The Onset and Magnitude of the Contractile Response to Commonly Used Digitalis Glycosides in Normal Subjects

By Wilbur Forester, B.S., Richard P. Lewis, M.D., Arnold M. Weissler, M.D., and Thomas A. Wilke, Ph.D.

SUMMARY
Controversy exists over the rapidity of onset of the inotropic effect of various digitalis glycosides. Shortening of the systolic time intervals (STI) provides a quantitative measure of the inotropic effect of digitalis glycosides in human subjects. Total electromechanical systole corrected for heart rate (QS₂I) is the most sensitive of the STI since it combines the shortening effect of digitalis glycosides on both the pre-ejection period and ejection time. Normal volunteer subjects were studied serially following i.v. injection of 1.6 mg cedilanid-D (C) (n = 18), 1.0 mg ouabain (O) (n = 12), 1.6 mg digoxin (D) (n = 16), and 1.6 mg digitoxin (DT) (n = 9). The shortening of QS₂I was corrected for the molecular weight of the digitalis glycoside. The onset of shortening of the QS₂I/mole proved to be exponential for each digitalis glycoside. This allowed estimation of the maximum shortening of QS₂I/mole (A) which would be exponential for each digitalis glycoside. This allowed estimation of the maximum shortening of QS₂I/mole (A) which would occur assuming zero excretion, from which the time constant (tₐ) of the curves could be determined. There was no significant difference in A among the digitalis glycosides. The tₐ were 5.8 min (O), 7.2 min (C), 23 min (D), and 56 min (DT). These tₐ were significantly different except for O and C. Thus both C and O have a rapid onset of activity which is significantly shorter than either D or DT. The tₐ for C in patients with congestive heart failure is the same as normals. This study provides a heretofore unavailable, accurate measure of the differences among commonly used glycosides.

Additional Indexing Words:
Digitalis  Systolic time intervals  Time constant  Congestive heart failure

DESPITE THEIR COMMON USE in patients with cardiovascular disease, precise data regarding the relative onset and magnitude of the positive inotropic effect of the various commonly employed digitalis glycosides are not available. In large part this reflects the fact that an easily applied measure of the contractile response to these agents has not been available. In the past, slowing of the heart rate in patients with atrial fibrillation has been used to estimate the onset of digitalis effect. However, other factors such as the presence of atrioventricular conduction disease, the rapidity of the initial heart rate, and level of adrenergic activity may influence the response of the heart rate to digitalis in atrial fibrillation. Thus studies in which slowing of atrial fibrillation is used as an end point of digitalis effect have shown wide variation in the range of response to various glycosides.

Recently the response of the systolic time intervals has been employed to provide a quantitative measurement of the positive inotropic effect of digitalis. Earlier studies employed shortening of the left ventricular ejection time index (LVETI) as a measure of the response to digitalis. More recent observations indicate that total electromechanical systole corrected for heart rate (QS₂I) is preferable to the LVETI. The magnitude of the response of the QS₂I is nearly double that of the LVETI, since both the LVETI and pre-ejection period index (PEPI) are shortened by inotropic agents in normal subjects. Furthermore, unlike the PEPI and LVETI, the QS₂I provides a better measure of...
the presence of positive inotropic effect in abnormal subjects. This is true because the response of the PEPI and LVETI in abnormal subjects is also conditioned by the hemodynamic effect of the drug.\textsuperscript{14}

The present study was undertaken to compare the relative onset and magnitude of positive inotropic effect of five commonly employed digitalis glycosides in normal subjects employing the change in the QS\textsubscript{2}I as the primary measurement of the contractile response.

**Material and Methods**

Normal volunteer male subjects (age 21 to 26) were studied by serial systolic time intervals for one hour following intravenous administration of a digitalizing dose of either acetyl strophanthidin, ouabain, cedilanid-D (deslanoside), digoxin, or digitoxin. Informed consent was obtained in all cases. All studies were performed in the fasting state and in the supine position between 8 and 10 A.M. Five control measurements were obtained at 10 min intervals and the results averaged. The digitalis glycoside was then administered uniformly over a 3 min period and systolic intervals obtained at 10, 20, 40, and 60 min thereafter. The technique of measuring systolic time intervals which was employed in this study has been presented in detail previously.\textsuperscript{18}

The number of subjects studied and the doses employed are listed in table 1. In order to compare the maximum response to each glycoside, the dose of each glycoside was corrected for the molecular weight and the QS\textsubscript{2}I was divided by the molar dose (table 1).

Figure 1 demonstrates the relationship between the heart rate and the QS\textsubscript{2} in normal subjects before and at various times after administration of cedilanid-D. The QS\textsubscript{2} values are shorter after cedilanid-D but the slope of the regression line is unchanged. Thus the underlying influence of heart rate upon the QS\textsubscript{2} was unchanged by cedilanid-D. Consequently all QS\textsubscript{2} values were corrected for heart rate using the baseline regression equations of Weissler et al.\textsuperscript{18} The corrected value is termed the QS\textsubscript{I} and provides a measure of the shortening of systole induced by digitalis.

The mathematical and statistical methods employed in this study were derived from techniques employed in pharmacokinetic studies and will be briefly outlined.\textsuperscript{* 19, 20} Empirically the relationship of change in the QS\textsubscript{1}/mole with time following administration of various digitalis glycosides appeared to be a first order or exponential relationship. Figure 2 shows a theoretical exponential curve of the form obtained experimentally in this study. In addition, figure 2 illustrates a mathematical transformation of the data employed for ease of evaluation. The formulae shown are exponential expressions of the form $Y = A (1 - e^{-kt})$ where the constant $A$ is the asymptote which symbolizes the theoretic maximum response if excretion and metabolism of the drug are disregarded. The constant $k$ is the rate constant. The time constant is defined as $t_c = 1/k$. When $t$ is equal to $t_c$, the exponential equation becomes $Y = A (1 - e^{-1})$. Since $e^{-1}$ is equal to 0.37, $Y = 0.63A$. Thus

\begin{table}[h]
\centering
\caption{Subjects and Dosages of Various Digitalis Glycosides}
\begin{tabular}{llll}
\hline
Drug & Dose & Molar dose & n \\
\hline
Acetyl Strophanthidin & 0.5 mg & 1.08 \textmu moles & 3 \\
Ouabain & 1.0 mg & 1.70 \textmu moles & 12 \\
Cedilanid-D & 1.6 mg & 1.70 \textmu moles & 18 \\
Digoxin & 1.6 mg & 2.04 \textmu moles & 16 \\
Digitoxin & 1.6 mg & 2.00 \textmu moles & 9 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} Details available upon request.

**Figure 1**

Effect of cedilanid-D on electromechanical systole (QS\textsubscript{2}) in normal subjects. QS\textsubscript{2} (ordinate) is plotted as a function of heart rate (beats/min) before (solid circles) and after (open circles) administration of cedilanid-D. The regression lines are indicated. The slope is unchanged after cedilanid-D.

**Figure 2**

The left panel describes a theoretical exponential curve of the form obtained in this study. $A$ represents the asymptote or theoretical maximum response. On the right the curve is shown after mathematical transformation.
t_c is the time at which 63% of the total response has been achieved.

An iterative optimization technique was employed for analysis of the onset curves in which a value for A was assumed. Least squares linear regressions were used on the transformed variables, ln (A – Y) versus t, for various values of A to determine the best least square fit. The best fit was determined by two criteria: correlation coefficient and agreement between the assumed value of A and the A determined from regression. From the curve with the best fit for A, t_c was calculated as well as the respective variance estimates for use in testing differences between values of A and t_c among the drugs studied.

Figure 3 shows the effects of variations of A and t_c upon theoretical exponential curves. On the left are shown four curves in which the maximum response (A) is the same but t_c differs. On the right are four curves in which the time constants are the same but the A values differ.

All statistical and mathematical computations were made with the aid of a Hewlett Packard 9100-A programmable calculator using standard statistical techniques.

**Results**

Figure 4 shows the mean QS_{2I}/mole versus time for the five drugs employed. Acetyl strophanthidin has an extremely rapid onset of activity and its effect is dissipated within one hour. Cedilanid-D and ouabain have a rapid onset and full effect is reached by 30 min. Digitoxin has a slower onset of activity and does not reach peak effect by one hour while both the onset of activity and peak effect of digoxin lies between those of ouabain and digitoxin. In addition, the curves appear to be similar to the theoretic curves in figure 3 in which A values are constant but time constants differ.

The least square regressions of the mean data employing a first order exponential model produced correlation coefficients of 0.99 or greater in all cases.

In the case of ouabain where only two data points were available, which is the minimum number acceptable for analysis, the results are statistically consistent with those obtained for the other drugs. Thus assumption of a first order model appears suitable for analysis of the onset of inotropic activity of digitalis glycosides. Figure 5 shows the data transformed for regression as discussed earlier.

The constants A and t_c and their standard deviation estimates were determined for each drug and are summarized in table 2. The maximum theoretal effect A showed no significant differences
Table 2

<table>
<thead>
<tr>
<th></th>
<th>Theoretical maximum AQS/mole (± SEM)</th>
<th>Time constant (min) (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouabain</td>
<td>17.6 (± 4.2)</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>Cedilanid-D</td>
<td>19.5 (± 5.2)</td>
<td>7.2 ± 3.3</td>
</tr>
<tr>
<td>Digoxin</td>
<td>16.6 (± 4.6)</td>
<td>23 ± 2.3</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>15.5 (± 1.8)</td>
<td>56 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>Ouabain and Cedilanid not different; all other pairs P &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Among the drugs, however, the time constants did show significant differences between all pairs except cedilanid-D and ouabain. The time constant for acetyl strophanthidin could not be determined because insufficient data on the upstroke portion of the response curve obviated mathematical and statistical analysis. However, acetyl strophanthidin clearly has a shorter time constant than that of ouabain. No inference could be made concerning the A value for acetyl strophanthidin.

**Discussion**

These studies provide a quantitative measurement of the onset and magnitude of the positive inotropic effect of commonly used digitalis glycosides. The standard digitalizing dose when given intravenously as a single dose produces the same theoretical maximum effect. This is of interest because the digitalizing doses used in this study were based solely on clinical experience. However, this maximum effect is calculated assuming that no excretion or metabolism of the drug occurs before the maximum effect is reached. There is no experimental data available on this problem but this study was confined to the first hour. Therefore the assumption of no excretion or metabolism is probably valid.

Comparisons between the onset of the positive inotropic and negative chronotropic effects were made for digoxin and digitoxin using Gold’s data for slowing of heart rate in atrial fibrillation following intravenous injection of 1.2 mg of digoxin and digitoxin.21 The chronotropic data produced time constants (calculated as outlined in Methods) of 25 min for digoxin and 50 min for digitoxin which are remarkably close to the time constants for inotropic effect of these drugs.

Standard medical texts state that cedilanid-D and digoxin have an equivalent time of onset and that ouabain has a faster onset than either agent. However, the data from this study demonstrate that the onset of the positive inotropic effect of cedilanid-D is equivalent to ouabain and significantly more rapid than digoxin. The clinical impression that ouabain has a more rapid onset than cedilanid-D is thus not substantiated. Obviously studies of the onset of the negative chronotropic effect of cedilanid-D are needed.

The quantitation of the onset of inotropic effect of the various digitalis glycosides is of considerable clinical significance. The digitalizing doses of the various glycosides which have been empirically derived appear to be valid. It would appear that a 30 min delay following intravenous injection is sufficient time for the full effect to develop if either cedilanid-D or ouabain is used, but this is not true for digoxin. When rapid slowing of supraventricular arrhythmias or rapid positive inotropic effect is desired, it appears that both cedilanid-D and ouabain offer a significant advantage over digoxin.

These studies were performed in normal subjects. However, in a recent study it was demonstrated that in patients with congestive heart failure the onset and magnitude of the positive inotropic effect of cedilanid-D is similar to that observed in normal subjects.14 From this data a time constant of 9 min was calculated for cedilanid-D in patients with heart failure, a value which is not stastically different from normal subjects.

*We have been unable to determine the basis for this assumption as no studies of the effects of deslanoside in atrial fibrillation are available.

**References**

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15. Wilson WS, Tolbert JH, DiGiulio W: Plasma digoxin levels and serial left ventricular ejection times after a digitalizing dose of digitoxin. Am J Cardiol 26: 102, 1970


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