Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation: A prospective, randomized clinical trial

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Purpose The role of digoxin and verapamil in the control of ventricular response in rapid atrial fibrillation is well established. This study investigates how clonidine compares with these standard therapies in rate control for new-onset rapid atrial fibrillation. We set out to test the hypothesis that clonidine effectively reduces heart rate in patients with new-onset rapid atrial fibrillation.

Subjects and Methods Forty patients were seen in the emergency department with new-onset (≤24 hours' duration), stable, rapid atrial fibrillation. Eligible patients were randomized to receive either clonidine, digoxin, or verapamil. Changes in heart rate and blood pressure over 6 hours, as well as frequency of conversion to sinus rhythm were recorded and analyzed.

Results The mean reduction in heart rate over 6 hours was 44.4 beats/min (95% confidence interval [CI] 28.4-60.4 beats/min) in the clonidine group, 52.1 beats/min (95% CI 40.8-63.4 beats/min) in the digoxin group, and 41.8 beats/min (95% CI 22.5-61.0 beats/min) in the verapamil group. Analysis of variance of the heart rate changes in the 3 groups after 6 hours was not significant (P = .55). At 6 hours, 7 of 12 clonidine patients, 8 of 15 digoxin patients, and 7 of 13 verapamil patients remained in atrial fibrillation (P = .962 on χ²).

Conclusion Clonidine controls ventricular rate in new-onset atrial fibrillation with an efficacy comparable to that of standard agents. (Am Heart J 2001;142:e3.)

Despite extensive literature on the subject, the acute management of rapid atrial fibrillation remains controversial. Pharmacologic management for acute rate control has consisted primarily of treatment with digitalis, calcium channel blockers, and β-blockers. 1-3 Sympathetic tone is known to play an important role in the genesis and maintenance of atrial fibrillation, as well as in the degree of atrioventricular node conduction and ventricular response. 4 It seems reasonable therefore to postulate that efforts to reduce sympathetic tone may result in better control of the ventricular rate in atrial fibrillation and perhaps also contribute to the restoration of sinus rhythm. Clonidine, an imidazolone, decreases discharges in sympathetic preganglionic fibers in the splanchnic nerve and in postganglionic fibers of cardiac nerves. 5 In addition, it acts directly at α₂-receptors in the lower brainstem region to suppress sympathetic outflow. 6 Clonidine also stimulates parasympathetic outflow, resulting in prolongation of the refractoriness of the atrioventricular node. It is through this shift in the balance of sympathetic and parasympathetic tone that clonidine may benefit patients with atrial fibrillation. So far, findings from a placebo-controlled study have suggested that clonidine is effective when used to control ventricular responses in patients with new-onset rapid atrial fibrillation. 7 We set out to test the hypothesis that clonidine effectively reduces heart rate in this patient group. We also wished to determine whether it is as effective as traditional treatments for acute rate control.

Methods We conducted a randomized, nonblinded clinical trial comparing clonidine with digoxin and verapamil in the treatment of new-onset rapid atrial fibrillation (see Table I for the medication protocol). Patients were assigned to 1 of 3 medication treatments in an un concealed manner (assignments were based on the final digit of patients' hospital identification numbers). Patients were followed up for a 6-hour period. The api-
cal heart rate, a 12-lead electrocardiogram, blood pressure, heart rhythm, and symptoms were all recorded at 0, 0.5, 1, 2, 3, 4, and 6 hours. At 6 hours subjects exited the study. Adult patients seen in the emergency departments of the 2 acute-care hospitals in Kingston, Ontario, Canada, were considered for entry into the study if they were in atrial fibrillation with a ventricular response exceeding 100 beats/min and if the symptoms had begun within the preceding 24 hours. Patients were specifically excluded if they had significant hemodynamic instability, were unable to take oral medications, had a pre-excitation syndrome, were currently on one of the three study drugs, or were unable or unwilling to give informed consent. The trial protocol was reviewed and approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

Analysis
The primary end point of the study was heart rate reduction. We also examined blood pressure changes and the rate of conversion to normal sinus rhythm. Changes in heart rate and blood pressure within groups between time 0 and time 6 hours were analyzed with the paired t test. These changes were also evaluated with 95% confidence intervals (CIs). Intergroup comparisons were made by analysis of variance (ANOVA) and unpaired t tests with Bonferroni correction of the calculated P values. The incidence of conversion to normal sinus rhythm was analyzed with the χ² test. An α value of 0.05 was used in all statistical tests. Power calculations showed that, with an average of 13 patients per treatment group, we had 81% power (ie, type II error rate 0.19) to detect between-group heart rate differences of 10 beats/min (assumptions for this calculation: μ₁ = 95 beats/min, μ₂ = 105 beats/min, σ = 9 beats/min).

Results
Study population
Patients were enrolled between May 7, 1994, and January 1, 1996. During this time 141 patients were admitted with a primary diagnosis of rapid atrial fibrillation. Of those, 82 were treated before they could be considered for enrollment. The remaining 59 were evaluated and considered for entry into the study. Forty-two of the 59 met eligibility criteria and were asked to participate in the study; 40 agreed to do so. Of the 17 who did not meet eligibility criteria, 6 were already on digoxin and 11 had atrial fibrillation that, by history, had been present for more than 24 hours. The eligibility criteria were therefore satisfied by 71% of those referred for consideration. All 40 patients were recruited from the emergency departments, all were admitted to the hospital, and all completed the 6-hour protocol. The baseline characteristics of the study patients are shown in Table II. Despite the randomization process, a greater proportion of women was randomized to the clonidine group compared with the other 2 groups.

Heart rate reduction
The change in heart rate over the 6-hour duration of the study is shown in Figure 1. The heart rate at time 0 was similar between groups (mean 135.0 beats/min, SD 15.6 beats/min for the clonidine group, mean 139.1 beats/min, SD 24.6 beats/min for the digoxin group, and mean 135.3 beats/min, SD 26.8 beats/min for the verapamil group). The mean reduction in heart rate over 6 hours was 44.4 beats/min (95% CI 28.4-60.4 beats/min) in the clonidine group, 52.1 beats/min (95% CI 40.8-63.4 beats/min) in the digoxin group, and 41.8 beats/min (95% CI 22.5-61.0 beats/min) in the verapamil group. ANOVA of the heart rate changes in the 3 groups after 6 hours was not significant (P = .55). Changes in heart rate for those patients remaining in atrial fibrillation throughout the study (ie, for the entire 6-hour period) were also examined. Again, the heart rate at time 0 was similar between groups (mean 134.3 beats/min, SD 18.5 beats/min for the clonidine group, n = 7; 139.4 beats/min, SD 24.3 beats/min for the digoxin group, n = 8; and 129.7 beats/min, SD 21.2 beats/min for the verapamil group, n = 7). The mean reduction in heart rate over 6 hours was 28.7 beats/min (95% CI 12.4-45.0 beats/min).
beats/min) in the clonidine group, 47.0 beats/min (95% CI 30.6-63.4 beats/min) in the digoxin group, and 21.6 beats/min (95% CI 6.5-36.7 beats/min) in the verapamil group. ANOVA of the heart rate changes at 6 hours for patients remaining in atrial fibrillation was significant ($P = .035$). Unpaired $t$ tests with Bonferroni correction for pairwise comparisons were not significant with the exception of the digoxin-verapamil comparison ($P = .040$).

Figure 2 shows intergroup comparisons for patients remaining in atrial fibrillation at various time intervals. The verapamil group had a greater reduction in heart rate compared with the other 2 groups at 0.5 hours ($P = .007$) and at 1 hour ($P = .027$), but no differences could be demonstrated between groups at 2, 3, or 4 hours. By 6 hours the subjects in the digoxin group who remained in atrial fibrillation had a lower mean heart rate than did subjects in the verapamil group who were still in atrial fibrillation (digoxin: mean 92.4 beats/min, SD 9.1 beats/min vs verapamil mean 108.1 beats/min, SD 15.3 beats/min), but the difference was not significant ($P = .120$). The clonidine group remaining in atrial fibrillation at 6 hours had a mean heart rate that was not significantly different than either of the other 2 groups, although there was a trend toward better control with digoxin (clonidine: mean 105.6 beats/min, SD 16.6 beats/min, vs digoxin: 92.4 beats/min, SD 9.1 beats/min; $P = .242$).

Conversion to normal sinus rhythm

Figure 3 depicts the proportion of patients remaining in atrial fibrillation in each of the 3 groups at various time intervals. At 6 hours the proportion of patients remaining in atrial fibrillation was very similar (7/12 clonidine patients, 8/15 digoxin patients, and 7/13 verapamil patients remained in atrial fibrillation) and $\chi^2$ analysis did not demonstrate a statistically significant difference among groups ($P = .962$). However, conversion to sinus rhythm was achieved more quickly in the clonidine and digoxin group compared with patients in

Table II. Baseline characteristics of study patients in the 3 treatment groups: clonidine, digoxin, and verapamil

<table>
<thead>
<tr>
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<th>Clonidine</th>
<th>Digoxin</th>
<th>Verapamil</th>
</tr>
</thead>
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<tr>
<td>No. of patients</td>
<td>12</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Percent male</td>
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<td>67</td>
<td>72</td>
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<td>Mean heart rate [beats/min [SD]]</td>
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<td>139 [25]</td>
<td>135 [27]</td>
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<tr>
<td>Mean systolic blood pressure [mm Hg [SD]]</td>
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<td>137 [24]</td>
<td>130 [24]</td>
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<tr>
<td>Mean diastolic blood pressure [mm Hg [SD]]</td>
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<td>80 [12]</td>
<td>80 [10]</td>
</tr>
<tr>
<td>History of paroxysmal atrial fibrillation</td>
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<td>3</td>
</tr>
<tr>
<td>History of chronic atrial fibrillation</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid disease*</td>
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</tbody>
</table>

*Measured thyroid-stimulating hormone at presentation outside the normal range.

Figure 2

Heart rate change over time for patients remaining in atrial fibrillation after 6 hours of treatment with clonidine, digoxin, or verapamil.

Figure 3

Percentage of patients remaining in atrial fibrillation at each time interval during treatment with clonidine, digoxin, or verapamil.
the verapamil group, although this difference was not statistically significant (P = .40 for χ² analysis at 2 hours).

**Systolic blood pressure changes**

In the clonidine group a mean change in systolic blood pressure of -18 mm Hg (95% CI -29.5 to -6.5 mm Hg) was observed. Although this drop in systolic blood pressure was statistically significant, it did not result in symptoms attributable to hypotension in any of the clonidine subjects. The digoxin group had a mean change of 2.1 mm Hg (95% CI -7.9 to 12.1 mm Hg) and the verapamil group had a mean change of -7.2 mm Hg (95% CI -17.9 to 3.6 mm Hg). ANOVA for the difference in systolic pressure at 6 hours was significant (P = .023). Pairwise comparisons between groups were not significant with the exception of the comparison between the digoxin and clonidine groups (P = .019).

**Diastolic blood pressure changes**

The clonidine group showed a mean change of -8.7 mm Hg, SD 19.4 mm Hg (95% CI -21.0 to 3.7 mm Hg, P = .151). The digoxin group had a mean change of -0.9 mm Hg (95% CI -6.4 to 4.5 mm Hg), and the verapamil group had a mean change of -6.8 mm Hg (95% CI -12.2 to -1.3 mm Hg). ANOVA and pairwise comparisons did not demonstrate any significant inter-group differences (P = .2897 on ANOVA).

**Adverse effects**

Symptoms (lightheadedness and palpitations) reported as “adverse effects” occurred in 2 patients from each group. All symptomatic subjects in the study reported their symptoms at time 0, before medications were administered. Four of the 6 symptomatic patients (2 in the clonidine group, 1 each in the other 2 groups) converted to sinus rhythm and their symptoms resolved. The other 2 patients (both in the digoxin group) reported some easing of the symptoms at 6 hours. These reported symptoms therefore appeared to represent symptoms of atrial fibrillation rather than adverse effects to the medication.

**Discussion**

The role of digoxin and verapamil in the control of ventricular response in atrial fibrillation is well established.8 β-Blocker therapy is also standard treatment for rate control in new-onset atrial fibrillation. In recent years intravenous diltiazem has also been established as a very safe and effective means of rate control.9-12 (We did not include a diltiazem arm in our study because it was unavailable at our center at the time.) These “tried and true” therapies have firmly established themselves as safe, effective, and well tolerated. Why, then, was it necessary to study the role of clonidine in this popula-

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ure, and conversion to normal sinus rhythm) were objective and not likely to be subject to significant observer or subject bias. Second, randomization was not concealed. Although this has the potential to introduce selection bias, Table II reassuringly shows that baseline heart rate and blood pressure were similar across groups. Third, we did not use a placebo arm because this would have meant that some patients would have gone untreated for 6 hours. Roth et al., however, found in their placebo group a spontaneous rate change of $-15 \pm 16.8$ beats/min over 4 hours. This does not approach the magnitude of change seen in each of our 3 treatment groups. Fourth, the study was small. Although we anticipated sufficient power to detect clinically significant differences in the main group comparisons, the subgroup comparisons were underpowered. Even for the main group comparisons we may have been somewhat underpowered because the SDs for heart rate were higher than the value of 9 that we had anticipated in our power calculation. Also, although the 3 medications appear to be similarly efficacious with respect to rate control and conversion to normal sinus rhythm, we cannot exclude the possibility that with a larger sample size our study might have shown significance for smaller differences among the 3 groups. Last, although the dosing protocols for digoxin and verapamil were standardized in this study, the dosing of clonidine was empirically determined. A more aggressive protocol using higher or more frequent doses might have eliminated the observed trend in favor of digoxin.

Conclusions

This study helps to place the previous study by Roth et al.7 in context. Clonidine results in a significant reduction in heart rate in patients with new-onset rapid atrial fibrillation, with an efficacy comparable to standard treatment. It appears to be a potential alternative to standard agents in the management of these patients, although larger studies may be required to establish its safety profile, efficacy, and optimal dosing. Although its low cost, wide availability, and easy administration make it a potentially attractive addition to the pharmacologic armamentarium against atrial fibrillation, its relatively slow onset of action and potential for blood pressure reduction may be a disadvantage for some patients. Given that clonidine appears to be effective as a rate-controlling drug in new-onset atrial fibrillation, further studies may now be indicated to explore the potential for this drug as a long-term rate-controlling agent in chronic atrial fibrillation.

References