Double-Blind Placebo-Controlled Trial of Digoxin in Symptomatic Paroxysmal Atrial Fibrillation

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Background—Digoxin is commonly prescribed in symptomatic paroxysmal atrial fibrillation (AF) but has never been evaluated in this condition.

Methods and Results—From a multicenter registry, 43 representative patients with frequent symptomatic AF episodes were recruited into a randomized, double-blind crossover comparison of digoxin (serum concentration, 1.29±0.35 nmol/L) and placebo. The study end point was the occurrence of 2 AF episodes (documented by patient-activated monitors), censored at 61 days. The median time to 2 episodes was 13.5 days on placebo and 18.7 days on digoxin (P<0.05). The relative risk (95% CI) of 2 episodes (placebo:digoxin) was 2.19 (1.07 to 4.50). A similar effect was seen on the median time to 1 episode: increased from 3.5 to 5.4 days (P<0.05), relative risk 1.69 (0.88 to 3.24). The mean±SD ventricular rates during AF recordings during placebo and digoxin treatment were 138±32 and 125±35 bpm, respectively (P<0.01). Twenty-four–hour ambulatory ECG recordings did not show significant differences in the frequency or duration of AF or in ventricular rate.

Conclusions—Digoxin reduces the frequency of symptomatic AF episodes. However, the estimated effect is small and may be due to a reduction in the ventricular rate or irregularity rather than an antiarrhythmic action. (Circulation. 1999;99:2765-2770.)

Key Words: arrhythmia ■ fibrillation ■ antiarrhythmia agents ■ drugs

Atrial fibrillation (AF) is the most common cardiac arrhythmia: in its permanent form, the prevalence is ≈2.3% in people >40 years old and 5.9% in those >65 years old. The paroxysmal form has been reported in 35% to 40% of patients attending hospital with AF, and in the general population its prevalence may equal or even exceed that of permanent AF. Antiarrhythmic therapy for paroxysmal AF generally aims for a reduction in symptom frequency or severity; total abolition of the arrhythmia is rarely possible. Few antiarrhythmic drugs have been evaluated in this specific condition by randomized controlled trials, and digitalis is the source of particular controversy. The present study aimed to determine the effect of digoxin in conventional doses on the frequency of symptomatic episodes of paroxysmal AF.

Methods

Study Population

The study population was recruited from 8 general hospitals and 1 regional cardiothoracic center. A registry was kept by each participating physician to determine whether the study group was representative of those patients likely to receive antiarrhythmic therapy for paroxysmal AF. This detailed the clinical features of outpatients seen by the participating physician who had at least 1 episode of AF, with return to sinus rhythm, in the preceding 6 months (irrespective of study eligibility).

Entry Criteria

Patients of either sex ≥18 years old were eligible for screening if they had a history of documented AF, with frequent (≥1/mo), symptomatic, self-terminating episodes. Patients taking antiarrhythmic drugs were eligible if they had met these criteria before treatment and were willing to discontinue treatment.

Exclusion Criteria

Patients were excluded if they had a history of AF requiring cardioversion on >1 occasion or a history of thromboembolism or symptoms such as syncope or angina judged by their physician to be related to AF and to preclude the ethical administration of placebo. Other exclusion criteria were uncorrected electrolyte imbalance; serum potassium <3.8 mmol/L; abnormal thyroid function; renal, hepatic, pulmonary, or cardiac insufficiency or valvular heart disease that might cause progression to persistent AF; left atrial diameter >45 mm; myocardial infarction, unstable angina, or cardiac revascularization procedure in the preceding 3 months; known or suspected accessory atrioventricular pathway; history of second- or third-degree atrioventricular block or sinus node dysfunction; implanted cardiac pacemaker; hypertrophic cardiomyopathy; or amiodarone or investigational drugs in the preceding 3 months. Female patients who were pregnant, lactating, or of childbearing potential and not using contraception were excluded.

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taking placebo. Unused tablets were counted at the end of each phase. Further dose adjustments were made if necessary. To keep both sampling was repeated.

Nomogram based on renal function. After Foundation Ltd. For each patient, initial dosing was determined by a digoxin (Lanoxin) or matching placebo, supplied by the Wellcome digoxin and placebo. Also studied were the intervals to the first documented episode, the ventricular rates during the documented portions of AF episodes, the number and duration of AF episodes on Holter recordings and their mean heart rates, and reported adverse events and side effects.

Screening Phase
Patients meeting the entry criteria underwent a 31-day screening phase after the withdrawal of antiarrhythmic medication for ≥5 half-lives. This included β-blockers, verapamil, and diltiazem: if these were prescribed for hypertension or angina, substitution was required. A 3-month discontinuation was required for amiodarone and investigational drugs. During screening, patients were instructed to transmit ECG recordings at the onset of and after each symptomatic episode. Patients in whom ≥1 symptomatic, self-terminating episode of AF was documented during screening were randomized into the evaluation phase.

Evaluation Phase
The evaluation phase of the study had 2 limbs. In each, evaluation was commenced only after loading/washout and documentation of an appropriate digoxin level. Each treatment continued until 2 symptomatic episodes of AF, separated by sinus rhythm, had been documented or for a maximum of 61 days. Each treatment was discontinued after a single AF episode if it was judged by the physician to be of sufficient clinical severity (in terms of symptoms, duration, or hemodynamic disturbance) to constitute treatment failure. Patients without any documented symptomatic episodes of AF during active or placebo treatment were replaced and not entered into principal statistical analysis. Recruitment continued until 40 patients had completed both phases.

Randomization and Dosing
Randomization was carried out in blocks of 4 at each center. Patients were instructed to take 1 to 4 tablets daily, each containing 125 μg digoxin (Lanoxin) or matching placebo, supplied by the Wellcome Foundation Ltd. For each patient, initial dosing was determined by a nomogram based on renal function. After ≥7 days of loading/washout, and ≥6 hours after the most recent dose, serum digoxin concentration was measured (TDX, Abbott Laboratories, Inc) by a nonblinded central laboratory. The laboratory instructed the trial coordinator to alter dosing in patients with serum concentrations outside the desired range (1.0 to 2.6 nmol/L, 0.8 to 2.0 μg/L). Blood sampling was repeated ≥7 days after changes in digoxin dose, and further dose adjustments were made if necessary. To keep both patients and investigators blinded, the laboratory issued an equivalent number of dose adjustment instructions for patients currently taking placebo. Unused tablets were counted at the end of each phase to assess compliance.

ECG Documentation of Symptomatic Arrhythmias
Thirty-two second ECG recordings were made by patients using a precordial event recorder (Cardiomemo, Instrumedix Inc). Patients were instructed to transmit a recording at the onset of each episode of symptoms and again after the episode ceased. To encourage compliance, patients also made weekly transmissions in the absence of symptoms. At the coordinating hospital, telephone transmissions were recorded onto chart paper at 25 mm/s (Lifesigns Receiving Station, Instrumedix Inc). Recordings were checked immediately for diagnostic quality, and repeat recordings were requested if necessary. Recordings were reviewed by a blinded observer. AF was diagnosed in the presence of ≥5 consecutive irregular RR intervals with no evidence of organized atrial activity. The heart rate for each recording was calculated as an average over all beats that clearly demonstrated AF.

Ambulatory Recording
Twenty-four-hour ambulatory recordings were made at the start of each evaluation phase after loading/washout. Three-channel (modified V_c, V_1, and aVF) recorders were used to maximize P-wave visibility (model 8500, Marquette Electronics, Inc). Tapes were digitized (Laser Holter XP, Marquette Electronics, Inc) then scrutinized to confirm R-wave labeling and exclude artifact. The exact timing of onset and termination of each episode of AF (defined as above) was manually marked by operators blinded to treatment. The data were merged with an RR interval file to obtain listings of the exact time, duration, and RR intervals for each episode of sinus rhythm and AF. The details and validation of this method have been published in full elsewhere.

Statistical Methods
The study size calculation was based on the premise that arrhythmic episodes occur independently with a fixed probability for each patient in any given time. The target number of 40 completed patients was calculated to give 90% power to detect a 3-fold increase in mean interval between attacks.

The study end point was the time to the second documented attack of AF (t_2), censored after 61 days. This was initially examined with Kaplan-Meier product-limit survival estimates. To make use of the paired data, the difference in t_2 between the first and second treatment periods (t_2−t_1) was calculated. The null hypothesis that t_2−t_1 did not differ according to treatment order (digoxin-placebo and placebo-digoxin) was examined by use of the Mann-Whitney test. For a numerical estimate of treatment effect, the Cox proportional hazards model, adapted to the analysis of failure times in crossover studies, was used (hazards being treatment and treatment period). Identical analyses were made of the intervals to the first documented attacks of AF. Mean heart rates during recordings were compared by parametric methods for crossover trials. Data resulting from ambulatory recordings were analyzed by nonparametric methods. Statistical analysis used SPSS for Windows (v6.0, SPSS Inc) and a program written for SAS/Stat software (v6.07, SAS Institute Inc). A 2-tailed P<0.05 was considered statistically significant.

Results
Patients
One hundred ninety patients with ≥1 episode of AF in the preceding 6 months were registered during recruitment. Of these, 113 failed to meet the entry criteria for the following reasons: insufficient symptom frequency (33), digoxin contraindicated (6), withdrawal of antiarrhythmic therapy contraindicated (12), withdrawal of amiodarone considered inappropriate (10), history of cerebral embolism (2), reversible cause for AF (3), pacemaker (3), patient refusal (22), physician declined because of probable poor compliance (13), or unspecified reasons (13). The remaining 77 patients were screened: randomization continued until 40 patients com-
completed the double-blind phase with documentation of at least 1 episode of AF. Two patients had no symptomatic episodes of AF during double-blind treatment, and a third withdrew consent on the day of randomization: these 3 patients were replaced, so that 43 patients were randomized. Table 1 summarizes clinical and echocardiographic features of the patients in the registry and randomized phases, which showed no significant differences. Echocardiography was not mandatory for the registry, but data were available in 144 patients (76%). Thirty-eight patients had a history of prior antiarrhythmic drug treatments: digoxin (32), Vaughan Williams class 1 (24), β-blocker (19), amiodarone or sotalol (19), and verapamil/diltiazem (13). These treatments were continuing in 22 patients up to screening for the present study; prior treatments had been discontinued due to inefficacy (43), side effects (27), or unspecified reasons (25).

**Digoxin Dosing and Levels**

Of the 40 patients evaluated, 20 had been randomized to each treatment order. During active treatment, 11 patients required an increase from the initial dose to achieve desired plasma levels; no patient required dose reduction. Final daily doses were 250 μg in 5 patients, 375 μg in 28 patients, and 500 μg in 7 patients. The mean±SD digoxin level on the final dose of active treatment was 1.29±0.35 nmol/L (1.01±0.27 μg/L). Plasma digoxin levels measured during placebo treatment were all <0.1 nmol/L. Residual tablet counts confirmed >95% compliance in all patients.

**Patient-Activated Recordings**

Digoxin was associated with a decrease in the frequency of documented symptomatic AF. The median interval before 2 transmitted attacks of AF was 13.5 days on placebo and 18.7 days on digoxin (P=0.041). The numbers of patients transmitting 0, 1, and 2 (the maximum) AF episodes were 0, 4, and 36 on placebo and 3, 5, and 32 on digoxin, respectively (P=NS). The estimated relative risk (95% CI) of 2 symptomatic AF recurrences on placebo compared with digoxin was 2.19 (1.07 to 4.50). Similarly, the median interval before the first attack was 3.5 days on placebo and 5.4 days on digoxin (P=0.037; relative risk, 1.69 [0.88 to 3.24]). Survival curves for the time to the first and second documented attacks of AF, based on Kaplan-Meier product-limit estimates, are shown in Figure 2. To illustrate the estimated relative risks, average event-free survival curves were constructed for the times to the first and second attacks, and each was corrected for the estimated effects of active and placebo treatment (Figure 3). In this model, the “median survival time” (at which 50% of patients would be expected to have had a first attack) was increased from 3.2 (95% CI, 2.0 to 5.4) to 6.4 (5.0 to 10.1) days, and the median survival time to the second attack from 13.1 (95% CI, 10.2 to 15.6) to 26.7 (16.8 to 43.1) days. The mean±SD heart rate during transmissions on placebo treatment was 137.9±32.1 bpm, and that on active treatment was 125.0±35.2 bpm. The estimated effect of treatment on heart rate was a reduction of 15.0 bpm (95% CI, 4.5 to 25.6 bpm, P=0.007).

**Ambulatory Recordings**

Ambulatory recordings were considered separately, and the analysis included the 2 patients who did not transmit symp-
tomatic AF episodes. Of the 42 pairs of recordings, 41 made on digoxin (mean duration, 24.6 ± 0.5 hours) and 37 made on placebo (mean duration, 24.8 ± 0.5 hours) were of sufficient quality throughout to be included in analysis. These contained 1076 episodes of AF, whose duration ranged from 5 beats to the entire duration of the recording. The number of episodes per recording varied from 0 to 138. To avoid skewing by those recordings showing large numbers of AF episodes, measures of heart rate were calculated as the mean over all the AFs in each recording.

The principal results of this analysis are shown in Table 2. No significant difference was detected between digoxin and placebo in terms of the number of AF episodes, their duration, the mean ventricular rate during AF overall, or the mean ventricular rate at the start of AF episodes. The analysis also failed to detect differences between placebo and digoxin when limited to AF episodes of >30 seconds’ duration and when daytime (8 AM to 8 PM) and nighttime (10 PM to 6 AM) episodes were analyzed separately.

**Treatment Failures and Side Effects**

On 3 occasions, treatment was discontinued on clinical grounds after a single attack of AF: this occurred twice on placebo medication and once on digoxin. Two patients reported gastrointestinal disturbances: this was minor in the first, but the second patient stopped study medication after 28 days of monitoring and 1 documented attack of AF: his data were censored at that point. In both patients, side effects occurred during active treatment: their digoxin levels were 1.5 and 2.2 nmol/L, respectively. No other side effects were reported.

**Discussion**

Digitalis glycosides have been used to treat AF for more than 2 centuries. However, their only known clinical benefits are a reduction in resting ventricular rate in patients with chronic AF and a modest inotropic effect: there is no evidence of a primary antiarrhythmic action. Retrospective studies suggest that digoxin does not affect the ventricular response during paroxysmal AF episodes, and randomized studies have found it ineffective in terminating acute AF. The vagotonic action of digitalis may even be proarrhythmic at the atrial level: cholinergic stimuli cause a nonuniform reduction in conduction velocity and effective refractory period and are used to facilitate AF induction in smaller animals. Increased arrhythmia frequency has been attributed to digoxin in individuals with paroxysmal AF, but controlled data have hitherto been lacking.

The principal goal of antiarrhythmic drug therapy in AF is to improve symptoms. Accordingly, the frequency of symptomatic AF episodes was the main object of study in this trial. Although subjective measures such as symptom diaries, physicians’ impressions of symptomatic status, and even the continuance of therapy have been used as primary study end points, ECG documentation of symptomatic episodes is advantageous. In the present study, event recorders were used: these were preferred to Holter monitoring, because the

**TABLE 2. Analysis of Ambulatory Recordings**

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of Tapes (Placebo: Digoxin)</th>
<th>Placebo (Mean ± SD)</th>
<th>Digoxin (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of AF episodes</td>
<td>37:41</td>
<td>16.0 ± 31.2</td>
<td>11.8 ± 22.0</td>
<td>0.126</td>
</tr>
<tr>
<td>No. AF episodes per hour</td>
<td>37:41</td>
<td>0.6 ± 1.2</td>
<td>0.5 ± 0.9</td>
<td>0.150</td>
</tr>
<tr>
<td>Total minutes of AF*</td>
<td>37:41</td>
<td>105.5 ± 220.0</td>
<td>115.9 ± 269.7</td>
<td>0.137</td>
</tr>
<tr>
<td>AF episode duration*</td>
<td>22:24</td>
<td>70.8 ± 130.7</td>
<td>84.4 ± 279.2</td>
<td>0.736</td>
</tr>
<tr>
<td>Ventricular rate during AF†</td>
<td>20:21</td>
<td>121.5 ± 29.0</td>
<td>118.4 ± 24.1</td>
<td>0.223</td>
</tr>
<tr>
<td>Ventricular rate at start of AF‡</td>
<td>19:21</td>
<td>120.1 ± 25.9</td>
<td>122.9 ± 23.7</td>
<td>0.668</td>
</tr>
</tbody>
</table>

*Calculated from all tapes containing AF episodes, irrespective of length.
†Calculated over all AF episodes lasting ≥30 seconds on recording.
‡First 30 seconds of all AF episodes lasting ≥30 seconds on recording.
latter is not practical over extended periods and correlates poorly with symptoms.22–24 Because of the large interindividual variation in attack frequency, the end point selected was a fixed number of episodes rather than a fixed monitoring period, and a crossover design was used to increase statistical power.25–27 The design selected a representative group of patients, able to document recurrent symptomatic paroxysmal AF, for whom neither digitalis nor placebo treatment would be contraindicated. To avoid bias, previous treatment with digitalis or other drugs was neither required nor a contraindication.

The study found that digoxin reduced the frequency of symptomatic attacks of paroxysmal AF. The relative risks (placebo:digoxin) for the times to first and second attacks were 1.69 and 2.19, respectively. If seen uniformly in the population studied, this effect would correspond to a doubling of the median event-free survival times (Figure 3).

The estimated effect of digoxin, although statistically significant, is small compared with that of other drugs. Flecainide was evaluated in symptomatic paroxysmal AF in a trial of similar design and sample size.25 The increase in median interval between actual attacks was >400% with flecainide and was ≈50% with digoxin in the present study. Likewise, a study with a broadly similar design found the relative risk of first arrhythmia recurrence to be 6.8 on placebo compared with high-dose propafenone26: the same calculations8 showed a relative risk of 1.7 for the times to first recurrence with digoxin in the present study. It should be noted that the Kaplan-Meier curves illustrating treatment effect in the flecainide study came from the raw data, whereas those used in the propafenone study were derived from the treatment by France et al8: a comparison of Figures 2 and 3 highlights the difference between data treatments.

The explanation for the observed effect of digoxin on the frequency of arrhythmic symptoms is of interest. A direct atrial antiarrhythmic action cannot be excluded, but no such effect has been described experimentally or clinically. As discussed earlier, digoxin might even be expected to promote AF. The inotropic action of digoxin on the ventricles may cause an indirect effect on atrial electrophysiology by reducing wall stress, but there is no evidence to support this.

A more plausible explanation is that the arrhythmia itself is unaffected by digoxin but that any reduction in ventricular rate or irregularity during AF causes more attacks to be asymptomatic. The ventricular rate appears to be an important determinant of symptoms in paroxysmal AF.28 Although 2 studies failed to demonstrate that digitalis slows the ventricular rate during AF episodes, both were retrospective and therefore possibly biased and may have been underpowered, because their data were few and unpaired.10,11 During both flecainide and placebo treatment, Anderson et al22 found that the ventricular rate during symptomatic AF episodes was ≈10 bpm lower in patients taking digoxin than in others. In the present study, the documented rate during symptomatic AF episodes was limited to daytime, nighttime, or the onset of AF episodes. It is possible that the symptomatic benefit from digoxin derives from more subtle effects. We have previously noted that during AF, digoxin causes significant reductions in both the irregularity of RR intervals at high rates and the overall variability of RR interval distributions.29,30 Although these findings provide a plausible explanation for symptom reduction, they do not account for the reduced ventricular rate seen during patient-activated recordings. It remains possible that the symptomatic effect derives from a reduction in ventricular rate that was simply not detected by ambulatory monitoring. Thus, despite the large number of AF episodes recorded, this study highlights the inadequacy of ambulatory monitoring in the detection of modest changes in arrhythmia frequency or ventricular rate against a background of great interindividual and intrindividual variability. Such treatment effects would not be detectable by ambulatory monitoring other than in patients with exceptionally frequent arrhythmia, whose mechanism appears to be unusual.31 The study also highlights our poor understanding of the determinants of symptom severity in this condition.

Limitations
This study examined a small patient group, with a lower age and less structural heart disease than the AF population as a whole.32 However, published epidemiological data relate largely to patients with permanent AF. Our registry indicates that the study group was indeed representative of patients attending hospital with symptoms caused by paroxysmal AF. As discussed above, although this study did not detect a significant effect on arrhythmia burden or ventricular rate by ambulatory monitoring, such an effect cannot be excluded.

Conclusions
Digoxin reduces the frequency of symptomatic episodes of paroxysmal AF. This may be due to a reduction in the ventricular rate or irregularity during AF, rather than a true antiarrhythmic action. Its benefit is marginal compared with that of other drugs. However, digoxin does not appear to be detrimental and need not be discontinued in patients with paroxysmal AF if indicated for other reasons.

Acknowledgment
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Appendix

CRAFT-1 Participants
Drug assay and dosing: Terence Lee, David Holt. Central pharmacy: Christopher Cairns. Transtelephonic ECG reception: Dynpma O’Farrell, Sharon Welby, Julie Critchley, and the Staff of the Cardiac High Dependency Unit, St George’s Hospital.

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