Studies of Plasma Quinidine Content

III. The Value of Delayed Absorptive Coated Tablets in Oral Quinidine Therapy

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Quinidine sulfate, orally administered in tablets coated with a material delaying their absorption, produces concentration curves in the blood serum similar to those of uncoated tablets. However, there is a delay in the appearance and the attaining of maximum concentrations with the coated tablets, although higher levels may persist for 12 hours. Defects in coating may cause faulty failure of absorption. The advantages of using such a preparation of quinidine are: (1) avoidance of nausea in susceptible persons, (2) providing effective concentrations of the drug during the night and thereby preventing nocturnal attacks of arrhythmias, and (3) providing greater concentrations of the drug in the morning, when attempts at conversions of arrhythmias may require therapy over several days or more.

In some patients the efficacy of quinidine therapy for cardiac arrhythmias is frequently hampered by the accompaniment of nausea, vomiting and, more frequently, by diarrhea. This latter disturbance may occur with doses too small to cause appreciable elevation of the plasma quinidine levels, to 2.0 mg. per liter or above. In the majority of patients nausea and vomiting develop only after sufficient quantity of the drug has been given to produce moderate to high levels of plasma quinidine content, levels over 5 mg. per liter. It is assumed that the gastrointestinal tract is sensitive to the physically irritant effect of the drug in certain individuals, whereas in others the symptoms may be due to neurogenic or other systemic influences. In the first instance it is possible that coating the tablets with material which slowly disintegrates in the gastrointestinal tract may carry the drug beyond the stomach or upper intestines which may be relatively more sensitive to local irritant effects than the lower bowel. It is one of the purposes of this paper to present the effectiveness of such coating* in preventing or diminishing the local irritant effect of quinidine.

Two other uses of delayed absorption of quinidine are suggested, namely (1) the release of the drug at a particular time when its maximum effect is needed, such as in nocturnal paroxysmal arrhythmias, and (2) when prolonged quinidine therapy is required to convert an arrhythmia to a sinus rhythm and awakening the patient at night for medication is undesirable.

The pattern of quinidine absorption has been determined by observing the quinidine content of the plasma after administration of the drug orally in uncoated tablets, rectally in cocoa butter suppositories, and intramuscularly as a solution of quinidine lactate. The rate and degree of absorption of quinidine sulfate in "delayed absorptive" coated tablets has not been reported. Rectal administration of quinidine sulfate in cocoa butter suppositories was found previously to give relatively low plasma concentrations of the drug; however, when given to a patient through a colostomy opening in the descending colon, excellent absorption was demonstrated. The plasma quinidine concentration in this patient with a 0.4 Gm. dose of

* Enseal Quinidine Sulfate (Lilly), 0.2 Gm. tablets (patented and submitted to American Medical Association Council on Drugs and Therapy for approval) were the coated tablets used.

Similar coatings have been prepared by other manufacturers and depend upon the slow disintegration in a warm, moist medium, such as the contents of the gastrointestinal tract. Enteric-coated capsules or tablets (with salol) dissolve in an alkaline but not an acid medium.
quinidine sulfate in a cocoa butter suppository was 3.6 mg. per liter three hours, and 2.9 mg. per liter five hours after insertion. Thus, it may be assumed that if dissolution of the enteric-coated tablets is delayed until they have reached even this level of the intestine, adequate therapeutic results could be attained.

The plasma quinidine concentrations were determined, using the method of Brodie and Udenfriend, after administering 0.2 Gm. enteric-coated tablets to seven subjects in doses of 0.6 Gm. and 0.8 Gm. (table 1). In this series of subjects minute amounts of quinidine were present in the plasma in two individuals in one and one-half to two hours after administration; appreciable amounts were detected in all but one in two and one-half to three hours after administration. Thus, plasma quinidine concentrations were obtained with both 0.6 and 0.8 Gm. doses. The variation in the time elapsed before maximum plasma concentration was observed suggests individual differences in the rate and effectiveness of absorption of the drug, with, however, significant maximum quinidine levels of 2.3 to 3.3 mg. per liter in all subjects. These are comparable to the maximum levels obtained with uncoated quinidine sulfate tablets given orally or with intramuscular quinidine lactate, although appearances of peak levels are materially delayed. In all instances, the 12 hour concentration was at least 66 percent of the quinidine content of the plasma at its peak. As would be expected with delay in absorption, no quinidine was found in the plasma in the one and one-half to two hour specimens, except in two subjects who exhibited minute amounts—due to a technical error in analysis or to more rapid dissolution of the coating on some of the tablets.

Figure 1 illustrates the curves of quinidine plasma content after single doses of 0.6 Gm. and 0.8 Gm. of quinidine sulfate in coated tablets in seven subjects referred to in table 1.

The tablets were used in these seven subjects within one month of their receipt from the pharmaceutical firm but similar evidence of adequate absorption was obtained on tests on this lot of tablets six months and one year after storage in original bottle containers. This is in contrast to an earlier lot which showed decreasing evidence of absorption after storage for six months, at which time seven out of nine subjects failed to show quinidine in the plasma at any time up to 12 hours after administration. Undissolved tablets were found in the stools of two of these subjects. This indicates that imperfect dissolution through changes in the compression or coating may not become evident until after prolonged storage. Such inadequate absorption of enteric-coated tablets has been previously reported and assurance must be obtained from the pharmaceutical firms that compression and coating of lots of tablets will produce uniformly satisfactory results after storage.

As will be mentioned later, certain patients, on whom the drug in coated tablets was used
to prevent or correct an arrhythmia, failed to exhibit any therapeutic effect. Whereas quinidine blood levels were obtained on most of these patients and showed expected concentrations, others were not so studied and could represent faulty absorption.

In order to obtain higher levels of plasma quinidine concentration, multiple doses of from 0.4 Gm. to 0.8 Gm. were given to six individuals (table 2). It will be noted that in four of these, where determinations were made 12 to 14 hours after the last dose, the plasma quinidine content at such times was always over 50 per cent of the maximum concentration obtained. In previous studies of the effects of quinidine administered orally in uncoated tablets the quinidine content in the plasma after 12 hours in-

example of high quinidine content in the blood 12 hours after the last dose of the drug in coated tablets is given in case 8 (fig. 3), to be discussed later. Thus, in multiple, as in single doses, the delay of the peak concentration and the decreased loss by 12 hours is demonstrated and confirms this rationale for use of such coated tablets clinically.

The coated quinidine sulfate tablets were given to 19 patients; eight with paroxysmal auricular tachycardia; two with paroxysmal ventricular tachycardia, one of whom had persistent ventricular ectopic beats; one with paroxysmal auricular flutter, and two with paroxysmal auricular fibrillation; four with auricular fibrillation; and two with showers of ventricular ectopic beats and sinus rhythm. Of

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Dose</th>
<th>Plasma Quinidine Content in mg./L.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hours after first dose</td>
<td>Hours after last dose</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>21-3</td>
<td>4-14</td>
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<tr>
<td>8. E. F.</td>
<td>F</td>
<td>20</td>
<td>Normal</td>
<td>0.4 q 2° 7</td>
<td>2.0</td>
</tr>
<tr>
<td>10. F. J.</td>
<td>F</td>
<td>25</td>
<td>Normal</td>
<td>0.4 q 2° 7</td>
<td>—</td>
</tr>
<tr>
<td>11. R. O.</td>
<td>M</td>
<td>70</td>
<td>Art. Ht. Dis., Aur. Fib.</td>
<td>0.6 q 2° 4</td>
<td>0.9</td>
</tr>
<tr>
<td>12. L. S.</td>
<td>M</td>
<td>73</td>
<td>Normal</td>
<td>0.4 q 2° 8</td>
<td>0.6</td>
</tr>
<tr>
<td>13. G. S.</td>
<td>M</td>
<td>50</td>
<td>Rh. Ht. Dis., Aur. Fib.</td>
<td>0.8 q 2° 4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

variably was between 10 per cent and 30 per cent of the maximum concentration obtained.

The maximum concentrations, namely from 4.7 to 12.8 mg. per liter, attained from the total dosages during the day of 2.4 Gm. to 3.2 Gm. compared favorably with those observed after similar dosage with uncoated quinidine sulfate tablets.

Figure 2 illustrates the curve of plasma quinidine concentration in L. S. (case 12, table 2), a normal male, age 72 years, during and following the administration of 0.4 Gm. of quinidine sulfate in coated tablets every two hours for eight doses. Although the maximum plasma quinidine concentration of 10.6 mg. per liter was obtained 15 hours after the initial dose, the residual concentration 12 hours after the last dose was more than 70 per cent of the maximum concentration observed. A similar

the 10 cases of paroxysmal tachycardia, three were diagnosed as auricular in origin from their clinical response to carotid sinus pressure and the constancy of rate. The other diagnoses were confirmed by electrocardiograms.

In our experience paroxysmal tachycardia
frequently occurs late at night or in the early morning although not exclusively so in most patients. Two of the patients with paroxysmal auricular tachycardia had attacks between 4 a.m. and 6 a.m. on three to five nights weekly prior to therapy. In one of the patients, the quinidine therapy abolished the attacks after three months of such recurrence, and in the other, their frequency was reduced to once every one or two weeks after a six week period of frequent episodes.

Ten of 19 patients had experienced prompt nausea and/or diarrhea with small doses of the uncoated tablets, and an eleventh, case 13, severe vomiting and diarrhea after 12 doses of 0.8 Gm. in two days which had failed to convert auricular fibrillation to sinus rhythm. This patient was able to tolerate 18 doses of 0.8 Gm. of quinidine sulfate in coated tablets in two days with only minor nausea and diarrhea, but still retained the auricular fibrillation. Of the 10 other patients who had experienced prompt gastrointestinal sensitivity to uncoated quinidine, seven tolerated therapeutic doses of the drug when coated. In three of these seven, although nausea was prevented, moderate diarrhea still occurred, and in another three individuals with diarrhea but no nausea the coated drug was not significantly different in its effect than the uncoated tablets. No case of nausea followed the use of coated tablets in doses under 2.0 Gm. per day.

Figure 3 illustrates the occurrence of nausea in a normal female (case 8) at a much lower quinidine plasma concentration when uncoated tablets were given than when coated tablets were used.

There were 10 patients in whom delayed absorption was desired to control frequent nocturnal or early morning attacks of paroxysmal arrhythmia. Five of these patients also exhibited gastrointestinal tract irritability and are included in the summary of that group previously mentioned. Six of these 10 patients were definitely relieved of the recurrences of the arrhythmias, although all six were also given uncoated quinidine tablets during the day and in 0.4 Gm. doses in the evening simultaneously with 0.4 Gm. of the coated medication. Four had previously continued to exhibit late nocturnal or early morning arrhythmias when uncoated quinidine alone had been given in similar dosage during the day and at bedtime.

In four patients with persistent auricular fibrillation an attempt was made to shorten the course of quinidine therapy necessary to correct the arrhythmia by giving a dose of the coated drug at night to attain a relatively high plasma quinidine concentration on the next morning. This effect could be anticipated from the data presented in tables 1 and 2. The arrhythmia in one of these patients was converted to sinus rhythm. The three patients whose auricular fibrillation was not converted to sinus rhythm likewise exhibited relatively high morning plasma quinidine concentrations.

This delayed absorption effect obviated the need for disturbing the patient's sleep for nocturnal doses. Nervous tensions accompanying loss of sleep, as well as from other causes, have been noted to increase the refractiveness of certain patients to the conversion of auricular fibrillation to sinus rhythm.

**Conclusions and Summary**

Quinidine sulfate administered in freshly prepared, delayed-absorptive, coated tablets has been shown to produce maximum concentrations in blood plasma similar to those obtained with equal doses of uncoated quinidine.

There is a delay in the appearance of the drug in the plasma, when so administered, of
about two hours and in the maximum concentration of from two to nine hours as compared with the results observed previously with uncoated tablets or capsules.

Imperfect dissolution of the coated tablets was observed in a trial lot after six months storage but not in a recent lot presumably with more perfect coating.

The chief therapeutic values suggested by the use of the coated tablets are:

1. Avoidance of nausea in certain susceptible patients who cannot tolerate even small doses of the ordinary compressed tablets or the powdered drug in gelatin capsules.

2. Utilizing the late development of maximum concentration of the quinidine in the blood to prevent nocturnal or early morning paroxysmal arrhythmias by administering the coated tablets on retiring at night.

3. Shortening the number of days required to convert persistent arrhythmia to sinus rhythm by starting each morning with a higher blood content of quinidine as a result of bedtime doses of the drug in this type of preparation.

REFERENCES


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Circulation. 1952;5:534-538
doi: 10.1161/01.CIR.5.4.534

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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