Comparison of Serum Digoxin Level Measurement with Acetyl Strophanthidin Tolerance Testing

By Michael D. Klein, M.D., Bernard Lown, M.D., Isaac Barr, M.D., Frans Hagemeijer, M.D., Henry Garrison, M.D., and Paul Axelrod, M.D.

SUMMARY

Serum digoxin levels (SDL) were compared with tolerance for the rapidly acting cardiac glycone, acetyl strophanthidin (AS). AS titration tests were performed on 133 patients with diverse cardiac disorders. All were receiving maintenance digoxin. Both exquisite AS sensitivity and tolerance for a 1.0 mg AS were associated with a wide range of SDL values. Concordance and discordance between the two methods in assessing degree of digitalization were evaluated by considering SDL of 1.4 ng/ml to be the mean value for patients without glycoside-induced cardiac arrhythmia. An SDL of 0.25 mg as dose and an SDL of 1.4 ng/ml with sensitivity to 1.0 mg AS or less constituted concordant responses. An SDL of 1.0 mg with intolerance for 1.0 mg AS and an SDL of >1.4 ng/ml with tolerance for 1.0 mg AS comprised discordant responses. In 60 of 144 (42%) AS titrations discordant results were observed. Severe pulmonary, coronary, and aortic valvular heart disease, as well as old age, contributed to unusual AS sensitivity. Titration with AS clarified pharmacologic quantification of SDL by providing insight into optimum therapeutic glycoside dose.

Additional Indexing Words:
Arrhythmia
Glycosides

Despite increasing understanding of the pharmacokinetics of the digitalis glycosides,16 guesswork and artistry continue to characterize the clinical usage of these drugs. The fact that 0.25 mg of digoxin constitutes the usual daily maintenance dose for a majority of patients with widely varying needs reflects the absence of a clear therapeutic objective. The ubiquity of digitalis intoxication7-16 attests to the faulty guidelines for defining drug sufficiency. Except for atrial flutter and atrial fibrillation where ventricular slowing provides some measure of digitalis adequacy, the only certain end point is the appearance of digitalis intoxication.17 Ectopic arrhythmias can derive from too little, as well as too much digitalis.18 These rhythm disturbances can connote an excess of glycoside activity in one patient, a deficiency in another.

From the Medical Clinics of the Peter Bent Brigham Hospital and the Cardiovascular Research Laboratories of the Department of Nutrition, Harvard School of Public Health, and the Department of Cardiology, Boston University Hospital, Boston, Massachusetts.

Supported in part by Grants HL-5242, HL-07776, HL-05719 and HE-07299 from the National Heart and Lung Institute, National Institutes of Health.

Address for reprints: Bernard Lown, M.D., Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

Received August 17, 1973; revision accepted for publication February 25, 1974.

Circulation, Volume XLIX, June 1974 1053
Factors can acutely alter this relationship. Ample clinical and experimental evidence attests to the fact that myocardial sensitivity can strikingly change at any one drug level. When arrhythmias arise in the digitalized patient with heart failure, the meaning of the serum digoxin concentration may be unclear, since blood levels do not in themselves define myocardial susceptibility to glycoside action. Furthermore, blood levels may fail to register changing myocardial drug sensitivity accompanying alteration in the clinical state. Definition of what constitutes a safe and what constitutes a toxic digoxin dose may, therefore, not be readily asanswerable from blood digoxin measurements alone.

In order to determine the degree of digitalization and to assess myocardial sensitivity to the glycosides, Lown and Levine in 1953 proposed a biologic titration employing the ultra rapid acting digitalis agent, acetyl strophanthidin. The present report describes a large clinical experience with acetyl strophanthidin in patients receiving maintenance digoxin therapy. Myocardial responsiveness to acetyl strophanthidin was correlated with serum digoxin concentration measurements. The relevance of digoxin blood levels was evaluated by comparing them with an alternative means for assessing the degree of digitalization.

Materials and Methods

One hundred and forty-four studies were carried out on 133 patients hospitalized with various cardiac disorders. There were 77 males (mean age 62) and 56 females (mean age 64). Many of the patients were critically ill. All were receiving digoxin maintenance doses varying from 0.125 to 0.75 mg daily. In each patient, questions arose as to proper digitals therapy. Major problems encountered were: a) intractable heart failure, despite conventional doses of cardiac glycoside and diuretic drugs; b) rhythm disturbances of the heart in which the role of digitals as a provocative agent was unclear; c) clinical events which suddenly changed myocardial sensitivity to digitals, and, by implication, altered daily maintenance requirements for glycoside drugs.

Serum Digoxin Level Measurement

Serum digoxin level (SDL) was determined by the radioimmunoassay technique, using an internal standard for quench correction. All samples were measured in duplicate. Blood was drawn just prior to AS testing and at least five hours after the last digoxin dose. At this time, blood-tissue equilibrium for digoxin had been achieved and SDL was presumed to be a proportionate fraction of myocardial drug levels. Unlabeled digoxin was estimated by its ability to displace tritium-labeled digoxin from digoxin-specific antibody sites. Standard curves were derived from control sera containing gravimetrically determined amounts of crystalline digoxin dissolved in 95% ethanol and serially diluted over the described concentration range. Accuracy of the method was ±0.2 ng/ml. Standard deviation for replicate samples over an SDL range of 0.5-10.0 ng/ml was 3%

Acetyl Strophanthidin Tolerance Tests

This procedure was employed as a rapid method for assessing the degree of digitalization. Prior to administration of acetyl strophanthidin, a twelve-lead electrocardiogram was taken. Cardiac rate, rhythm and PR, QRS and QT intervals were noted. A fifteen-minute rhythm strip was transcribed on a Brush Mark 220 two-channel recorder set at a speed of 1 mm/sec or on a special purpose analog computer designed to detect ventricular ectopic beats and print them out in a conventional ECG format as well as on a trend record which served to identify, as well as to quantify, ventricular premature beats. BUN and electrolytes were routinely surveyed. If hypokalemia (K⁺ < 3.5 mEq/L) were present, the acetyl strophanthidin test was deferred until this electrolyte imbalance was corrected. Patient medication during the preceding 24 hours was also reviewed. Antiarrhythmic drugs being given at the time of the test were stopped so as not to conceal an early phase of digitals toxicity. Short acting agents, such as lidocaine, were stopped at least 30 minutes prior to AS infusion. Longer acting drugs, such as procaaine amide (dominant serum half-time 3 hours) were stopped four to six hours earlier with the anticipation that their antiarrhythmic activity at the time of AS testing would be minimal.

Strophanthidin-3-acetate, in sterile ampoules containing 0.5 mg, was diluted with 0.9% saline to a concentration of 0.05 mg/ml. Under supervision of a cardiologist, 4 ml (0.2 mg) of the drug was given intravenously every five to six minutes until 1.0 mg had been infused or until some mild toxic end point resulted. Electrophysiologic action of acetyl strophanthidin upon the heart is extremely rapid with earliest effects apparent within five minutes. Therefore, the interval between sequential doses of the drug accommodated latency in onset of activity. Routine acetyl strophanthidin dosage schedule was reduced by the supervising physician if any change in heart rate or rhythm occurred. In such a case, 0.1 mg doses were administered. Before each successive acetyl strophanthidin increment, the following were checked: a) atrial and ventricular rate, b) PR interval, c) frequency of atrial or ventricular premature beats, d) change in P wave contour, e) blood pressure. Mild Increases in blood pressure were usually observed, consistent with the known vasoconstrictor properties of digitals drugs. Rarely did the blood pressure increment exceed 30/15 mm Hg. In no case did the rise in blood pressure precipitate an attack of angina pectoris.

Response to acetyl strophanthidin (AS) was graded according to the presence or absence of toxic side effects during or within 30 minutes of injection of drug. Group I: patients tolerating a full 1.0 mg of AS without side effects. Group II: patients who developed gastrointestinal side effects but no arrhythmia with 1.0 mg or less of AS. Group III: patients manifesting an arrhythmia with 0.7-1.0 mg AS. Group IV: patients exhibiting an arrhythmia with 0.6 mg AS or less.

The authors wish to thank Dr. Thomas W. Smith for his assistance in the radioimmunoassay determinations.

---

†Generously supplied by Dr. G. C. Chiu, Eli Lilly Corp., Indianapolis, Indiana.

SERUM DIGOXIN LEVELS

These categories were utilized to characterize degrees of digitalis sensitivity ranging from none to extreme (table 1).

Comparison between Serum Digoxin Levels and Acetyl Strophanthidin Tolerance

Serum digoxin levels were compared with myocardial response to AS. To make such a comparison, a blood digoxin level was selected below which digitalis intoxication would be considered unlikely. Several reports have indicated that the mean SDL values for patients without glycoside-induced cardiac arrhythmia is 1.3-1.4 ng/ml.18-20, 21 Therefore, if a patient's SDL were <1.5 ng/ml, it was assumed he would show no sensitivity to AS. If his SDL exceeded 1.4 ng/ml, he should exhibit sensitivity to AS. These categories constituted a discordant response between the two methods. AS tolerance of 1.0 mg with SDL of >1.4 ng/ml and AS tolerance of <1.0 mg with SDL of 1.4 ng/ml or less comprised a discordant response between the two methods.

Results

In 59 of the 144 AS tests, full tolerance to this drug was manifest (group I response). The mean SDL was 1.0 ± 0.08 ng/ml (SEM). By contrast, the 53 tests in patients who developed arrhythmias with 1.0 mg of AS or less, (group III or IV response) had a SDL of 1.77 ± 0.20 ng/ml (SEM) (P < 0.01) (fig. 1). The higher the SDL, the greater the likelihood that AS would evoke arrhythmias. With a serum concentration range of 0.8 to 1.4 ng/ml, 26% of patients reacted with toxic arrhythmias to AS; this increased to 36% at serum digoxin levels between 1.5 to 2.1 mg/ml and 60% between 2.2 to 2.8 ng/ml. At serum digoxin concentrations exceeding 2.8 mg/ml, 84% of cases developed toxic arrhythmias with AS challenge (fig. 2). No significant difference in mean daily digoxin dose was evident among the four categories of response to AS (table 2). Thus in group I the daily dose was 0.29 ± 0.02 mg (SEM), while in group IV it was 0.28 ± 0.03 mg. Similarly, there was no difference among the groups in serum potassium concentration. A higher percentage (20 of 53, 38%) of patients responding with arrhythmia to AS (groups III and IV) had a BUN >30 mg% than those (5 of 32, 15%) with gastrointestinal side effects (group II) or those (6 of 59, 10%) fully tolerant of AS (group I). More striking, however, was the effect of age upon AS tolerance. Cases fully tolerant of 1.0 mg AS (group I) were significantly younger (58.3 ± 1.3 years SEM) than subjects developing gastrointestinal side effects (group II) (63.5 ± 1.8 years) (P < 0.05) or arrhythmic side effects with 0.7-1.0 mg AS (group III) (63.5 ± 1.9 years) (P < 0.05). Group IV cases developing

Table 1

Classification of Patient Response to Acetyl Strophanthidin

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tolerance of 1.0 mg AS without gastrointestinal or electrocardiographic side effects.</td>
</tr>
<tr>
<td>II</td>
<td>Gastrointestinal side effects occurring with 1.0 mg AS or less.</td>
</tr>
<tr>
<td>III</td>
<td>Development or increase in atrial or ventricular arrhythmias or, 2° or 3° atrioventricular block with 0.7-1.0 mg AS.</td>
</tr>
<tr>
<td>IV</td>
<td>Development or increase in atrial or ventricular arrhythmias or, 2° or 3° atrioventricular block with 0.6 mg AS or less.</td>
</tr>
</tbody>
</table>

Circulation, Volume XLIX, June 1974
clinical features of patients grouped into four categories depending upon response to AS administration (mean ± SEM)

<table>
<thead>
<tr>
<th>Group (No of pts)</th>
<th>Age (yr)</th>
<th>BUN (mg/100 ml)</th>
<th>Kf (mEq/L)</th>
<th>Digoxin dose (mg/day)</th>
<th>Serum digoxin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (59)</td>
<td>58.3 ± 1.3</td>
<td>23 ± 2</td>
<td>4.52 ± 0.06</td>
<td>0.29 ± 0.02</td>
<td>1.00 ± 0.08</td>
</tr>
<tr>
<td>II (32)</td>
<td>63.5 ± 1.8†</td>
<td>23 ± 3</td>
<td>4.38 ± 0.10</td>
<td>0.30 ± 0.02</td>
<td>1.30 ± 0.14 NS</td>
</tr>
<tr>
<td>III (26)</td>
<td>63.3 ± 1.9†</td>
<td>27 ± 3</td>
<td>4.51 ± 0.12</td>
<td>0.28 ± 0.03</td>
<td>1.52 ± 0.24†</td>
</tr>
<tr>
<td>IV (27)</td>
<td>69.9 ± 2.1*</td>
<td>28 ± 2</td>
<td>4.28 ± 0.06</td>
<td>0.28 ± 0.03</td>
<td>1.82 ± 0.29†</td>
</tr>
</tbody>
</table>

Compared with group I: * = P < 0.001; † = P < 0.01; ‡ = P < 0.05, NS = Not significant.

Arrhythmias with 0.6 mg AS or less were notably older (69.9 ± 2.1 years) (P < 0.001) than group I subjects.

Both exquisite AS sensitivity and full AS tolerance were associated with a wide spectrum of SDL values (fig. 2). Thus, of 43 patients with digoxin concentrations of 0.7 ng/ml or less, 22% developed a group III or IV response. Conversely, among the 13 patients with SDL in the range of 2.2 to 2.8 ng/ml, one-third tolerated 1.0 mg AS without side effects. These results indicate that the same SDL level could be associated with different responses to AS, and by inference, different myocardial responsiveness to digoxin. Attempts to determine optimum digoxin dose from the SDL value alone proved to be misleading as the following two cases illustrate.

PBBH #1-68-64. A 73-year-old female had suffered several myocardial infarctions which left her with a ventricular aneurysm, severe heart failure and papillary muscle dysfunction. Therapy included digoxin 0.25 mg/day and daily furosemide. Serum K+ was 4.4 mEq/L. Severe orthopnea and sinus tachycardia were present. Injection of only 0.2 mg AS produced paroxysmal atrial tachycardia with block indicating that she was hovering close to digitalis toxicity (fig. 3). SDL at this time was 1.1 ng/ml.

PBBH #10-05-30. A 40-year-old male had sustained three acute myocardial infarctions in 15 months. Severe heart failure, associated with ventricular aneurysm had developed. Maintenance digoxin of 0.5 mg/day resulted in SDL of 0.9 ng/ml. A 1.0 mg dose of AS was administered without adverse reaction. Because of lingering heart failure and tolerance for AS, digoxin maintenance dose was increased to 0.75 mg/ml. Amelioration of heart failure was observed as SDL rose to 2.6 ng/ml. No manifestations of digoxin intoxication developed, though proximity to toxicity was proved during subsequent AS testing where bigeminy developed with 0.6 mg AS.

If one were to select an average serum digoxin concentration which would separate a majority of digitalis toxic from a majority of nontoxic patients, such a concentration might be 1.4 ng/ml. On the basis of such an arbitrary demarcation, the response to AS testing was classified into two categories, one in which there was agreement between the two methods — the concordant group — and the other in which a disparity in result was observed — the discordant group. There were two subgroups in each. In the concordant group, subgroup (a) consisted of patients with SDL of less than 1.4 ng/ml who tolerated a full milligram of AS; while subgroup (b) included those with digoxin concentrations greater than 1.4 ng/ml who did not tolerate 1.0 mg of AS. The discordant group also consisted of two subgroups: (a) included patients having SDL less than 1.5 ng/ml who responded adversely to AS, while subgroup (b) consisted of those with a SDL greater than 1.4 ng/ml who tolerated 1.0 mg AS.

In 84 of 144 AS tests, or in 58%, the result was concordant, while in 60 tests discordance was observed (42%) (table 3). In 40 AS tolerance tests, though the SDL was less than 1.5 ng/ml, a toxic reaction followed...
Table 3
Comparison between Groups with Serum Digoxin Levels < 1.5 or > 1.4 ng/ml and Tolerance (+) or Intolerance (-) for 1.0 mg of Acetyl Strophanthinid

<table>
<thead>
<tr>
<th></th>
<th>Concordant group</th>
<th>Discordant group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Serum digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>level (ng/ml)</td>
<td>&lt;1.5</td>
<td>&gt;1.4</td>
</tr>
<tr>
<td>AS tolerance</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Number of tests</td>
<td>59</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>60</td>
</tr>
</tbody>
</table>

AS administration. In another 20 instances, SDL exceeded 1.4 ng/ml but no digitalis sensitivity was demonstrable upon challenge with 1.0 mg AS. These two types of discordance are illustrated in the following two case reports:

Case 1: PBBH *14-87-86. A 54-year-old male had rheumatic heart disease with aortic stenosis, mitral insufficiency, tricuspid insufficiency and biventricular failure. Cardiac decompensation progressed despite digoxin and diuretics. Because of multiple atrial arrhythmias, digoxin was temporarily withheld and fluid restricted. Two days later, SDL was 0.6 ng/ml, BUN 24 mg%, K+ 4.1 mEq/L. Sinus tachycardia at 109 beats/min and APBs and VPBs were present. Digitalis tolerance was tested with acetyl strophanthinid. After 0.4 mg AS, atrial rate accelerated to 113 beats/min and VPBs became more frequent (fig. 4). Despite very low SDL, exquisite digitalis sensitivity was demonstrable with AS. Sinus tachycardia, though associated with severe failure, presaged serious digitalis intoxication.

![Figure 4](image)

A 54-year-old male with rheumatic heart disease. A low SDL of 0.6 ng/ml, biventricular failure, and uncertainty as to cause of a tachycardia with a T⁺ atrioventricular block prompted an acetyl strophanthinid test. After only 0.4 mg of AS, atrial rate accelerated from 109 to 113 beats/min and ventricular premature beats increased. Results indicated patient was digitalis toxic.

Case 2: BUH *49-23-18. A 49-year-old male was hospitalized for control of episodic tachycardias (fig. 5). Various antiarrhythmic agents, including quinidine, procaine amide, diphenylhydantoin, propranolol resulted either in toxic side effects or inadequate control of symptoms. Digoxin therapy was begun. Guided by sequential acetyl strophanthinid tests indicating the safety of increasing glycoside dose, digoxin therapy was steadily increased to 0.75 mg per day. At this time, SDL was 2.5 ng/ml, BUN 12 mg%, K⁺ 4.2 mEq/L. A 1.0 mg dose of AS was administered without side effects and the digoxin dose increased to 1.0 mg per day. Two weeks later, the SDL was 3.4 ng/ml. Because of excessive fatigue, digoxin dose was reduced to 0.75 mg/day. SDL ranged between 2.4-2.8 ng/ml thereafter, and the patient’s symptoms of palpitations were suppressed.

Analysis of the clinical features in relation to age, sex, blood urea nitrogen concentration and serum potassium levels showed no significant differences among the concordant and discordant subgroups (table 4). Pulmonary congestion was present in 33% of the concordant and in 28% of the discordant groups. Patients who were evaluated because of primary arrhythmia, in the absence of left ventricular dysfunction, gave primarily a concordant response and displayed high AS tolerance. Thus, among 15 such patients, 11 were concordant. The type of heart disease did not appear to be a decisive factor, except for the group with pulmonary heart disease, among whom 6 out of 8 had a discordant response. The following patient with pulmonary heart disease is illustrative of the group.

PBBH *13-99-29. A 74-year-old male suffered from emphysema and chronic bronchitis. He had also sustained one previous myocardial infarction. He was hospitalized with acute bronchitis and episodes of supraventricular tachycardia, rate 140-220 beats/min. Cardioversion restored sinus rhythm only transiently. Pulmonary congestion developed. Daily digoxin dose had been 0.25 mg. SDL was 1.0 ng/ml, BUN was 19...
and K⁺ 4.3 mEq/L. After 0.4 mg AS ventricular irritability appeared. Digoxin was withheld for five days as heart failure and infection were treated with diuretics and antibiotics. A repeat AS test was under-

taken. Heart rate was now 120-140 beats/min. SDL at this time was 0.5 ng/ml, BUN 19, Na 129, K⁺ 4.3; on room air arterial pO₂ was 65 mm Hg, pCO₂ 39 mm Hg, pH 7.50. After 0.6 mg AS, a short burst of ventricular tachycardia developed (fig. 6). Digoxin was withheld for 4 more days, by which time heart rate was 86 and SDL was 0.3 ng/ml. Digoxin maintenance of 0.25 mg/day was now resumed with safety. Deterioration in pulmonary function with attendant hypoxemia had sensitized the myocardium to digoxin. More than one week was required for this susceptibility to digoxin action to subside.

In three cases, tolerance for 1.0 mg AS was demonstrable despite SDL of >2.0 ng/ml. By contrast, in seven cases, arrhythmias developed with 0.4-0.8 mg AS while SDL levels were 0.5-1.5 ng/ml. Two of three patients believed to have ruptured mitral chordae tendineae developed arrhythmias with 0.4-0.6 mg AS while having SDL of 1.0-1.4 ng/ml (fig. 7).

**Table 4**

<table>
<thead>
<tr>
<th>Concordance</th>
<th>Age (yr)</th>
<th>M</th>
<th>Sex</th>
<th>BUN (mg/100 ml)</th>
<th>K⁺ (mEq/L)</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. (59)</td>
<td>59.8 ± 10.0*</td>
<td>36</td>
<td>23</td>
<td>21.4 ± 9.6</td>
<td>4.5 ± 0.5</td>
<td>44</td>
</tr>
<tr>
<td>b. (25)</td>
<td>66.7 ± 10.6</td>
<td>16</td>
<td>9</td>
<td>20.0 ± 19.5</td>
<td>4.3 ± 0.3</td>
<td>12</td>
</tr>
<tr>
<td>Discordance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. (40)</td>
<td>64.6 ± 11.5</td>
<td>22</td>
<td>18</td>
<td>23.3 ± 7.6</td>
<td>4.3 ± 0.3</td>
<td>19</td>
</tr>
<tr>
<td>b. (20)</td>
<td>62.6 ± 11.4</td>
<td>15</td>
<td>5</td>
<td>25.6 ± 14.1</td>
<td>4.5 ± 0.5</td>
<td>10</td>
</tr>
</tbody>
</table>

*Figures in parentheses represent number of tests in each subgroup.*

*mean ± SD.

**Figure 6**

A 74-year-old male with emphysema, bronchitis, pulmonic and coronary heart disease developed pneumonia. Because of recurrent supraventricular tachyarrhythmias maintenance digoxin was withheld. SDL fell to 0.5 ng/ml. ECG showed multifocal atrial tachycardia, rate about 135 beats/min with occasional ventricular extrasystoles. After only 0.2 mg AS atrial rate slowed to about 120 beats/min. After 0.6 mg atrial rate accelerated to 140 and a brief run of ventricular tachycardia was observed.

**Figure 7**

A 67-year-old female with severe mitral regurgitation. While receiving 0.25 mg digoxin per day, serum digoxin level was 1.0 ng/ml. Trend record from analog computer (top strip) showed variable but frequent ventricular premature beats not related to heart rate. After only 0.4 mg acetyl strophanthidin (AS) ventricular extrasystoles increased in frequency and complexity (bottom panel). Subsequent cardiac surgery revealed ruptured mitral valve chordae tendineae.

Circulation, Volume XLIX, June 1974
Discussion

The introduction of radioimmunoassay technique for quantifying blood glycoside concentration represents a significant advance. It will necessarily contribute to rationalizing digitalis treatment which is now still based on the original principles defined by Withering nearly two centuries ago.33 But, as with any new development, there are tendencies to lose sight of the limitations implicit in a technique. A serum glycoside level in a stable patient without renal impairment on constant maintenance digitalis therapy probably reflects myocardial drug concentration.35 Yet, the extracellular drug represents but a small fraction of glycosides distributed in the tissues, and fourfold variations in serum to myocardial digoxin ratios have been demonstrated between individual patients.35, 39 Changes in electrolyte and hormonal balance are known to alter cardiac to serum digoxin ratios,40, 41 while ischemia can affect the distribution of digoxin within the myocardium.42 Moreover, fluctuations in serum digoxin concentration are influenced by absorption, distribution, metabolism and excretion of the drugs whereas myocardial susceptibility to the toxic action of digitalis can be rapidly altered by other factors.43, 44

What, then, is the significance of a blood glycoside level in the individual patient? It has been stated that 85% to 90% of toxic patients had levels of 2 ng/ml or greater and that 85% to 87% of nontoxic patients had levels of less than 2 ng/ml.18, 22 Others have likewise reported significantly higher serum digoxin levels in patients with presumed digitalis intoxication, compared with nontoxic subjects free of adverse drug effects.13, 20, 21, 45-48 There are two possible objections to the above conclusions; first, that extremes — those who are definitely regarded overdigitalized against those who are unequivocally free of digitalis intoxication — are being compared. But even in these studies, there are substantial overlaps at both the higher and lower digoxin blood level range. A more serious criticism is that a judgment concerning the presence of digitalis intoxication is rarely certain. Both subjective complaints as well as objective manifestations lack specificity for digitalis intoxication. Even ventricular bigeminal rhythm in the digitalized subject may be an expression of inadequate digitalization. In fact, conclusions correlating arrhythmias due to digitalis intoxication with levels of serum glycoside may be circularly derived. Where the finding of a serum concentration above a certain level imputes the arrhythmia to be due to drug overdosage, the fact that a toxic rhythm has been established is adduced as proof that certain digoxin blood concentrations are associated with digitalis toxicity. When the drug is stopped and the arrhythmia disappears, the above argument is deemed incontrovertible. However, in patients with cardiac decompensation, removal from a stressful environment, institution of strict rest, a low sodium diet, diuretics and other supportive measures reduce congestion and cause abatement of arrhythmia. To assess the meaning of serum glycoside levels requires an independent objective measure which can define the degree of existing digitalization. The acetyl strophanthidin tolerance test provides such an independent assay.17

Acetyl strophanthidin (AS) is a cardioactive steroid with inotropic and electrophysiologic properties similar to that of digitalis glycosides. Its time course of action, however, is much faster than that of digitalis drugs in common clinical usage. Changes in automaticity induced by AS appear 5 to 6 times earlier than with ouabain and 10 to 12 times earlier than with digoxin during constant infusion of these drugs.49 Pharmacokinetic studies of AS have revealed a dominant serum half time of 1.2 ± 0.3 hrs in dogs and 2.3 ± 0.2 hrs in man.50 Pharmacodynamic studies in man have shown a biologic half time of 40-42 min as assessed by changes in systolic time intervals51 and 70 min as interpreted from ventricular rate slowing in atrial fibrillation.52 Promptness in onset of activity, brevity in duration of action, swiftness in dissipation of toxic side effects make AS a suitable agent for assessing the prevailing level of digitalization.17

Clinical application of AS tolerance testing rests upon the additional observation that action of this drug is additive to that of cardiac glycosides already in the body.17 Digoxin and AS have combined effects on cardiac automaticity and, over a wide range of SDL (0-14 ng/ml), SDL is inversely correlated with AS tolerance.17

The selection of an AS dose of 1.0 mg was based on observations derived from 430 AS tests performed during the past five years. It has been noted that patients with atrial fibrillation, who, while on maintenance digitalis, have well-controlled ventricular rates, tolerate this dose without adverse effects. On the other hand, those who develop ventricular arrhythmia with 0.6 mg or less, generally are close to digitalis intoxication, or, indeed, are already experiencing the effects of glycoside overdosage. The choice of 1.4 ng/ml as the cutoff for differentiating between concordant and discordant responses to AS was based on the observation that this represents a mean value for large groups of digitalized patients free of any evidence of intoxication.13-15, 20, 21 Had a 2.0 ng/ml cutoff been selected, there would have been a greater number of discordant tests. The bulk of discordant responses to AS derive from patients with
SDL of less than 1.5 ng/ml who did not tolerate 1.0 mg of AS. Thus of 99 patients with SDL of less than 1.5 ng/ml, 40 reacted adversely to AS and 29 of these experienced significant arrhythmia. In 20 others, a full milligram of AS was tolerated though the SDL exceeded 1.4 ng/ml. Three subjects received 1.0 mg AS without any untoward manifestations, even though the SDL exceeded 2.0 ng/ml. At the same level of serum digoxin concentration, different patients showed varying response patterns to AS and by inference, different myocardial tolerance for digoxin. The present experience indicates that the SDL may afford but imprecise information as to the proper state of digitalization. Smith, who has had extensive experience in development and use of radioimmunoassay techniques for glycoside detection, stated that there is no arbitrary serum level for digoxin or digitoxin which enables the clinician to differentiate patients with and without toxicity.53

Use of AS provided insight into those clinical features associated with unusual cardiac sensitivity to digitalis. Increasing age correlated with reduced AS tolerance, corroborating the high frequency of digitalis toxic arrhythmias observed in the elderly.54 Digitalis sensitivity in this group has been ascribed to a gradual decline in glomerular filtration concomitant with aging.55 Since digoxin is primarily excreted through the kidney,56 diminished renal function might be expected to augment digoxin concentration in the heart and reduce AS tolerance. Though a larger percentage of patients showing ECG side effects with AS had azotemia, mean value for BUN in this group was not statistically different from those cases displaying normal AS tolerance. Serum K⁺, which can profoundly influence myocardial uptake and responsiveness to digitalis,17, 40, 57-59 was normal in all cases. As has been noted in dogs, potent intravenous diuretics can facilitate digitalis-induced arrhythmias by promoting myocardial potassium egress, even in presence of normal serum K⁺.60 Instances of exquisite myocardial sensitivity to the toxic properties of digitalis were observed in patients given moderate doses of digoxin and intravenous furosemide.

Both AS testing and SDL measurements showed the effects of hyperthyroidism upon the heart. These methods gave concordant results in two cases with recurrent arrhythmias. SDL of 0.6-1.0 ng/ml with a digoxin maintenance dose of 0.5 mg/day was consistent with the observation that hyperthyroid patients exhibit lower SDL levels than euthyroid subjects.41 The high tolerance for AS despite moderately large maintenance digoxin dose confirmed previous work showing that unusually large doses of this drug were necessary to control ventricular response rates in atrial fibrillation.61 By contrast, one patient, in whom hypothyroidism complicated coronary heart disease, exhibited a SDL of 1.0 ng/ml while receiving 0.125 mg digoxin daily.42 Exquisite sensitivity to AS was nonetheless demonstrable, as ventricular premature beat frequency increased after only 0.4 mg of AS.

Perhaps the most striking examples of discordance between SDL and AS tolerance occurred in six patients with chronic obstructive lung disease. These individuals had cor pulmonale and coronary heart disease, as well. Pulmonary infections triggered respiratory failure with concomitant hypoxemia, which in turn precipitated left ventricular dysfunction and congestive heart failure. Recurrent atrial tachyarrhythmias, refractory to cardioversion, were associated with digoxin blood levels of 1.0 ng/ml or less. Guided by repetitive AS testing, protracted sensitivity could be shown after stopping digitalis. Generally, it persisted for a week or longer, at which time the SDL was 0.4 ng/ml or less. By the time tolerance to AS developed, the arrhythmias had disappeared.

It can be argued that factors other than myocardial sensitivity influenced cardiac tolerance for AS. Drug distribution space and metabolism are known to be important determinants of serum glycoside levels and myocardial glycoside concentration after fixed digoxin dose. AS tolerance in dogs has not been shown to correlate with body weight (B. Lown, unpublished observations). In both dogs and normal human subjects, AS appears to be eliminated through hepatic and gastrointestinal rather than renal routes.50 The degree of plasma protein binding of AS, its distribution space, and the effects of congestive heart failure and liver dysfunction upon AS catabolism remain unknown. Many examples of discordant results between SDL and AS titration testing, however, could not be wholly accounted for by deranged liver function or a shrunken skeletal muscle mass, diverting larger amounts of AS to the heart and thereby reducing myocardial tolerance.

Pharmacologic quantification provides significant insight in therapeutic management. In the case of digoxin, serum concentration measurements yield valuable information about the composite of drug absorption, distribution and excretion. The crucial question does not relate to SDL alone, but rather to whether an optimal therapeutic effect is being achieved and toxic action eschewed. If the blood level is high, adverse reactions are absent, and therapeutic effect not yet accomplished, there is need for more drug; on the other hand, in the presence of a low blood level, the presence of a clearly toxic response mandates less or no further drug administration.
In selecting the optimal dose of digitalis, physicians will continue to utilize biologic titration. Acetyl strophanthidin tolerance testing, by recapitulating the titration process within a brief time interval, will rapidly establish myocardial sensitivity, and will give SDL measurements added meaning.

References
35. Lely AN, Venteren CHG: Non-cardiac symptoms of digitalis intoxication. Am Heart J 83: 149, 1972
37. Withering W: An Account of the Foxglove and Some of Its Medical Uses, with Practical Remarks on Dropsey and Other Disease. Birmingham, Robinson, Paternoster-Row, 1785


KLEIN MD, NEJAD N, LOWN B, HAGEMEIJER F, BARR I: Correlation of the electrical and mechanical changes in the dog heart during progressive digitalization. Circ Res 29: 635, 1971


DAUL JLC: Digitalis intoxication in elderly patients. Lancet 1: 194, 1965


MARCUS FI, KAPADIA GG, GOLDSMITH C: Alteration of the body distribution of tritiated digoxin by acute hyperkalemia in the dog. J Pharmacol Exp Ther 165: 136, 1969

MARCUS FI, NIMAL L, KAPADIA GG, GOLDSMITH C: The effect of acute hypokalemia on the myocardial concentration and body distribution of tritiated digoxin in the dog. J Pharmacol Exp Ther 178: 271, 1971


Comparison of Serum Digoxin Level Measurement with Acetyl Strophanthidin Tolerance Testing
MICHAEL D. KLEIN, BERNARD LOWN, ISAAC BARR, FRANS HAGEMEIJER,
HENRY GARRISON and PAUL AXELROD

Circulation. 1974;49:1053-1062
doi: 10.1161/01.CIR.49.6.1053

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/49/6/1053

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/