acidified with trichloroacetic acid. Absolute ethanol is added to minimize absorption. The fluorescence is then measured on the Coleman photofluorometer. Subtraction of a blank specimen of serum or urine containing no quinidine permits determination of the net fluorescence of quinidine in the unknown sample. This value is then compared with the net fluorescence of 2 standard solutions containing known amounts of quinidine.

The extraction method of analysis was used throughout this study. It should be noted that this technic gives lower readings than the precipitation method.

Results

Over-all Experience

A total of 214 attempts at conversion to sinus rhythm was made in 177 patients; 153 were successful, 61 were failures. Chronic atrial flutter was present in 8 patients; atrial fibrillation in the rest. Successful conversion of atrial flutter to sinus rhythm with quinidine was achieved in 5 patients; in 3 patients the attempt failed. The number of attempts is greater than the number of patients because in some cases additional attempts were required after
relapses due to what proved to be inadequate maintenance doses of quinidine (see below).

Figure 1 shows the daily dose of quinidine required for conversion; the mean was 2.2 Gm./day.

Figure 2 shows the cumulative percentage of successful attempts in both atrial fibrillation and flutter with increasing daily dose schedules in 153 conversions. As shown, in approximately 85 per cent of all patients in whom sinus rhythm could be restored without myocardial toxicity, conversion was effected by daily doses of 3 Gm. or less.

Figure 3 reveals the cumulative percentage of 127 successful conversions in both atrial fibrillation and flutter in which peak levels of serum quinidine concentration at conversion were obtained. It will be seen that approximately 80 per cent of all conversions that were achieved without clinical myocardial toxicity occurred at serum concentrations of approximately 8 μg./ml. or less. Of the 55 conversion attempts in which serum levels of more than 8 μg./ml. were reached, less than half were successful.

Figure 4 shows the distribution curve of successful conversions in relation to serum concentration of quinidine; in most cases conversion occurred at levels between 3 and 6 μg./ml., with a mean of 6.1. Conversion during the night, with falling serum quinidine levels, occurred in 23 instances, an incidence of 15 per cent of the 153 conversions.

Figure 5 gives the peak serum levels in the
61 patients who failed to convert to sinus rhythm. The high serum concentrations achieved are clearly seen. The average daily dose of quinidine required for conversion in the successful cases was 2.2 Gm./day, whereas the mean peak daily dose in the failures was 3.1 Gm./day. Twenty-three of the 61 patients were given more than 3 Gm. of quinidine daily. The conversion failures, therefore, cannot be attributed to an inadequate therapeutic trial, except in 7 cases (indicated by cross-hatching) where the attempt, in retrospect, was considered desultory.

Etiology of the Underlying Cardiac Disease

It became apparent that a clear relationship existed between the etiology of the underlying cardiac disease and successful conversion (fig. 6). The highest percentage of failures occurred in the patients with rheumatic heart disease. Conversion attempts were successful in only 61 per cent of the patients in this group, in contrast to 80 to 85 per cent in all other etiologic groups. The experience with rheumatic heart disease is discussed later, when an effort is made to assess the probability of conversion in relation to different valve lesions.

Duration of Atrial Fibrillation

The influence of duration of atrial fibrillation on successful conversion with quinidine is illustrated in figure 7. The exact duration of the arrhythmia was often difficult to determine because some patients were unaware of its onset. The data approximate the duration as reliably as possible from the history of the patients; the limitations must be kept in mind.

In both the rheumatic and the nonrheumatic groups, conversion decreased sharply as the duration of the arrhythmia exceeded 6 months. The slope of the fall is less marked after 12 months, but is still definite.

Table 1 defines the relationship between duration and etiology more precisely, and shows that conversion was achieved in 95 per cent of nonrheumatic patients with atrial fibrillation of less than 6 months' duration. The conversion rate in rheumatic patients whose fibrillation had persisted only 6 months or less was 83 per cent, which is far higher than the rate in the rheumatic cases in general. When atrial fibrillation had persisted more than 6 months, the percentage of conversions fell more sharply in the rheumatic than in the nonrheumatic group. In an attempt to eliminate the influence of associated cardiac failure, only patients who did not have cardiac failure were included in table 1.
TABLE 1.—Relationship Between Duration and Etiology of Atrial Fibrillation and Successful Conversion in the Absence of Cardiac Failure

<table>
<thead>
<tr>
<th>Duration of AF</th>
<th>Successful attempts</th>
<th>Failures</th>
<th>Total attempts</th>
<th>Per cent successful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrheumatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 6 mo</td>
<td>36</td>
<td>2</td>
<td>38</td>
<td>95</td>
</tr>
<tr>
<td>More than 6 mo</td>
<td>24</td>
<td>8</td>
<td>32</td>
<td>75</td>
</tr>
<tr>
<td>$p = 0.26$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 6 mo</td>
<td>29</td>
<td>6</td>
<td>35</td>
<td>83</td>
</tr>
<tr>
<td>More than 6 mo</td>
<td>17</td>
<td>16</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td>$x^2 = 6.25$</td>
<td>$p = .01$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiac Failure

Table 2 presents data regarding the effect of the presence or absence of failure at the time of the attempts at conversion in the rheumatic and nonrheumatic patients. Some of the patients who did not have cardiac failure at the time of the attempt had experienced it in the immediate or remote past, but it had responded to appropriate treatment. Although the percentage of successful conversions was slightly higher in the patients who did not have cardiac failure at the time quinidine was given, the difference is statistically significant only in the combined group ($p = 0.02$).

The presence of cardiac failure seemed related to successful conversion in patients with pure mitral stenosis: in 21 patients without failure, attempts at conversion succeeded in 18 (86 per cent) but were unsuccessful in 3; in 9 patients with cardiac failure, attempts succeeded in 4 (44 per cent) but failed in 5. Although the numbers are small, the difference in the percentage of successful conversions approaches statistical significance ($p = 0.06$).

Systemic Emboli

In both the rheumatic and nonrheumatic patients, conversion to sinus rhythm was not significantly affected by the occurrence of emboli prior to the attempt. In 38 rheumatic patients with history of emboli there were 25 successes (65 per cent) and 13 failures; in 74 rheumatic patients with no history of emboli, 43 successes (59 per cent) and 31 failures; in 28 nonrheumatic patients with history of emboli, 23 successes (82 per cent) and 5 failures; in 75 nonrheumatic patients with no history of emboli, 62 successes (83 per cent) and 13 failures.

Valve Lesion

Examination of the influence of the nature of the valve lesion on the likelihood of conversion showed what appears to be clear evidence of the deleterious effect of associated mitral insufficiency. Associated or dominant mitral insufficiency was diagnosed when a long systolic murmur at the mitral area was combined with electrocardiographic or radiologic evidence of left ventricular hypertrophy in the absence of an aortic lesion or hypertension. In 21 patients with pure mitral stenosis without cardiac failure, conversion was successful in 18 (86 per cent) and failed in 3. In 38 patients with mitral stenosis plus mitral insufficiency without cardiac failure, conversion was successful in 18 (47 per cent) and failed in 20. Thus, the presence of mitral insufficiency decreased the likelihood of conversion from 86 per cent in the cases of pure mitral stenosis to 47 per cent in those with associated regurgitation; this difference is statistically significant ($p = 0.01$). In uncomplicated mitral stenosis alone, in the absence of cardiac failure, conversion is accomplished as readily as in nonrheumatic heart disease.

In our series only 11 patients had a predominant aortic lesion. Conversion was successfully achieved in 8 (73 per cent) of these patients.

TABLE 2.—Relationship of Cardiac Failure to Successful Conversion

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiac Failure at Time of Conversion Attempt</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Attempt Succeeded</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>32 15 (47%) 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 50 (67%) 67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = 0.11$</td>
<td></td>
</tr>
<tr>
<td>Nonrheumatic</td>
<td>22 17 (77%) 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73 62 (85%) 11</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>54 32 (60%) 22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>148 112 (80%) 36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$x^2 = 5.21$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = 0.02$</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Size
The x-ray films of the chest of 54 of the patients with rheumatic heart disease were reinterpreted by Dr. Howard Steinbach of our Radiology Department. The following features were graded 0 to 4 plus, and the data analyzed to determine whether any of the radiologic features were correlated with successful conversion: over-all cardiac size, individual chamber size, size of the conus artery segment, size of the pulmonary arteries and hilar vessels, and degree of pulmonary hypertension and Kerley's lines. The only radiologic finding that showed a suggestive influence was over-all cardiac size. Small cardiac size (2 plus or less) favored success, with \( p = 0.12 \) for the difference between the 2 groups. It is surprising that no significant difference was found in the conversion percentage in patients with relatively small, as compared to large, left atria.

Age
Age was found to have no influence on the likelihood of conversion. No significant differences were found between the mean age of those in whom conversion was successful and those in whom the attempt failed. Mean ages were as follows: rheumatic heart disease, 43.1 years; coronary heart disease, 63 years; hypertensive cardiovascular disease, 61 years; thyrotoxic heart disease, 52.5 years.

Toxicity
The toxic symptoms manifested by our patients after treatment with quinidine were classified as follows: mild—blurred vision, transient deafness, anorexia, nausea, weakness, vertigo, tinnitus, slight diarrhea, headache; moderate—vomiting, diarrhea, hypotension, QRS duration increased more than 25 per cent but less than 50 per cent of the control value, rare to occasional ventricular extrasystoles; marked—frequent extrasystoles (1 or more every 6 beats), ventricular tachycardia, ventricular fibrillation, complete A-V block, QRS duration increased 50 per cent or more. The rare idiosyncrasy manifested by purpura, fever, or rash did not occur in this series. The manifestations noted as marked were considered indicative of myocardial toxicity and required cessation of quinidine therapy (table 3). Although some patients were unaware of any difficulty, the electrocardiographic changes indicated discontinuance of quinidine as a precautionary measure. Hypotension (fall in diastolic pressure of 20 mm. Hg) rarely occurred with oral quinidine, although it is an important finding following parenteral quinidine.29

Figure 8 illustrates the relationship between serum quinidine concentration and toxicity. The presence or absence of toxicity is correlated at all serum levels (the number of serum quinidine determinations are in parentheses under the figures giving the concentrations). Important myocardial toxicity occurred with levels less than 6 \( \mu g./ml. \) only 7 times in 429 observations (1.6 per cent), and never with levels below 3 \( \mu g./ml. \). The percentage of such toxicity rose progressively with increasing serum concentrations to reach 12 per cent at levels between 6 and 8 \( \mu g./ml. \), 30 per cent at levels between 8 and 10, 45 per cent at levels from 12 to 13, and 65 per cent at levels over 14. Whereas successful conversion occurs in a relatively small percentage of cases not converted at serum levels of 8 \( \mu g./ml. \) (fig. 3), myocardial toxicity increases rapidly when this level is exceeded (fig. 8).

Table 3—Tabulation of Incidence of Electrocardiographic Signs of Myocardial Toxicity during Conversion Attempt

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Successful</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration 50 per cent or more of control value</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Frequent ventricular premature beats</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Runs of ventricular tachycardia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Supraventricular premature beats</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Complete A-V block</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

\* in 17 patients
\+ in 19 patients

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is 6 μg./ml. The serum concentration of quinidine varies strikingly in different individuals receiving the same dose of the drug. For example, at a daily dose of 3 Gm./day the serum concentration in different patients varied from 3 to 16 μg./ml.; however, manifestations of myocardial toxicity with this dose were seen only in those patients whose serum concentrations were high. The average serum concentration rises progressively with increasing doses of quinidine per day, but in any given patient the toxicity seems to be related to the serum concentration rather than to the daily dose.

The serum concentration alone, while apparently more important than the dose itself, is not the only factor influencing toxicity. The state of the heart, the degree of cardiac failure, the associated degree of digitalis saturation, the state of electrolyte balance, the degree of nervous tension, all play a role in conversion and toxicity with quinidine. With changing states of the myocardium or the internal environment of the patient, success, failure, or toxicity might occur at the same serum levels on different occasions.

Delayed toxicity, appearing for the first time as the serum level was falling, was rare in our study. Myocardial toxicity usually occurred within 5 hours of the peak serum concentration, and the manifestations rapidly waned and were usually gone in 12 hours (fig. 12).

This is of some interest since approximately 15 per cent of the successful conversions occurred as long as 12 hours after the peak serum concentration was achieved. This conversion associated with falling serum concentrations may be related to the combination of rest and sleep with residual quinidine in the serum, since on occasion we have found sedation helpful during the day to effect conversion.

"Rapid" versus "Slow" Administration

We have observed that some patients who manifested toxic symptoms when quinidine was given by the "rapid" method (i.e., every 2 hours for 5 doses) were able to tolerate equivalent levels reached by the "slow" method of administration (i.e., 4 times a day). Table 4 summarizes our experience with both methods of administration. Marked toxicity resulted somewhat more frequently at any given serum level when the "rapid" method was used.

![Fig. 8. Relationship between serum quinidine concentration and toxicity.](http://circ.ahajournals.org/)

![Fig. 9. Relationship between daily dose, peak serum quinidine concentration, and myocardial toxicity.](http://circ.ahajournals.org/)
TABLE 4.—Comparison of Toxicity Between Slow and Rapid Quinidine Schedules

<table>
<thead>
<tr>
<th>Serum levels</th>
<th>Total levels</th>
<th>% Moderate toxicity</th>
<th>% Severe toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>6.0-7.9</td>
<td>45</td>
<td>51</td>
<td>11.1</td>
</tr>
<tr>
<td>8.0-9.9</td>
<td>13</td>
<td>33</td>
<td>7.7</td>
</tr>
<tr>
<td>10.0-20.0</td>
<td>14</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>

Successful conversion occurred with about equal frequency with the 2 methods at comparable serum levels, although conversion was effected in 5 patients with the "rapid" method after the "slow" method had failed. The reverse occurred in only 1 patient.

Emboli

No discussion of toxicity is complete without reference to the incidence of emboli. In our series, 30 patients (43 conversions) had a history of emboli prior to conversion. Of these, 1 patient had an embolus again at the time of conversion, and 4 at the time of subsequent relapse to atrial fibrillation. Eighty-six patients (110 conversions) had no history of emboli prior to conversion. Of these, 1 patient had a probable embolus at the time of conversion, and 3 at the time of relapse from sinus rhythm to atrial fibrillation.

Relapses

Our data on relapses and the optimal quinidine doses and levels required for successful maintenance of sinus rhythm are relatively incomplete. Sufficient follow-up data, however, is available on 99 of the 153 conversions to permit some observations on the relationship between relapse and varying daily maintenance doses of quinidine. Relapses occurred promptly in 36 (85 per cent) of 42 patients when maintenance doses were discontinued or if no quinidine was given after conversion. The majority of relapses took place within a week.

In contrast, of the 43 patients receiving daily maintenance doses of 1.6 Gm. or more of quinidine, only 9 had relapses; the remaining 34 were successfully maintained as long as this dose was continued. The duration of follow-up on this schedule ranged from 7 to 1460 days, with a mean of 209 days. Of the 9 who had relapses on this maintenance schedule, 2 had relatively low serum quinidine levels at the time of relapse (1.0 and 2.5 µg./ml on doses of 0.4 Gm. 4 times daily and 0.6 Gm. 4 times daily, respectively). In the remaining 7 patients, the serum quinidine levels were considered average for this dose range.

Of the 42 patients receiving less than 1.6 Gm. of quinidine daily, 19 (44.2 per cent) had relapses; the remaining 23 (55.8 per cent) were successfully maintained as long as the drug was continued. In this group the maintenance doses were given from 6 to 960 days, with a mean of 173 days.

One of the 6 patients who remained in sinus rhythm despite the discontinuation of quinidine had chronic atrial flutter as a result of excessive thyroid intake; he had had no relapse in the 4 years since conversion.

These data were analyzed further to determine the relationship between adequate maintenance blood concentration and the likelihood of relapse. Serum levels in patients receiving maintenance doses of quinidine were determined at approximately 2 p.m., 2 hours after the second dose of the day. All serum concentrations described as "maintenance levels" were those taken at this time of day. As shown in table 5, a maintenance level of 5 µg./ml usually prevented relapse. This concentration was achieved on the average with a dose of 0.4 Gm. of quinidine 4 times daily. The distribution curve of the mid-day levels in patients on this maintenance schedule is presented in figure 10.

TABLE 5.—Relationship Between Maintenance Levels and Likelihood of Relapse

<table>
<thead>
<tr>
<th>Maintenance level</th>
<th>Total number</th>
<th>Number relapsed</th>
<th>Per cent relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 µg./ml. or less</td>
<td>37</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>More than 5.0 µg./ml.</td>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Totals</td>
<td>47</td>
<td>16</td>
<td>34</td>
</tr>
</tbody>
</table>

p = 0.14
Since a maintenance dose of 1.6 Gm. of quinidine/day results in an average serum level of approximately 5 mcg./ml., the concentration found to be generally effective in preventing relapse, the group of patients maintained on this dose was analyzed further to relate the adequacy of this maintenance dose to the size of the conversion dose. Of the 28 patients in whom conversion was accomplished with less than 3 Gm. of quinidine, only 2 (7 per cent) had relapses while receiving maintenance doses of 1.6 Gm./day. In contrast, relapses occurred in 7 (41 per cent) of the 17 patients who required a dose of 3 Gm./day or more for conversion. Thus, the relapse rate in the group receiving the routine maintenance dose of 1.6 Gm. was greater in the patients who had required the larger amount of quinidine for conversion.

The relationship between relapses and maintenance blood levels expressed as a per cent of the conversion level is shown in figure 11. The relapse rate in patients given no maintenance dose of quinidine was 85 per cent. In contrast, when the maintenance blood level was more than 60 per cent of the conversion level, the percentage of relapses fell progressively, reaching a low of between 10 and 20 per cent. This figure is based on 88 conversions in which both

conversion and maintenance serum quinidine levels were obtained.

Since 0.4 Gm. of quinidine 4 times daily was found to be an effective maintenance dose, 93 patients on this schedule were studied to determine the incidence of toxicity. It was found that this dosage schedule caused no serious toxicity in the overwhelming majority, 91 per cent of the group. Moderately toxic symptoms occurred in 6 patients (nausea and vomiting in 4, significant diarrhea in 1, QRS increased 25 per cent in 1). In the remaining 3 patients moderate toxicity occurred but the relationship to quinidine was questionable.

In summary, of the patients in whom sinus rhythm was restored with quinidine, and who could be followed adequately, 85 per cent relapsed if no maintenance dose of quinidine was given, if the maintenance dosage was insignificant, or if maintenance was discontinued. If the maintenance dose was less than 1.6 Gm. daily, approximately 45 per cent of patients relapsed; if the dose was 1.6 Gm./day or more, only 21 per cent of patients relapsed. In the

![Fig. 10. Distribution of 2 p.m. serum quinidine levels, dose of 0.4 Gm. q.i.d. (53 patients).](image)

![Fig. 11. The relationship between relapses and maintenance blood levels, expressed as a per cent of the conversion level.](image)
latter group approximately 8 per cent of the patients who required less than 3 Gm. for conversion had relapses when given a maintenance dose of 1.6 Gm. daily or more, whereas 41 per cent of those requiring a conversion dose of more than 3 Gm./day had a relapse on this dosage schedule. Relapse occurred in only 1 of 11 patients who had a maintenance level of 5 μg./ml. or more; in this patient a level of less than 5 μg./ml. was obtained prior to relapse. On the basis of maintenance level expressed as per cent of conversion level, relapses occurred in only 4 of 24 patients in whom the serum level was maintained at 61 per cent or more of the conversion level, and in 12 of 23 patients who had maintenance levels below this figure. It appears, therefore, that sinus rhythm can usually be maintained with a dosage schedule sufficient to give a mid-day concentration of 5 μg./ml. or 60 per cent or more of the conversion level.

Our data are inadequate to indicate the length of time, beyond a year or 2, that sinus rhythm can be maintained, partially because many of our patients come from widely scattered areas, and it is difficult to keep them on a maintenance dose of quinidine once they have been returned to their private physicians. Furthermore, with worsening of the cardiac status, particularly in rheumatic heart disease, patients may break through the quinidine barrier even when the maintenance dose and serum level are satisfactory.

**Rheumatic Heart Disease**

A number of the tables and figures in this report illustrate the difference between the rheumatic and nonrheumatic patients. From a consideration of the various tables, it seems clear that in rheumatic patients with uncomplicated mitral stenosis and atrial fibrillation of short duration without cardiac failure, the conversion rate is high, comparing quite favorably with the rate in the nonrheumatic patients. When mitral incompetence complicates the mitral valvular disease, when cardiac failure is present, or when the atrial fibrillation persists more than 6 months, the percentage of successful conversions falls progressively. As a result, in rheumatic patients with predominant mitral incompetence, fibrillation of long duration and cardiac failure, less than half the conversion attempts will be successful.

The cases of rheumatic heart disease were studied further to determine the significance of the following factors: history of emboli prior to the attempt at conversion, the presence of both a history of emboli and cardiac failure prior to the attempt, the presence or absence of electrocardiographic evidence of right or left ventricular hypertrophy, and various radiologic evidences of cardiac size. No statistically significant differences were noted, although a suggestive trend was found with cardiac failure (p = 0.11) and over-all cardiac size (p = 0.12).

**Atrial Tachycardia**

One interesting finding resulting from the frequent electrocardiographic studies during

![Fig. 12. Reversible change from atrial fibrillation to atrial flutter and tachycardia with quinidine therapy.](http://circ.ahajournals.org/lookup/fig/12)
conversion was the demonstration that patients progressed through a stage of atrial flutter and then atrial tachycardia as the rate of discharge of the ectopic focus in the atria was slowed by quinidine. The atrial rate may fall as low as 140 to 150/min.; at this rate, variable 2:1 and 1:1 conduction occurred.

The use of the atrial rate as an indication of the myocardial effect of quinidine has proved a valuable adjunct in our attempts to quantify the effect of treatment. The electrocardiographic tracings in figure 12 illustrate the change from atrial fibrillation to atrial flutter to atrial tachycardia as quinidine failed to effect a conversion to sinus rhythm in 1 of our patients. The quinidine blood levels at the various stages of change are also given. When quinidine was discontinued, the atrial rate increased promptly and progressed through flutter back to fibrillation. At the height of the quinidine effect when the atrial rate had slowed to 136, widening of the QRS had occurred and the electrocardiographic pattern superficially resembled that of ventricular tachycardia. The differentiation of these 2 conditions is important. On a number of occasions during quinidine therapy the electrocardiographic changes will resemble ventricular tachycardia (fig. 12), but close study will reveal that the rhythm is atrial tachycardia with an intraventricular conduction defect. The latter is an indication for discontinuing quinidine, but it does not have the ominous significance of ventricular tachycardia.

Slowing of the atrial rate, prolongation of the Q-T interval, widening of the QRS complexes, and the appearance of ventricular premature beats correlated roughly with increasing concentrations of quinidine in the blood. There were notable exceptions, as when widening of the QRS complexes occurred without other manifestations of toxicity or when marked slowing of the atrial rate occurred without significant widening of the QRS complexes.

Fig. 13. Improvement after conversion from atrial fibrillation to sinus rhythm.
As a general rule, however, considerable slowing of the atrial rate indicated that conversion was near. In most cases conversion took place at atrial rates between 200 and 250, although rates as low as 140 were occasionally required.

Benefits of Conversion

A complete discussion of this aspect of the subject is not the purpose of this report, but one case may be cited to illustrate the possible benefits of conversion in resistant cardiac failure. The patient was a 48-year-old man who continued to have severe, disabling congestive failure, despite full therapy and hospitalization for 3 months. He was unable to get out of bed because of marked dyspnea. Figure 13 shows the changes in weight, vital capacity, and venous pressure following conversion to sinus rhythm. Diuresis occurred, the vital capacity and venous pressure returned toward normal, and the patient became ambulatory and returned to work. The patient showed considerable improvement for a year or 2, then developed cardiac failure again, despite sinus rhythm. He died 3 years later. At autopsy chronic idiopathic (Fiedler's) myocarditis was found.

Other examples could be cited, but the usual evidence of improvement in patients with sinus rhythm is the cessation of embolic phenomena, decreased dyspnea, and relief from the disturbing palpitations. In addition, patients who were relatively asymptomatic before conversion volunteered that their exercise tolerance improved considerably after sinus rhythm had been restored, suggesting the previous existence of mild cardiac failure that had been subclinical and unrecognized.

Discussion

The data presented indicate that conversion of chronic atrial fibrillation and flutter with quinidine can be accomplished in the great majority of patients without serious myocardial toxicity. The use of quinidine blood levels provides a more rational basis for the use of the drug, facilitates determination of optimal dose schedules, and aids in judging whether progressively larger doses of quinidine can be administered safely. In our series, conversion, as well as toxicity, usually occurred about the time of the peak level in the blood, but in approximately 15 per cent of cases conversion took place during the night, some hours after the peak level had been reached. Delayed toxicity was quite rare, although in his extensive experience Sampson has seen 4 examples of paroxysmal ventricular fibrillation with blood quinidine levels below 3.5 µg./ml. in patients with severe mitral stenosis. In 3 of the 4, it occurred on the day following conversion, after the first maintenance dose of quinidine.

The great individual variation in serum concentrations of quinidine shown by patients on similar doses of the drug was quite striking and had to be considered in each case. When relatively low serum concentrations occurred after administration of relatively large doses of quinidine, this fact encouraged an increase in the dose of quinidine, provided clinical toxicity was absent. Conversely, when modest doses of quinidine resulted in high quinidine blood levels, considerable caution was used in increasing the dose to avoid raising the quinidine level into the toxic range. Toxic symptoms, both gastrointestinal and myocardial, increased progressively with rising concentrations in the blood, although there were important individual variations, especially with the gastrointestinal symptoms.

Determination of the blood concentration was also found to be important in assessing the relative likelihood of conversion as compared to toxicity. As blood levels exceed 8 µg./ml., not only does the likelihood of conversion decrease but the likelihood of serious toxicity increases. In our patients, 80 per cent of the successful conversions were accomplished with doses of 3 Gm./day or at blood levels of 8 µg./ml. or less. Failure to obtain sinus rhythm after 3 Gm./day of quinidine have been given and a blood concentration of 8 µg./ml. has been achieved requires re-evaluation of the total attempt and a new decision.

Our data indicate that the major factors that interfere with successful conversion of chronic atrial fibrillation with quinidine are rheumatic etiology, duration of atrial fibrilla-
tion longer than 6 months, the presence of cardiac failure, and the existence of unusual gastrointestinal sensitivity to the drug. A changing state of the myocardium, depletion of electrolytes, significant malnutrition, infection, and the use of associated drugs, all are important as nonspecific factors influencing conversion.

In cases of rheumatic etiology, conversion was readily achieved in patients with pure mitral stenosis without cardiac failure and in patients with predominant aortic valvular lesions. Successful conversion was found to be least likely in patients with predominant mitral incompetence, particularly when associated with fibrillation of long duration or with cardiac failure. This difficulty was thought to be related to the large size of the left atrium, which is so characteristic of patients with mitral incompetence, especially when combined with mitral stenosis; but we could not establish this fact. The presence of emboli in the immediate or remote past had no apparent effect on the likelihood of conversion.

The data described define more sharply the patients in whom successful conversion can be expected, and when utilized in conjunction with the serum quinidine concentration and clinical and electrocardiographic observations, enables the physician to determine the likelihood of toxicity as related to the likelihood of conversion. One cannot speak of the likelihood of successful conversion of atrial fibrillation as such; the percentage of successful conversions will vary from 95 per cent in patients without rheumatic atrial fibrillation of short duration without cardiac failure to 45 per cent in patients with mitral incompetence with atrial fibrillation of more than a year's duration associated with congestive failure. The potential benefits of the therapy must always be weighed against the therapeutic risk, and one must appreciate that the risk in attempted conversion varies in different phases of the therapeutic trial.

Serious hazards of quinidine therapy in this study were minimal; the only death followed parenteral administration of quinidine to a patient critically ill with severe mitral stenosis, at a level of 6.1 μg./ml. Ventricular tachycardia had occurred 4 hours after a series of 4 injections of 0.8 Gm. of quinidine gluconate intramuscularly at approximately 3 hourly intervals and was intermittent until ventricular fibrillation and death occurred 7 hours after the last dose.

The relatively low incidence of serious clinical toxicity is probably due to a number of factors, including thorough treatment of cardiac failure, correction of imbalances of electrolytes and vitamins, postponement of the trial of quinidine until infection, pulmonary infarction, or other acute conditions had subsided and the patient was stabilized on a program of rest, diet, digitalis, etc. Myocardial toxicity during attempted conversion occurred with sufficient frequency to indicate that one should always recognize the potential hazards and use quinidine only as a calculated risk. Close supervision during the attempt at conversion and frequent clinical and electrocardiographic examinations of the patients, in addition to the use of quinidine blood levels, were important as guides to the need for caution or boldness in further therapy. When marked myocardial toxicity is noted clinically or electrocardiographically, the drug should be stopped promptly. The total situation should be re-evaluated when high serum quinidine concentrations are obtained, and the drug continued only with due appreciation of all the factors involved.

**Summary and Conclusions**

1. Conversion of chronic atrial fibrillation to flutter with quinidine was attempted 214 times in 177 patients. Successful conversion was achieved in 74 per cent of the total group, but the percentage varied, depending upon etiology, duration of the fibrillation, presence of cardiac failure, and, in the patients with rheumatic heart disease, the type of valve lesion.

2. Atrial fibrillation of more than 6 months' duration decreased the likelihood of conversion in both the rheumatic and nonrheumatic patients. The incidence of conversion can be as high as 95 per cent in nonrheumatic patients.
with fibrillation of short duration, and as low as 45 per cent in patients with rheumatic mitral incompetence with fibrillation of more than a year's duration.

3. In the group with rheumatic heart disease, the poorest results occurred in patients with predominant mitral incompetence, even when the effects of duration and presence of cardiac failure were excluded. In patients with uncomplicated mitral stenosis or with predominant aortic valvular disease the rate of conversion was almost as high as that in the nonrheumatic group.

4. The presence of cardiac failure decreased the likelihood of successful conversion \((p = 0.02)\).

5. The presence of systemic emboli in the immediate or remote past did not interfere with successful conversion of atrial fibrillation.

6. One definite and 1 probable embolus occurred at the time of conversion, although approximately 15 per cent of the patients had a history of previous emboli. Emboli occurred in 7 patients when they relapsed from sinus rhythm to atrial fibrillation.

7. The average serum quinidine concentration required for conversion was 6.1 \( \mu \text{g.}/\text{ml.} \) This level was achieved with an average daily dose of 2.2 Gm./day.

8. Eighty per cent of the successful conversions were accomplished with a daily dose of 3 Gm. or less of quinidine. With increasing doses, the additional yield of conversions without toxicity requiring cessation of the drug was only 20 per cent.

9. Eighty-five per cent of the successful conversions occurred at serum concentrations of 8 \( \mu \text{g.}/\text{ml.} \) or less.

10. Myocardial toxicity was infrequent at serum concentrations less than 6 \( \mu \text{g.}/\text{ml.} \), but progressively increased as the serum concentration exceeded this figure. Toxicity was not always correlated with high serum levels, since 7 instances of myocardial toxicity were observed in 429 observations at levels of less than 6 \( \mu \text{g.}/\text{ml.} \). Caution must therefore be exercised, even when serum concentrations are low or falling.

11. Toxicity was related more closely to the serum quinidine concentration than to the daily dose of the drug. A wide individual variation in serum concentrations was found in patients receiving the same dose of quinidine.

12. Conversion of atrial fibrillation with quinidine requires awareness of the potential hazards of the drug, careful clinical and electrocardiographic supervision of the conversion attempt in the hospital, and cessation of quinidine if the QRS duration exceeds 50 per cent of the control value, if frequent ventricular premature beats occur, if marked hypotension results, or if severe gastrointestinal symptoms develop. Caution and reconsideration of the total situation should be the rule when 3 Gm./day of quinidine does not effect conversion or when the serum concentration reaches 8 \( \mu \text{g.}/\text{ml.} \).

13. The use of quinidine in established atrial fibrillation should be considered a calculated risk, and the physician must weigh the potential benefits against the possible hazards. Control of therapy with knowledge of the serum quinidine concentration should decrease the risk by indicating the statistical likelihood of toxicity at increasing concentrations of the drug.

14. Relapses to atrial fibrillation occurred in 85 per cent of patients who did not receive maintenance doses of quinidine, but in only 20 per cent of those given a maintenance dose of 1.6 Gm./day or in whom the maintenance serum concentration was more than 60 per cent of the peak conversion serum level.

16. The changing pattern of the atrial arrhythmia with increasing doses of quinidine and progressive slowing of the atrial rate supports the concept that atrial fibrillation, atrial flutter, and atrial tachycardia are different manifestations of an ectopic focus and that the electrocardiographic differences between the 3 arrhythmias is a function of the atrial rate (rate of discharge of the atrial ectopic focus).

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follow-up of the patients. Mr. James Lingoes was most helpful in statistical evaluation.

**SUMMARY IN INTERLINGUA**

1. Le conversion de chronic fibrillation o flutter atrial per medio de quinidina esseva essayate 214 vices in 177 patients. Le essayo succedeva in 74 pro cento del gruppo total, sed le procentage variava secundo etiologia, dura-
tion del fibrillation, presentia de disfallimento cardiac, e typo de lesion valvular in le patientes
corn rheumatic morbo cardiac.

2. Un duration del fibrillation in excesso de 6 menses reduceva le probabilitate de conversion
in le patientes non solmente rheumatic sed etiam non-rheumatic. Le incidentia de con-
version pote montar a usque a 95 pro cento in patientes non-rheumatic con fibrillation of breve
duration; illo pote descender a usque a 45 pro cento in patientes con rheumatic in-
competentia mitral e fibrillation de un duration of plus que un anno.

3. In le gruppo de patientes con rheumatic morbo cardiac, le pejor results occurreva in
casos de predominante incompetentia mitral, mismos se le effectos del duration del fibrilla-
tion e del presentia de disfallimento cardiac non esseva prendite in consideracion. In pa-
ientes con non-complicate stenosis mitral o con predominantia de morbo aorto-valvular,
le proportion del conversions esseva quasi tanto alte como in patientes del gruppo non-
rheumatic.

4. Le presentia de disfallimento cardiac reduceva le probabilitate de successo in le
effectuation del conversion ($p = 0,02$).

5. Le presentia de embolos systemic in le
passato immediate o distante non reduceva le procentage de successos in le effectuation de
conversion in fibrillation atrial.

6. Un definite e un probabil embolo occu-
rreva al tempore del conversion, ben que circa
15 pro cento del patientes habeva un historia
de embolos in le passato. Embolos occurreva in
7 patientes quando illes recadeva ab rhythmsinusal a fibrillation atrial.

7. Le concentration medie de quinidina
seral requirit pro effectuar le conversion
esseva 6,1 $\mu$g per ml. Iste nivello esseva ef-
fectuabile per un dose medie de 2,2 g per die.

8. Octanta pro cento del successos in con-
verter fibrillation atrial esseva obtenite con
doses diurne de 3 g de quinidina o minus. Aug-
mentos del dosage a nivellos non resultante in
toxicitate de grados que requireva le cessation
dele administration del droga produceva un
proportion additional de successos amontante
ta a solmente 20 pro cento.

9. Octanta-cinque pro cento del successos
in le conversion de fibrillation atrial occurreva
ta concentrationes seral de 8 $\mu$g per ml o minus.

10. Toxicitate myocardial esseva infrequent
a concentrationes seral de 6 $\mu$g per ml o minus,
sed illo deveniva progressivamente plus fre-
quente in tanto que le concentration seral ex-
cedeva le nivello mentionate. Toxicitate esseva
non semper associate con alte nivellos seral.
Septe casos de toxicitate myocardial esseva
observe in 429 tests a nivellos de minus que
6 $\mu$g per ml. Es necessari per consequente
prender precautiones mesmo si le concentra-
tiones seral es basse o decrescente.

11. Le toxicitate esseva relationate plus
intimemente con le concentration de quinidina
in le sero que con le doses diurne del droga.
Extense variationes individual del concentra-
tiones seral esseva constatate inter patientes
qui recipeva le mesme dosage de quinidina.

12. Le conversion de fibrillation atrial per
medio de quinidina require complete familiarita-
tate con hasardos potential del droga, un caute
surveillantia clinic e electrocardiographic del
tentativa conversional al hospital, e le cessa-
tion immediate del administration de quinidina
si le duration de QRS excede 50 pro cento del
valor de controlo, si prematur pulso ventricular
ocurre frequentemente, si marcate grados de
hypotension es manifeste, o si sever symptomas
gastro-intestinal occurre. Le plus caute recons-
deration del situation total es a recommandar
quando doses de 3 g de quinidina per die non
effectua le conversion desiderate o quando le
concentration seral attinge le valor de 8 $\mu$g per
ml.

13. Le uso de quinidina in casos de establite
fibrillation atrial deberea esser considerate
como un "risco calculate," e le medico debe
ponderar le beneficios potential in comparation
con le hasardos possibile. Le regulation del
therapia super le base de observationes del
concentration séral de quinidina reduce le risco in tanto que illo indica le probabilitate statistic de toxicitate con augmentate concentrationes del droga.

14. Recidivas de fibrillación atrial ocurrieva in 85 pro cento del patientes qui non recipeva doses de mantenentia de quinidina sed in solmente 20 pro cento del patientes qui recipeva doses de mantenentia de 1,6 g de quinidina per die o in qui le nivello de mantenentia del concentration séral de quinidina excedeva 60 pro cento del culmine que habeva effectuate le conversion.

15. Le alterate configuration del arrhythmia atrial effectuate per crescente doses de quinidina e le concomitante reduction del rapiditate atrial es factos que supporta le concepcion que fibrilllation atrial, flutter atrial, e tachycardia atrial es differente manifestationes de un foco ectopic e que le presentia de differentias inter le 3 arrhythmias es un function del rapiditate atrial (i.e. del rapiditate de discarga del ectopic foco atrial).

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Factors Influencing Conversion of Chronic Atrial Fibrillation with Special Reference to Serum Quinidine Concentration

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