A Controlled Trial of Digoxin in Congestive Heart Failure

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Because of conflicting results from studies examining the usefulness of digoxin in congestive heart failure (CHF) patients in sinus rhythm, a cross-over trial was conducted in which 20 patients received 7 weeks of digoxin titrated to a level of 1.54 to 2.56 nmol/liter and 7 weeks of matched placebo. The order of treatments was determined by random allocation and patients, clinicians and research staff were blind to allocation. In patients with deteriorating condition, the treatment period was terminated and outcome measures were obtained. If deterioration occurred during the first period, the patient was crossed over without the code being broken. Seven patients required premature termination of study periods because of increasing symptoms of CHF. All 7 were taking placebo at the time (p = 0.016). Small differences in dyspnea (p = 0.044), walking test score (p = 0.055), clinical assessment of CHF (p = 0.036) and ejection fraction (p = 0.004) favored the digoxin treatment group. Patients with more severe CHF were more likely to benefit from digoxin administration. It was concluded that oral digoxin, in doses titrated to produce a serum level of 1.54 to 2.56 nmol/liter, improved quality of life and functional exercise capacity in some patients with CHF in sinus rhythm. (Am J Cardiol 1988;61:371–375)

The value of digoxin in patients with congestive heart failure (CHF) in sinus rhythm remains controversial. Of the 3 controlled trials of digoxin in patients with well-documented CHF in sinus rhythm, only 1 has shown a statistically significant treatment effect. The 2 negative trials may have missed a clinically important effect of digoxin because of inadequate sample size or because of factors related to patient selection. The single positive trial is limited in that its primary measure of outcome was an aggregate clinical score, which has not been reported as an outcome measure in clinical trials before or since; the effect of the treatment on exercise capacity was not measured; and the study used a crossover design, but a substantially larger treatment effect was found before the crossover than after it, rendering the primary analysis question-able.

Therefore, we undertook a double-blind, randomized, crossover trial of digoxin in patients with CHF in sinus rhythm to determine the drug’s effects on cardiac function, exercise capacity and quality of life.

Methods

Potentially eligible patients were recruited from the practices of participating physicians, through review of admissions to 4 local hospitals of patients with a diagnosis of CHF and through review of echocardiograms showing impaired cardiac function. Patients were enrolled if they were willing to participate and met the following criteria while in a stable clinical condition: (1) significant functional disability as indicated by identifying at least 3 important and frequent activities of daily living in which the patient experienced dyspnea; (2) cardiac dysfunction as documented by fractional shortening of <28%, E-S distance ≥1 cm and left ventricular end-diastolic diameter of >3.2 cm/m², all measurements obtained from an M-mode echocardiogram; and (3) sinus rhythm.

Patients were excluded for the following reasons: (1) exercise capacity limited by factors other than dyspnea; (2) primary valvular disease; (3) hypertrophic

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cardiomyopathy; (4) inability to complete the quality of life questionnaires; (5) forced expired volume in 1 second or vital capacity <60% of predicted; (6) hospitalization within a month of randomization; (7) inability to tolerate a digoxin level in the therapeutic range; and (8) patient’s family physician or consultant deciding that his or her participation was inappropriate.

**Study design:** All eligible patients had their digoxin dose titrated to achieve a level between 1.54 and 2.56 nmol/liter. Baseline measurements, including demographic information, history and physical examination, New York Heart Association functional class, M-mode echocardiogram, chest radiograph and electrocardiogram, were obtained. Patients were then given digoxin, in the dose necessary to achieve the therapeutic digoxin level, and an identical placebo, each for 7 weeks. The order was determined by random allocation. Subjects, clinicians and research staff were blind to the order of the treatments.

When the condition of the patients deteriorated, they were seen immediately. The policy of the study established that no changes in medication were to be made in response to deterioration. Rather, patients were assessed, and, if the deterioration was sufficiently severe and included both subjective (increased symptoms) and objective (physical examination and radiographic evidence) changes, the treatment period was called a “treatment failure.” If a treatment failure occurred, all outcome measures were obtained and the patient was started on the next period’s medication without the code being broken (or, if the treatment failure occurred during the second period, the study was terminated after outcome measures were obtained). The criterion for determining a treatment failure was the assessment by the study physician that the CHF had worsened to the point where it was not ethically permissible to continue without change in medication. In regular clinical practice, medication change such as a diuretic dose increase would have been prescribed in response to such deterioration.

Compliance was monitored by pill counts and by measurement of digoxin level at the third, fifth and seventh week of each period. Digoxin levels were monitored by 1 investigator not involved in either the patients’ care or the study assessment who made dose adjustments as necessary. Comparable adjustments were made during placebo periods to maintain blindness.

**Measures of outcome:** All such measures were obtained at the end of each study period and these included echocardiographic measurement of fractional shortening and end-diastolic left ventricular dimensions, a clinical CHF score, the 6-minute walking test and a cycle ergometer exercise test, and quality of life measured by questionnaire.

The CHF score, identical to that used by Lee et al in their controlled trial of digoxin, simulated the clinical judgment of the severity of CHF. The CHF score combined findings from history (dyspnea) and physical examination (pulse rate, jugular venous distension, chest auscultation), with radiographic findings. The chest radiographs were read by 2 members of the team who were blind to allocation. In addition to the vari-

ables required for the CHF score, cardiothoracic ratio also was measured. Discrepant readings were resolved by consensus.

The progressive multistage cycle ergometer exercise test was performed according to the method of Jones and Campbell. Patients began at 100 kpm and power output was increased by 100 kpm each minute until the point of exhaustion. Exercise duration, heart rate, oxygen consumption and carbon dioxide production were all measured. Because of the very high correlation between exercise duration and the other variables, only the former are reported.

In the 6-minute walking test the patients were asked to cover as much ground as they could during a 6-minute period. When conducted under standardized conditions, including uniform encouragement by the test supervisor, the 6-minute walk has been demonstrated to be a reproducible and valid measure of functional exercise capacity in patients with CHF.

A disease-specific, quality of life questionnaire was used, based on the CHF questionnaire—an instrument that has proved reproducible, valid and responsive in previous testing. The questionnaire measured dyspnea (5 items), fatigue (4 items) and emotional function (7 items). Clinical experience with the questionnaire revealed that a minimal clinically important difference was approximately 0.5 per question. That is, patients who improved by a mean of 0.5 per question (for example, 2 points on a dimension with 4 questions), reported that the improvement was important in their day-to-day lives.

**Statistical analysis:** The primary analysis for each outcome used the procedure suggested for crossover trials by Hill and Armitage, which first examines for treatment-period interaction and, in its absence, continues with an analysis of treatment effect. All p values reported are 1-tailed.

The results were examined to see whether predictors of digoxin effect could be identified. A patient was classified as a “digoxin responder” if a placebo period was shortened because of symptomatic or clinical deterioration attributed to increasing CHF. Variables tested as possible correlates of digoxin response included cause of CHF, fractional shortening, left ventricular dimensions, walk-test score, exercise duration, heart-failure score, cardiothoracic ratio on chest radiograph, jugular venous distension >6 cm, or an S3. For dichotomous or categorical variables 2 x 2 tables were constructed and a Fisher’s exact test was used to determine if the association was statistically significant. For continuous variables an unpaired t test compared scores of responders to nonresponders. For variables in which the unpaired t test was statistically significant (p < 0.05), an appropriate cut-off was chosen and a 2 x 2 table constructed to determine the sensitivity and specificity of each variable in predicting digoxin response.

**Results**

**Recruitment and dropout rates:** Three-hundred and fifty patients eligible on the basis of chart review or echocardiogram results proved ineligible. The most
common reason was the objection of the family physician or consultant to the patient's participation. The most common objections included judgments that the patient was too ill as a result of CHF or some coexistent illness, was limited by angina or claudication, was not limited by exertional dyspnea, was housebound or was in atrial fibrillation. Some physicians were unwilling to enter patients because they questioned whether the study was ethical.

One-hundred and thirty-four patients met the eligibility screen but refused to participate; of these, 50 felt too ill. Other common reasons for refusal included difficulty with travel arrangements to the study center and lack of interest.

Five subjects were randomized but dropped out before completing the study. One sustained a massive myocardial infarction and died during the digoxin phase, and 2 patients developed unstable angina while receiving the drug. Two participants had exacerbations of CHF, 1 while taking digoxin and 1 placebo, which required increased diuretics. After their exacerbations these 2 patients declined to continue in the study. Myocardial infarction, unstable angina and spontaneous deterioration in CHF are all common events in patients with ischemic cardiomyopathy and we do not believe they were related to digoxin in patients who experienced them while taking this drug.

Twenty-three subjects completed the study. When data collection was complete, 5 investigators, still blind to allocation, reviewed each patient's course to determine if there were other events that could have affected his or her status and constituted grounds for invalidating the analysis. Three patients were excluded on the basis of this review: one developed increasing airflow obstruction and hypercarbia, one had a number of changes in his CHF medication made by his attending physician (who was not part of the study team) and a third developed unstable angina believed unrelated to the study drugs.

Patient characteristics: Of the 20 patients who completed the study 18 were men and 2 women, ages 63 ± 11 years (mean ± standard deviation). The cause of CHF was ischemic cardiomyopathy in 17, hypertensive cardiomyopathy in 1 and idiopathic cardiomyopathy in 2. Patients were classified according to the New York Heart Association functional classification by 1 of the 2 cardiologic investigators: 2 patients were in New York Heart Association class 1, 10 in class II and 8 in class III. All patients had been hospitalized with CHF on at least 1 occasion. Prior to participating in the study, 18 patients were taking diuretics, 17 digoxin and 11 oral vasodilators. The mean digoxin dose required to reach the specified serum level was 0.391 mg (range 0.125 to 0.937). The first study period was digoxin in 11 patients and placebo in 9.

Compliance: The mean digoxin level administered was 1.75 ± 0.45 nmol/liter and the lowest 1.1 nmol/liter. All but 2 patients consistently had digoxin levels of 0 while on placebo and on only 1 occasion was a digoxin level of >1.0 obtained during a placebo period. These findings were consistent with pill counts, which showed that every patient took 89% or more of the given medication.

Treatement failures: There were 7 treatment failures, all occurring during placebo periods (p = 0.016). The length of these shortened periods varied from 6 to 40 days, with a mean of 18 days. One patient required termination because of dizziness after 14 days of a period on active drug.

For all subsequent analyses, the initial test for a treatment-period interaction did not approach conventional levels of statistical significance, permitting data analysis based on the crossover design. For some measures, results were not available for each treatment period. The extent of missing data, and the reasons, are listed in Table I.

Primary outcomes: Dyspnea improved during active treatment (Table II). However, the difference was small.

The walking test scores were 19 meters greater during digoxin administration than during placebo treatment (Table II). This difference approached conventional levels of statistical significance (p = 0.056). Previous experience suggests that the minimal clinically important difference in 6-minute walk test score is approximately 30 meters. Thus, the effect size is small.

Clinical assessment of the degree of CHF demonstrated statistically significant deterioration during the placebo phase of the trial (Table II).

Echocardiogram results revealed that the fractional shortening was greater and the left ventricular end-diastolic volume smaller when patients were taking digoxin. However, the digoxin effect on the former variable was much larger and was statistically significant (Table II).
The cardiothoracic ratio showed a small, but statistically significant, reduction while patients were taking digoxin (Table II).

Only 13 patients completed the exercise test on 2 occasions. The exercise time was almost identical in the 2 periods (a mean of 6.5 minutes on placebo and 6.4 on digoxin). Given that exercise time was not obtained during most periods when deterioration occurred, this result is not surprising.

**Predicting response:** The following variables were associated with a response to digoxin (p < 0.05): cardiothoracic ratio, heart-failure score, New York Heart Association functional class, walking test score and jugular venous distension. The sensitivity and specificity of each of these variables, and of S3, are listed in Table III.

**Discussion**

In comparison with patients given digoxin, patients with CHF receiving placebo deteriorated more often than would be expected by chance. Small improvements with digoxin were found in dyspnea (as measured by questionnaire) and functional exercise capacity (as measured by the 6-minute walking test). The drug had little if any impact on fatigue and emotional function. Cardiac function, as measured by ejection fraction on M-mode echocardiography and cardio-thoracic ratio on chest radiograph, was better while patients were taking digoxin.

There have been many studies examining the effect of digoxin in patients with CHF in sinus rhythm, but the most important evidence comes from 3 randomized control trials, all of which used a crossover design. These studies were difficult to compare because they used different measures of outcome. However, in each trial one could identify the patients who experienced deterioration to the point where a study period had to be terminated prematurely. These data from the 3 previous trials and the present study are listed in Table IV.

Overall, the 4 trials showed that most patients with CHF who are in sinus rhythm did not gain clinically important benefit from digoxin. However, the 2 definitively positive trials, Lee et al's and our own, showed that a minority of CHF patients did benefit from the drug. The issue, then, was to identify these patients, whom we called 'digoxin responders.'

We found that an S3 and a larger cardiothoracic ratio (but not larger left ventricular internal dimensions by echocardiogram) were more common in digoxin responders. We also identified poorer exercise capacity as measured by the 6-minute walking test, poorer functional capacity according to the New York Heart Association functional classification and jugular venous distension >6 cm as predictors of digoxin response (Table III).

None of these variables was perfect in predicting digoxin response. Further, because of our small sample size, the sensitivities and specificities listed in Table III are imprecise estimates of the value of each variable in predicting digoxin response. Perhaps most important was that each of the variables associated with digoxin response reflected increasing severity of CHF. Thus, clinicians could limit the number of patients unnecessarily treated with the drug by restricting digoxin use in patients in sinus rhythm to those with more severe failure (such as patients who remain symptomatic after optimal use of diuretics). A more precise delineation of whether digoxin should be administered to a given patient will require a randomized trial in that individual, an approach we have described elsewhere.  

### Table III: Predictors of Digoxin Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-Off to Predict Responders</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>S3 Present</td>
<td>0.66</td>
<td>0.46</td>
<td>0.18</td>
</tr>
<tr>
<td>Heart size</td>
<td>&gt;0.54</td>
<td>0.86</td>
<td>0.65</td>
<td>0.004</td>
</tr>
<tr>
<td>Walk score</td>
<td>&lt;300</td>
<td>0.71</td>
<td>0.65</td>
<td>0.022</td>
</tr>
<tr>
<td>NYHA</td>
<td>Class 3</td>
<td>0.96</td>
<td>0.65</td>
<td>0.004</td>
</tr>
<tr>
<td>functional</td>
<td>and 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart-failure score</td>
<td>&gt;2</td>
<td>0.71</td>
<td>1.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>&gt;6 cm</td>
<td>0.57</td>
<td>0.92</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Proportion of digoxin responders with "positive" or "abnormal" test.
† Proportion of digoxin nonresponders with "negative" or "normal" test.
‡ Fisher's exact test on 2 × 2 table.
NYHA = New York Heart Association.

### Table IV: Randomized Controlled Trials of Digoxin in Patients with Congestive Heart Failure in Sinus Rhythm

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients</th>
<th>No. of Digoxin Responders*</th>
<th>No. of Placebo Responders†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleg et al 1982</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lee et al 1982</td>
<td>25</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Taggart 1983</td>
<td>22</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Present Study</td>
<td>20</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

* Patients whose deteriorating condition during a study period on placebo required premature termination.
† Patients whose deteriorating condition during a study period on digoxin required premature termination.
In applying the results of this work the clinician should note that the dose of digoxin was titrated to produce a “therapeutic” digoxin level and was considerably higher than is standard in clinical practice. This was also true of the other randomized trials (the mean dose in the Lee et al study was 0.5 mg). Titrating digoxin to a therapeutic level may be required to achieve the degree of clinical response found in our study. On the other hand, neither the present study nor previous work have established whether or not a lower dose (and thus a decreased digoxin level) would have been equally effective. This is an important question for further research.

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References


