The Therapeutic Range of Gitalin (Amorphous) Compared with Other Digitalis Preparations

By Robert C. Batterman, M.D., Arthur C. DeGraff, M.D., and O. Alan Rose, M.D.

The therapeutic ranges of amorphous gitalin, digitalis leaf, digoxin and Digoxin were compared in terms of rapid and slow methods for initial digitalization and maintenance of the digitalized patient. Gitalin (amorphous) possesses a therapeutic range greater than any available digitalis preparation or glycoside. In a group of 18 ambulatory patients, gitalin (amorphous) was found to possess an average of 41 per cent increase in therapeutic range when compared with digitalis leaf. Advantages of the use of gitalin (amorphous) as compared with other digitalis preparations are discussed.

During an investigation on the use of amorphous gitalin for the management of the patient with congestive heart failure, it became evident that this medication possessed advantages over other available digitalis preparations and glycosides. It is the purpose of this report to furnish further evidence that the therapeutic range of amorphous gitalin is greater than that of other digitalis preparations. On the basis of this, it will be demonstrated that amorphous gitalin possesses a greater safety factor when used for either initial digitalization or maintenance.

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The gitalin used in this investigation was supplied under the trade name of Gitaligin by White Laboratories, Inc.

Initial Digitalization—Rapid Method

The use of a digitalis preparation for the treatment of a patient with congestive heart failure is a twofold problem including initial digitalization and maintenance. For initial digitalization, assuming that an oral route is required, the patient is usually given an initial dose and subsequent increments of this dose at intervals of six hours until a therapeutic effect is achieved or toxicity supervenes. The amount of a digitalis preparation required for a satisfactory therapeutic effect cannot be predicted in advance. It must be attained for each individual patient by a trial and error procedure which resembles in many respects a chemical titration for determination of the endpoint. In terms of clinical effect this endpoint is a restoration of myocardial efficiency. As a rule, in the usual patient with congestive heart failure, particularly if this is the first bout of failure, the optimum dose of the digitalis preparation for a satisfactory therapeutic effect can be attained with ease and it is unnecessary to continue further administration of the digitalis preparation at six hour intervals until toxicity occurs. The latter is, of course, undesirable, and may be dangerous. However, with many patients in advanced heart disease, and with patients where the therapeutic effect is not easily discernible, it may be necessary to reach toxicity to assure full digitalization.

When one considers the majority of patients requiring initial digitalization, it is evident that
they possess a good cardiac reserve and that they can achieve digitalization with optimum restoration of myocardial efficiency. It is possible to demonstrate in such patients a therapeutic range for various digitalis preparations. This therapeutic range is obtained by determining the amount of a digitalis preparation required for a therapeutic effect and then cautiously continuing the administration of the digitalis preparation until minor signs or symptoms of toxicity occur. The percentage of the digitalis preparation required for a therapeutic effect in terms of the total dose required for toxicity represents the therapeutic ratio. The smaller the ratio the greater the range. Previous experience with Digoxin and digitoxin indicated that both preparations possess similar ratios (table 1) and that the usual patient required approximately 60 per cent of the toxic dose of the preparations to attain a therapeutic effect. Thus, the therapeutic range under the best circumstances is small. In patients who have marked diminution in cardiac reserve and a small or absent therapeutic range, the use of long-acting glycosides may be dangerous. Overshooting into the toxic level is not uncommon and the toxic manifestations may persist for several days. A review of our patients receiving either U.S.P. XII or XIII digitalis leaf for initial digitalization according to the methods described elsewhere revealed that the therapeutic ratio (table 1) is similar to that for Digoxin and digitoxin. In terms of therapeutic range, and indirectly, the safety factor for adequate digitalization with least likelihood of toxicity, digitoxin and Digoxin have no advantage over digitalis leaf. Our experiences with other digitalis preparations including lanatoside C, Urginea maritima, Urginea indica, and Digilan also indicate that these preparations have similar therapeutic ratios. Data on the initial digitalization with amorphous gitalin reveal (table 1) that the therapeutic ratio is significantly smaller than that for digitalis leaf, digitoxin and Digoxin and is indicative of a considerably greater therapeutic range. The usual patient would thus require, in terms of the toxic dose, a smaller dose of amorphous gitalin for a therapeutic effect.

With advanced heart disease, the dose of a digitalis preparation required for a therapeutic effect may approach or equal the dose which will result in toxicity. Because of the very small or absent therapeutic range, digitalization in such a case is usually very difficult. Amorphous gitalin under such circumstances offers an advantage since its greater therapeutic range allows digitalization of some of these patients. However, there are many patients with far advanced heart disease, or with a complication of their heart disease, who manifest toxicity before any therapeutic effect is discernible. Since there has been a complete reversal of the therapeutic range, amorphous gitalin will not compensate for this and it would, therefore, be impossible in this group of patients to achieve satisfactory digitalization regardless of digitalis preparation used. This phenomenon of reversal of therapeutic range cannot be accurately predicted in advance and can only be appreciated after digitalization is attempted. During the process of digitalization, therefore, wherein repeated doses are administered as cautiously as possible to attain a therapeutic effect, it would be expected that

<table>
<thead>
<tr>
<th>Digitalis Preparation</th>
<th>Number of Patients</th>
<th>Therapeutic Dose</th>
<th>Toxic Dose</th>
<th>Therapeutic Ratio (Therapeutic Dose / Toxic Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Gitalin (Amorphous)</td>
<td>24</td>
<td>3.0–10.5 mg.</td>
<td>5.59 mg.</td>
<td>5.25–25.5 mg.</td>
</tr>
<tr>
<td>Digitalis Leaf (U.S.P. XII–XIII)</td>
<td>36</td>
<td>0.9–2.7 Gm.</td>
<td>1.49 Gm.</td>
<td>1.2–3.6 Gm.</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>27</td>
<td>0.9–4.8 mg.</td>
<td>2.39 mg.</td>
<td>1.5–9.3 mg.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22</td>
<td>2.0–6.0 mg.</td>
<td>3.77 mg.</td>
<td>3.0–12.0 mg.</td>
</tr>
</tbody>
</table>
all of these patients will manifest some type of digitalis toxicity. This toxicity occurs, as a rule, inadvertently, since it results from a dose ordinarily considered to be a safe one and usually below the estimated toxic dose. Nevertheless, its occurrence, although unavoidable, is undesirable. For this reason it is an advantage to utilize a digitalis preparation which possesses a more rapid rate of dissipation than digitoxin or digitalis leaf. This is true of amorphous gitalin. The safety factor for amorphous gitalin used for rapid initial digitalization is therefore twofold. First, digitalization in the usual patient can be attained with a relatively smaller dose of gitalin in terms of the toxic dose than of any other digitalis preparation. Second, toxicity, if it inadvertently occurs with gitalin, will not persist as long as the slowly dissipated preparations.

<table>
<thead>
<tr>
<th>Table 2.—Comparison of Gitalin (Amorphous) and Digitalis Leaf (U.S.P. XII–XIII) Dosage</th>
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<tbody>
<tr>
<td>Gitalin (Amorphous)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Range</strong></td>
</tr>
<tr>
<td>Therapeutic Dose</td>
</tr>
<tr>
<td>Toxic Dose</td>
</tr>
</tbody>
</table>

**INITIAL DIGITALIZATION—SLOW DAILY DOSE METHOD**

Initial digitalization can also be attained slowly by administration of a daily dose which is at least two to three times the estimated daily maintenance dose of the patient. If the patient was previously under observation this dose can readily be chosen. However, if the patient is under observation for the first time, one must rely upon accumulated data indicative of predictability of attaining maintenance or toxicity with any daily dose level. Predictability data for digitoxin, Digoxin, lanatoside C, and for amorphous gitalin have been previously published. Data for digitalis leaf are similar to data for digitoxin. It is the usual practice for patients who are ambulatory and/or not in severe congestive heart failure to attain slow digitalization by this daily dose schedule. Under this regime the average total dosage to attain satisfactory digitalization and digitalis preparation was noted. The average total dose for a satisfactory therapeutic effect by both the slow and rapid methods of digitalization was the same, but it was impossible to duplicate the average total dose for toxicity. Several patients continued to take a daily dose, two to three times the predicted maintenance dose, for many days or weeks beyond the anticipated total dose for toxicity. This again reflected the greater therapeutic range for amorphous gitalin. Utilizing this fact, it was possible to digitize with comparative ease and safety a group of ambulatory patients with mild or moderate signs or symptoms of congestive heart failure.

**THERAPEUTIC RANGE—DAILY DOSES—AMBULATORY PATIENTS**

Studies on daily dosage required for either maintenance or toxicity also revealed a greater therapeutic range for amorphous gitalin as compared...
pared with digitoxin, Digoxin, and lanatoside C. The classic method of determining the percentage of patients who manifest toxicity upon doubling the minimal maintenance dose revealed that the therapeutic ratio for amorphous gitalin was 41 per cent as compared with 64 per cent, 65 per cent, and 63 per cent for Digoxin, digitoxin, and lanatoside C respectively.

**Comparison of Amorphous Gitalin with Digitalis Leaf**

Although it would appear that for initial digitalization and for maintenance amorphous gitalin possesses a greater therapeutic range than other digitalis preparations, the studies have been performed in different patients. It was, therefore, thought advisable to repeat the studies utilizing the same patient for comparison between amorphous gitalin and digitalis leaf (U.S.P. XII and XIII). Eighteen patients who could be maintained with digitalis leaf were chosen for this phase of the investigation. The minimal daily undivided dose required to achieve adequate maintenance and minimal signs and symptoms of toxicity was determined for both digitalis leaf and amorphous gitalin. Eleven patients presented a greater range with amorphous gitalin than with digitalis leaf. Six patients presented the same range for both preparations, whereas only one patient had a greater range for digitalis leaf. In terms of therapeutic ratio, 12 out of the 18 patients receiving digitalis leaf manifested toxicity upon doubling the minimal maintenance dose, thus giving a ratio of 67 per cent. On the other hand, this occurred in only six of the patients receiving amorphous gitalin, which therefore had a ratio of 33 per cent.

Table 2 presents the range and average dosage for therapeutic effect and toxicity for both amorphous gitalin and digitalis leaf. In terms of average dosage, 0.1 Gm. of digitalis leaf resulted in a therapeutic effect equivalent to 0.46 mg. of amorphous gitalin. The doses for toxicity revealed an average dose of 0.1 Gm. of digitalis leaf equivalent to 0.65 mg. of amorphous gitalin. If the ratio of dosage obtained for the therapeutic effect held for the toxic level then the predicted average amount of digitalis leaf required to produce toxicity should have been 0.257 Gm. Actually the amount was 0.183 Gm. The 41 per cent increase in the average equivalent dosage of amorphous gitalin for the toxic level as compared with the therapeutic dose reflects again the greater therapeutic range of this preparation.

**Utilization of Amorphous Gitalin for Patients Not Responding to Digitalis Leaf**

Our next consideration was to apply this favorable property of greater therapeutic range of amorphous gitalin for the treatment of patients no longer responding to daily doses of the commonly employed digitalis preparations. It has been our observation that with advanced heart disease, regardless of etiology, the patient may manifest toxicity with a daily dose of a digitalis preparation which previously was adequate for maintenance. Since this dose is no longer capable of producing satisfactory maintenance, it would appear that the therapeutic range for the digitalis preparation is no longer existent. In fact, the range may be reversed, since toxicity occurs with a dose which is insufficient for maintenance. This represents the extreme. There are many patients who present a very small therapeutic range which would require exacting care and skill to achieve satisfactory digitalization and maintenance without toxicity. It is under such circumstances that a digitalis preparation possessing a greater therapeutic range would be of advantage.

This possibility was studied in 20 ambulatory patients who were no longer responding to a digitalis preparation. Every patient required frequent injections of a mercurial diuretic and many, in addition, used daily maintenance doses of an orally administered mercurial diuretic and ammonium chloride. The smallest daily undivided dose of digitalis leaf which would result in minimal signs and symptoms of toxicity was determined in every patient. This was done by increasing at 8 to 10 week intervals the daily dosage of digitalis leaf by increments of 0.05 Gm. until toxicity occurred. The dosage was then decreased to the maximum tolerated dose. All of these patients continued to accumulate edema in spite of this daily maximum
tolerated dose. Since in none of these patients were we able to attain satisfactory maintenance, and toxicity occurred at the next dose level, it was concluded that the therapeutic range for digitalis leaf was either very small and not determinable by the dose schedule used in this investigation or that there was obliteration or reversal of the therapeutic range. Each of these patients was then observed on a daily undivided dose of amorphous gitalin.

Since it was demonstrated that approximately 0.5 mg. of amorphous gitalin was equivalent to 0.1 Gm. of digitalis leaf in terms of therapeutic effect, this dosage schedule was used. The assumption was made that if the therapeutic range was the same for both preparations then the same dosage equivalents should hold for the toxic level. However, if the therapeutic range was greater for amorphous gitalin then the patient should be capable of tolerating an equivalent dosage of amorphous gitalin without toxicity. Thus, 0.5 mg. of amorphous gitalin was substituted for each 0.1 Gm. of digitalis leaf required to produce toxicity. Eleven of the 20 patients manifested toxicity with this dosage schedule. Toxicity occurred within the first four weeks of therapy in eight of these patients, but in three it required from 8 to 16 weeks of continuous daily administration of amorphous gitalin before toxicity occurred. Of greater significance was the fact that 9 of the 20 patients were able to tolerate the equivalent high dose of amorphous gitalin for eight weeks or longer without toxicity. Three of these patients required the next dose level of amorphous gitalin before toxicity occurred, while in one instance a further increase in dosage was still insufficient for toxicity. Improvement in the patient’s ambulatory status with a decrease in the severity of the congestive heart failure was noted in 6 of the 20 patients. In one patient improvement was progressive, but at the end of the sixteenth week of therapy toxicity occurred. In another patient, an increase in dosage beyond the estimated toxic dose was required before improvement occurred. Two patients presented a complete control of the decompensation so that it was no longer necessary to administer mercurial diuretics and acidifying salts.

The improvement of six patients and ability of 9 of the 20 patients with advanced heart disease to tolerate dosages of amorphous gitalin which ordinarily should have been toxic are again indications of the greater therapeutic range of amorphous gitalin.

**Discussion**

The introduction and clinical use of the purified cardiac glycosides have represented an important advance in the treatment of congestive heart failure. The expectancy that the great disadvantage of crude digitalis leaf, that is, the variation from lot to lot, would be obviated by the use of purified glycosides has been fulfilled. It was also hoped that individual glycosides would possess properties unobtainable with the crude galenic digitalis preparations. It was thus possible to utilize the property of a short latent period to attain rapid digitalization with the intravenous administration of ouabain (g. strophanthus), Digoxin and lanatoside C. The oral administration of these preparations, however, did not reflect this desirable property. Similarly, the property of rapid dissipation was of importance since toxic manifestations occurring inadvertently would subside promptly upon cessation of glycoside therapy. This was noted to be true for Digoxin and lanatoside C, but not for digitoxin. These properties of purified glycosides are of importance and allow the physician greater flexibility in the control of his patients with congestive heart failure. However, it has been increasingly evident that even though digitoxin, Digoxin, and lanatoside C, the three purified glycosides in popular use at present, have advantages over crude digitalis leaf, these advantages are not of sufficient magnitude to warrant discontinuation of the use of digitalis leaf. The reasons for this are several. First, the therapeutic range for these three glycosides is similar to that of digitalis leaf. The safety factor for initial digitalization as well as for maintenance is, therefore, the same for digitoxin, Digoxin, and lanatoside C, and digitalis leaf. This should not be confused with the dissipation of toxic manifestation which, because of rapidity for certain glycosides, has been misconstrued to represent greater safety during digitalization. This is true in the sense that
toxicity, no matter how severe, is usually short-lived. However, the possibility of developing severe toxicity is the same for all preparations. Of greater importance is the amount of a digitalis preparation required to restore maximum cardiac efficiency with the least likelihood of producing toxicity. The usual patient requires approximately two-thirds of the toxic dose for digitalis leaf, digitoxin, Digoxin, and lanatoside C to attain a good therapeutic effect. Patients with advanced heart disease and with certain complications of their heart disease may have a narrow therapeutic range. In such a patient the therapeutic dose approaches the toxic dose so that digitalization may be extremely difficult. Overshooting and development of toxic manifestations are not uncommon. The use of digitoxin, Digoxin, and lanatoside C has not corrected this shortcoming of digitalis leaf. If digitalization is difficult with digitalis leaf because of the patient's poor cardiac reserve, the same results will ensue if the aforementioned glycosides are used.

The second disappointment in the use of glycosides is their inability to induce a greater cardiac efficiency than could be achieved with digitalis leaf. As a rule, if the patient no longer responds to digitalis leaf, the substitution of digitoxin, Digoxin, or lanatoside C will not result in a better control of compensation. In our experience, patients with advanced heart disease do not respond to digitalization because they manifest toxicity before the maximum therapeutic effect is evident. In other words, the therapeutic range has been abolished. All digitalis preparations which possess the same therapeutic range will be equally as ineffective for the treatment of the advanced cardiac patient.

Third, the safety of purified glycosides in regard to incidence, type, and severity of toxicity has been misinterpreted. With the exception of local gastrointestinal irritation, and possibly the occurrence of yellow vision, the problems of toxicity associated with digitalis leaf are similar to those of the purified glycosides. Thus, if the patient manifests nausea, vomiting and ventricular premature systoles with coupling following administration of digitalis leaf, the substitution of digitoxin, Digoxin, and lanatoside C in equivalent doses will result in the same type of toxicity. It has been claimed\textsuperscript{7} that digitoxin may result in a greater incidence of arrhythmias. There is no doubt that a greater number of arrhythmias have occurred since the use of digitoxin. However, in our opinion it is related to the huge dosage of digitoxin commonly employed rather than the administration of this particular glycoside, per se. In our previous studies\textsuperscript{6} with administration of equivalent doses, digitoxin had the same incidence of toxic arrhythmias as Digoxin and lanatoside C. All digitalis preparations in toxic doses may produce very severe and even fatal toxic manifestations. The rapidly dissipating glycosides in this regard have an advantage since toxicity as a rule subsided promptly upon cessation of therapy.

Fourth, it became apparent that "completeness" of absorption of any particular glycoside is not the significant factor for satisfactory clinical usage. The great emphasis placed on the ability of the digitalis preparation to be "completely" absorbed implied that such a glycoside will be more effective than one only partially absorbed. However, digitoxin, the glycoside considered to be one that is "completely" absorbed, will not result in any better or more efficient digitalization than crude digitalis leaf. Of greater importance than the factor of "complete" absorption is the factor of uniformity or constancy of absorption. It is essential that the same amount of the digitalis preparation be absorbed with each dose so that predictability in dosage is a possibility. This is a major problem for the maintenance of the digitalized state since fluctuation in absorption may result in poor maintenance or toxicity. Lanatoside C when administered orally is not very satisfactory because, on the basis of erratic absorption, it is difficult to predict the daily dose in any particular patient. On the other hand, it is relatively easy to do so for digitalis leaf, Digoxin, and digitoxin.

Our studies with amorphous gitalin revealed that many of these criticisms that have arisen with the use of glycosides have been obviated or at least have diminished in importance. On the basis of its greater therapeutic range, it is the safest digitalis preparation available for the treatment of the usual patient with congestive
heart failure. Instead of requiring two-thirds of the toxic dose before attaining a therapeutic effect, the usual patient will respond when approximately one-third of the total toxic dose is administered. This is true for both initial digitalization and maintenance of the digitalized state. Patients not responding to other digitalis preparations because of attainment of toxicity before therapeutic effect may respond to amorphous gitalin. The greater therapeutic range of this preparation permits an easier titration of the patient's cardiac reserve so that a level of dosage may be attained resulting in cardiac efficiency without the occurrence of toxicity. Such patients in the past have been considered refractory to digitalization.

Since the preparation is dissipated at a rate between that noted for digitoxin and Digoxin, amorphous gitalin offers an additional advantage over both these preparations. In some patients, the rapidity of dissipation of Digoxin may result in an inadequate maintenance. On the other hand, the slow dissipation of digitoxin may result in prolonged toxicity if such occurs. Maintenance with amorphous gitalin is very satisfactory. If toxicity occurs, its manifestations will subside more quickly than those noted with digitoxin. This does not exclude the possibility of severe or even fatal toxic manifestations which may occur with all cardiac glycosides. Fortunately, such occurrences are uncommon. It is, however, a definite advantage to have a preparation whose rate of dissipation would make prolonged toxicity unlikely.

Finally, amorphous gitalin possesses uniformity in potency and absorption. Variation from lot to lot was not observed in the clinical use of four different batches of amorphous gitalin. Uniformity in absorption assures satisfactory digitalization and maintenance with predictable doses.

**Summary and Conclusions**

1. Gitalin (amorphous) possesses a therapeutic range greater than any available digitalis preparation or glycoside.
2. Initial digitalization by either rapid or slow methods and maintenance of the digitalized state can be attained with gitalin (amorphous) with a greater degree of safety than heretofore.
3. The usual patient requires, in terms of the toxic dose, a much smaller dose (approximately one-third) of amorphous gitalin for a therapeutic effect.
4. When compared with digitalis leaf by determining the minimal therapeutic and toxic doses in the same patient, gitalin (amorphous) was found to possess an average of 41 per cent increase in therapeutic range.
5. Patients refractory to digitalis because of inability to attain improvement in cardiac efficiency without the occurrence of toxicity, may do so with amorphous gitalin on the basis of its greater therapeutic range.
6. On the basis of therapeutic range, dissipation, uniformity from lot to lot, constancy in absorption, gitalin (amorphous) is the digitalis preparation of choice for the treatment of the usual patient with congestive heart failure.

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6. Unpublished data.
The Therapeutic Range of Gitalin (Amorphous) Compared with Other Digitalis Preparations

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