Effects of Maintenance Digoxin Therapy on Systolic Time Intervals and Serum Digoxin Concentrations

By Nathan H. Carliner, M.D., Charles A. Gilbert, M.D., Albert W. Pruitt, M.D., and Leon I. Goldberg, Ph.D., M.D.

SUMMARY
Systolic time intervals (STI) and serum digoxin concentrations (SDC) were measured in eight patients with compensated atherosclerotic and/or hypertensive heart disease who received oral digoxin 0.25 mg/day or 0.5 mg/day for alternate two-week periods without a loading dose. Control data were obtained both before and after the four weeks of treatment. After 13 days treatment with digoxin, 0.5 mg/day, there was a significant decrease in total electromechanical systole corrected for heart rate (Q50), pre-ejection period (PEP), pre-ejection period corrected for heart rate (Q50/PEP), and PEP/left ventricular ejection time (LVET). After the thirteenth dose of 0.25 mg/day there was significant shortening of PEP, and PEP/LVET. Shortening of Q50 correlated significantly with SDC 24 hours after the thirteenth dose of 0.5 mg. These data suggest that after 13 days of treatment with 0.25 and 0.5 mg/day of digoxin, a positive inotropic effect occurs as reflected by STI shortening. A greater effect was recorded with the 0.5 mg dose.

Additional Indexing Words:
- Total electromechanical systole
- Pre-ejection period
- Serum digoxin concentration
- Systolic time interval
- Left ventricular ejection time
- Inotropic effect

The development of a radioimmunoassay for cardiac glycosides has made it possible to measure serum concentrations of these drugs in large numbers of patients. Many reports have indicated a positive correlation between serum glycoside levels and incidence of digitalis toxicity. Much less information is available concerning possible relationships between serum glycoside levels and therapeutic efficacy. Ventricular rate has been studied in patients with atrial fibrillation, and patients have been graded according to “clinical response.”

There have been only limited attempts to relate serum digoxin concentrations (SDC) to an objective index of contractility in patients receiving oral maintenance regimens of digoxin.

In the present study, patients with compensated heart disease (New York Heart Association Class I or II) received digoxin, 0.25 mg or 0.5 mg/day, for alternate two-week periods without a loading dose. For each dosage regimen, SDC and systolic time intervals (STI) were measured at intervals of 24 hours after the thirteenth dose, and ½, 1, 2, and 4 hours after the fourteenth dose. These values were then compared to control data obtained before and after the four weeks of treatment. This information has provided an estimate of the inotropic effectiveness of usual maintenance regimens of digoxin in outpatients and has permitted the comparison of STI and SDC.

Methods
Eight patients, all in normal sinus rhythm, with compensated atherosclerotic and/or hypertensive heart disease were studied. Four patients were male and four patients were female. Ages ranged from 35 years to 68 years. Five patients were receiving maintenance doses of digoxin, orally, at the time of selection for the study. Digoxin was discontinued at least two weeks prior to the first control observation. In all patients, SDC at the time of the first control observation was less than 0.4 mg/ml. Diuretics, antihypertensive agents, and sedatives were continued in unchanged doses. Patients taking diuretics received supplemental oral potassium chloride. The purpose of the study was fully explained to each patient and written informed consent was obtained.

The initial evaluation of each patient included determinations of blood urea nitrogen, serum creatinine, sodium, potassium, chloride, carbon dioxide combining power, calcium, carotene, and thyroxine. The results of these studies were all within the normal range. Chest X-rays and 12-lead electrocardiograms were compatible with the clinical diagnoses.

Two sets of control observations (C1 and C2) were obtained two weeks before starting digoxin. Four of the patients then received digoxin 0.25 mg/day for two weeks
DIGOXIN AND SYSTOLIC TIME INTERVALS

and 0.5 mg/day for the next two weeks. The other four patients received 0.5 mg/day for the first two weeks and 0.25 mg/day for the second two weeks. Treatment values were recorded on the last day of each two-week treatment period. A third set of control observations (C4) was obtained two weeks after digoxin was discontinued.

Baseline STI recordings were made between 8:30 and 9:30 a.m. in the fasting state after the patient had been resting quietly in bed for at least 15 minutes. Patients who smoked had been instructed to abstain on the day of study. Additional STI were obtained at ½, 1, 2, and 4 hours after baseline recordings. A light meal without coffee, tea or cola drinks was permitted after the two-hour recording.

On days C1, C2, and C3, blood for SDC was obtained at the times of the baseline STI recordings. The fourteenth daily dose of digoxin (either 0.25 or 0.5 mg) was given in the laboratory 24 hours following the previous day’s dose and immediately after the baseline STI recording and SDC. On the days of study, blood for SDC was also obtained at the time of each subsequent STI recording through an indwelling intravenous catheter. All patients received the same brand of oral digoxin (Lanoxin, Burroughs Wellcome Co.).

Serum digoxin concentration was determined by the tritiated digoxin radioimmunoassay method1 utilizing a commercially available kit (Schwarz Mann Co.). All determinations were performed in duplicate and the two results were averaged. The mean difference between the duplicate determinations was 0.04 ng/ml with a standard error of the difference of 0.016 ng/ml. In this study, assay results of less than 0.4 ng/ml were considered as 0.4 ng/ml.

Electrocardiograms, phonocardiograms, and carotid arterial pulse tracings were recorded on a six-channel photographic recorder at a speed of 100 mm/sec. The electrocardiographic leads selected were the bipolar chest lead CMx, and the Frank orthogonal leads X, Y, and Z. The earliest onset of ventricular depolarization noted in any lead was utilized for measurements. The phonocardiographic microphone was placed in the second or third left intercostal space near the sternum. The carotid arterial pulse tracing was recorded by means of a funnel-shaped pickup attached to a Statham P23D strain gauge by polyethylene tubing of length 98 cm and internal diameter 3 mm.

Total electromechanical systole (QS4) was measured from the onset of ventricular depolarization to the first high frequency vibrations of the aortic component of the second heart sound. Left ventricular ejection time (LVET) was measured from the beginning upstroke to the trough of the incisura of the carotid pulse tracing. Pre-ejection period (PEP) was obtained by subtracting LVET from QS4. Heart rate was calculated by dividing 60 into the R-R interval. All values represented the average of at least ten consecutive beats. QS2, LVET, and PEP corrected for heart rate and sex (QSj, LVETi, and PEPi) were calculated from regression equations for normal subjects obtained by Weisell and Garrard.

Changes induced by digoxin in the systolic time intervals were obtained by subtracting the average of two control periods \((C1 + C2)/(2)\) from the STI. Paired t-tests and correlation coefficients were calculated according to standard techniques.

Results

Systolic Time Intervals

The mean values for STI recorded 24 hours after the thirteenth dose of digoxin (0.25 and 0.5 mg) are shown in table 1. Mean values for QS2i, PEP, PEPI, and PEP/LVET were less than in the two pre-digoxin control periods (C1 and C2). Shortened STI returned to pre-digoxin control values 14 days after the last dose of digoxin (C3). Mean PEPI and PEP/LVET were significantly less than the average control values with the 0.25 mg dose; mean values for PEPI, PEP/LVET, QS2, and PEP were significantly less with the 0.5 mg dose.

Table 1

Systolic Time Intervals and Serum Digoxin Concentrations (STI and SDC) After Two Weeks of Treatment with Digoxin (D) 0.25 or 0.5 mg Daily

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C2</th>
<th>D (0.25 mg)</th>
<th>D (0.5 mg)</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS2 (msec)</td>
<td>431</td>
<td>445</td>
<td>438</td>
<td>430</td>
<td>433</td>
</tr>
<tr>
<td>QS2i (msec)</td>
<td>533</td>
<td>566</td>
<td>548</td>
<td>540</td>
<td>550</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>317</td>
<td>324</td>
<td>327</td>
<td>327</td>
<td>317</td>
</tr>
<tr>
<td>LVETi (msec)</td>
<td>415</td>
<td>425</td>
<td>419</td>
<td>416</td>
<td>411</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>114</td>
<td>117</td>
<td>111</td>
<td>102</td>
<td>116</td>
</tr>
<tr>
<td>PEPI (msec)</td>
<td>138</td>
<td>142</td>
<td>129</td>
<td>125</td>
<td>139</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.363</td>
<td>0.367</td>
<td>0.341</td>
<td>0.3162</td>
<td>0.371</td>
</tr>
<tr>
<td>SDC (ng/ml)</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>0.50</td>
<td>0.88</td>
<td>&lt;0.4</td>
</tr>
</tbody>
</table>

C1, C2, and C3 did not differ significantly.

*C1 and C2 are pretreatment control values obtained two weeks apart and C3 is a posttreatment control obtained two weeks after the completion of therapy. STI and SDC during treatment were measured 24 hours following drug administration.

1P < 0.05: P values measure whether the difference found between cardiac measurements in patients after digoxin and the measurements determined in C1 + C3 divided by 2 are significant.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in QS2i with Digoxin</td>
<td></td>
</tr>
<tr>
<td>Hours after last dose</td>
<td></td>
</tr>
<tr>
<td>+10</td>
<td>0.25 mg(±S.E.)</td>
</tr>
<tr>
<td>-10</td>
<td></td>
</tr>
<tr>
<td>-20</td>
<td></td>
</tr>
<tr>
<td>-30</td>
<td></td>
</tr>
<tr>
<td>-40</td>
<td></td>
</tr>
</tbody>
</table>

Changes in QS2i after 0.25 mg or 0.5 mg digoxin following two weeks of maintenance therapy. Differences shown are from control values \((C1 + C3)/2\). P values refer to the probability that the observed differences from control occurred by chance (paired data analysis).

Circulation, Volume 50, July 1974
Table 2

**PEP, QS₂ᵢ and SDC in Patients after Two Weeks of Digoxin Therapy**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean control* PEP msec</th>
<th>Mean control* QS₂ᵢ msec</th>
<th>SDC† mg/dl</th>
<th>PEP msec</th>
<th>QS₂ᵢ msec</th>
<th>SDC mg/dl</th>
<th>PEP msec</th>
<th>QS₂ᵢ msec</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.S.</td>
<td>155</td>
<td>571</td>
<td>0.47</td>
<td>144</td>
<td>556</td>
<td>0.94</td>
<td>134</td>
<td>557</td>
</tr>
<tr>
<td>M.J.</td>
<td>123</td>
<td>545</td>
<td>&lt;0.40</td>
<td>119</td>
<td>543</td>
<td>0.52</td>
<td>116</td>
<td>542</td>
</tr>
<tr>
<td>V.M.</td>
<td>138</td>
<td>553</td>
<td>&lt;0.40</td>
<td>122</td>
<td>543</td>
<td>0.60</td>
<td>119</td>
<td>546</td>
</tr>
<tr>
<td>C.H.</td>
<td>115</td>
<td>553</td>
<td>0.03</td>
<td>106</td>
<td>551</td>
<td>1.80</td>
<td>104</td>
<td>520</td>
</tr>
<tr>
<td>L.B.</td>
<td>134</td>
<td>552</td>
<td>0.46</td>
<td>121</td>
<td>547</td>
<td>0.60</td>
<td>112</td>
<td>543</td>
</tr>
<tr>
<td>A.McC.</td>
<td>137</td>
<td>550</td>
<td>&lt;0.40</td>
<td>135</td>
<td>522</td>
<td>0.87</td>
<td>134</td>
<td>522</td>
</tr>
<tr>
<td>J.H.</td>
<td>165</td>
<td>568</td>
<td>&lt;0.40</td>
<td>168</td>
<td>583</td>
<td>0.85</td>
<td>147</td>
<td>567</td>
</tr>
<tr>
<td>G.S.</td>
<td>140</td>
<td>559</td>
<td>0.83</td>
<td>142</td>
<td>537</td>
<td>0.83</td>
<td>130</td>
<td>524</td>
</tr>
<tr>
<td>Mean</td>
<td>138</td>
<td>552</td>
<td>0.50</td>
<td>132</td>
<td>548</td>
<td>0.88</td>
<td>125</td>
<td>540</td>
</tr>
<tr>
<td>se</td>
<td>5.7</td>
<td>4.9</td>
<td>0.05</td>
<td>6.8</td>
<td>6.2</td>
<td>0.14</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* C₁ + C₂

† The SDC during the control periods in all patients were <0.40 ng/ml. STI and SDC measurements during treatment were obtained 24 hours after drug administration.

There was considerable individual variation in the degree of shortening with both doses of digoxin. Values of PEP and QS₂ᵢ for each patient are shown in table 2. PEP shortened in all the patients receiving 0.5 mg digoxin, and in six of the eight patients receiving 0.25 mg. The QS₂ᵢ shortened in all the patients receiving 0.5 mg digoxin and in seven of the eight patients receiving 0.25 mg.

Changes in QS₂ᵢ, PEP, and PEP/LVET occurring at ½, 1, 2, and 4 hours after the last dose of digoxin are shown in figures 1–3. Although there was fluctuation in the degree of shortening at the various time levels, all mean QS₂ᵢ, PEP, and PEP/LVET levels were less than control values obtained at the same time period with both the 0.25 and 0.5 mg doses. A clear dose–response relationship is apparent, since all mean values obtained at the 0.5 mg dose were less than those obtained at the 0.25 mg dose except for the four-hour recording of QS₂ᵢ.

Serum Digoxin Concentrations

Twenty-four hours after the thirteenth dose of digoxin, 0.25 mg, SDC in four patients was less than 0.4 ng/ml and the average value of 0.5 mg/ml was not statistically different from control. With the 0.5 mg/day dose, however, all SDC were greater than control values and the mean figure of 0.88 ng/ml was statistically greater than control. As with the STI, there was considerable variation in individual values of SDC (table 2).

Correlation coefficients were calculated between STI shortening and SDC. Because of the low SDC values, such calculations were not feasible with the 0.25 mg dose. Shortening of QS₂ᵢ correlated

---

**Figure 2**

Changes in PEP, after 0.25 mg or 0.5 mg digoxin following two weeks of maintenance therapy. Statistical analysis is the same as figure 1.

**Figure 3**

Changes in PEP/LVET after 0.25 mg or 0.5 mg digoxin following two weeks of maintenance therapy. Statistical analysis is the same as figure 1.
DIGOXIN AND SYSTOLIC TIME INTERVALS

97

significantly with increase in SDC ($r = -0.906$). However, shortening of PEP$_t$ and PEP/LVET did not correlate significantly with increase in SDC. Individual values for PEP$_t$ and SDC illustrate pronounced discrepancies between shortening of PEP$_t$ and increase in SDC (table 2).

Changes in serum digoxin levels at several time intervals after the fourteenth dose are shown in figure 4. Peak values were obtained at the 1 and 2 hour time intervals. Comparison of figure 4 with figures 1, 2, and 3 demonstrate that greater shortening of the STI did not occur with the higher SDC obtained at the 1 and 2 hour intervals. Shortening of QS$_i$ correlated significantly with increase in SDC at the following time intervals: $\frac{1}{2}$ hour: $r = -0.871$; 1 hour: $r = -0.772$, and 2 hours: $r = -0.81$. There was no significant correlation of SDC and PEP$_t$ at any time interval.

Discussion

Although previous investigators demonstrated shortening of STI following large parenteral or oral doses of cardiac glycosides,$^1, 8, 9$ these results are the first demonstrations of significant shortening of STI with small doses of digoxin in nonhospitalized patients. In this investigation, as in the previous studies by Weisserl and Schoenfeld,$^8$ QS$_i$ and PEP$_t$ were better indicators of the positive inotropic action of digoxin than LVET$_t$. These results also agree with the pharmacokinetic studies of Marcus et al.$^{10}$ which predicted that significant shortening of the STI could be obtained by daily doses of digoxin without a loading dose.

An attempt was made to correlate increases in serum digoxin levels with shortening of STI. Such correlation was not feasible with the 0.25 mg dose since several SDC were less than 0.4 ng/ml. Similarly low SDC were also reported by Gilfrich et al.,$^11$ Brown and Abraham,$^{12}$ and Taxman et al.$^4$ in patients receiving this daily dose of digoxin. Significant correlation between SDC and shortening of QS$_i$ was found with the 0.5 mg dose. Significant correlations were not obtained between PEP$_t$ or PEP/LVET and SDC, although both of these STI were shortened to a greater extent than QS$_i$.

Despite demonstrations of statistically significant changes in mean STI and SDC when compared with pre- and postdigoxin control values, there were considerable individual variations. Similar variation in STI and SDC has been demonstrated in most other studies.$^1, 4, 8, 13-14$

The relation between SDC and therapeutic effect has not been extensively studied. The most easily quantitated therapeutic effect of digitalis is ventricular rate in atrial fibrillation. Chamberlain et al.$^2$ found a poor correlation between serum glycoside levels and resting ventricular rates. However, in a similar investigation, Redfors$^8$ noted a good correlation between SDC and ventricular rate in individual patients and pointed out that the poor correlation in the group analysis was largely due to the wide variation in individual ventricular rates. Less information is available concerning the relation of SDC to inotropic effect. Shapiro et al.$^8$ investigated the relation between SDC and STI after administering digoxin 1.0 mg intravenously to six normal volunteers. Shortening of LVET$_t$ and QS$_i$ paralleled the concentration of the drug in plasma. Davidson and Gibson$^8$ studied the inotropic action of digoxin in patients with aortic valve prosthesis. Maximal decrease in time from onset of the Q wave to the opening click of the prosthetic aortic valve (Q-A$_t$ time) occurred 4 to 6 hours after 1.0 mg digoxin orally.

The same investigators, however, were not able to demonstrate significant shortening of Q-A$_t$ time with daily 0.75 mg doses of digoxin, even though SDC was 1.1 ng/ml. It is possible that this lack of positive inotropic effect was related to extensive ventricular damage in these patients.

The best correlation between changes in STI and SDC in the present study occurred 24 hours after the thirteenth dose, at which time serum and tissue concentrations of the drug should have equilibrated. Serum digoxin concentrations were maximal at 1 to 2 hours, but an acute change in STI did not occur with the increase in SDC. Such dissociation of inotropic effect and SDC is not surprising in view of the kinetics of digoxin distribution.$^1, 13-15$ A similar lack of correlation

Figure 4

Serum digoxin concentrations after single oral doses of 0.25 mg or 0.5 mg following two weeks of maintenance therapy.

Circulation, Volume 50, July 1974
between peak SDC and Q-A1 time was observed by Davidson and Gibson after acute administration of digoxin.5

In conclusion, the present study demonstrates that two weeks of therapy with 0.25 mg digoxin daily exerts a positive inotropic effect as reflected by shortening of STI. At a higher oral maintenance dose of 0.5 mg/day, greater shortening of STI occurred and shortening of QS2i significantly correlated with increase in SDC. Further refinement of SDC and STI measurements and study of larger numbers of patients would probably improve the correlation between mean SDC and STI values. However, it is likely that individual variations will still not permit an assessment of extent of positive inotropic effect solely on the basis of SDC levels.

Acknowledgments

We are pleased to acknowledge the expert technical assistance of Ms. Suzanne Thorpe and Mrs. Mirjana Clark. We also want to thank Dr. Elmer Hall, Chairman, Department of Biometry, Emory University, for statistical consultation.

References

Effects of Maintenance Digoxin Therapy on Systolic Time Intervals and Serum Digoxin Concentrations
NATHAN H. CARLINER, CHARLES A. GILBERT, ALBERT W. PRUITT and LEON I. GOLDBERG

_Circulation_. 1974;50:94-98
doi: 10.1161/01.CIR.50.1.94

_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/50/1/94

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/