Irbesartan Reduces QT Dispersion in Hypertensive Individuals

Pitt O. Lim, Marleen Nys, Abdullah A.O. Naas, Allan D. Struthers, Mary Osbakken, Thomas M. MacDonald

Abstract—Angiotensin type 1 receptor antagonists have direct effects on the autonomic nervous system and myocardium. Because of this, we hypothesized that irbesartan would reduce QT dispersion to a greater degree than amlodipine, a highly selective vasodilator. To test this, we gathered electrocardiographic (ECG) data from a multinational, multicenter, randomized, double-blind parallel group study that compared the antihypertensive efficacy of irbesartan and amlodipine in elderly subjects with mild to moderate hypertension. Subjects were treated for 6 months with either drug. Hydrochlorothiazide and atenolol were added after 12 weeks if blood pressure (BP) remained uncontrolled. ECGs were obtained before randomization and at 6 months. A total of 188 subjects (118 with baseline ECGs) were randomized. We analyzed 104 subjects who had complete ECGs at baseline and after 6 months of treatment. Baseline characteristics between treatments were similar, apart from a slight imbalance in diastolic BP (irbesartan [n=53] versus amlodipine [n=51], 99.2 [SD 3.6] versus 100.8 [3.8] mm Hg; P=0.03). There were no significant differences in BP normalization (diastolic BP <90 mm Hg) between treatments at 6 months (irbesartan versus amlodipine, 80% versus 88%; P=0.378). We found a significant reduction in QT indexes in the irbesartan group (QTc dispersion mean, –11.4 [34.5] milliseconds, P=0.02; QTc max, –12.8 [35.5] milliseconds, P=0.01), and QTc dispersion did not correlate with the change in BP. The reduction in QT indexes with amlodipine (QTc dispersion, –9.7 [35.4] milliseconds, P=0.06; QTc max, –8.6 [33.2] milliseconds, P=0.07) did not quite reach statistical significance, but there was a correlation between the change in QT indexes and changes in systolic BP. In conclusion, irbesartan improved QT dispersion, and this effect may be important in preventing sudden cardiac death in at-risk hypertensive subjects. (Hypertension. 1999;33:713-718.)

Key Words: irbesartan ■ amlodipine ■ electrocardiography ■ QT dispersion ■ aged ■ hypertension, essential

QT dispersion is the difference between maximal and minimal QT intervals within a 12-lead surface electrocardiogram (ECG).1 It is thought to represent the degree of repolarization inhomogeneity in the heart.2 Abnormal values are found in heart failure and myocardial infarction, and these are predictive of a high rate of malignant arrhythmias and of sudden death.3,4 In the elderly hypertensive population, a raised QTc dispersion (>60 milliseconds) is associated with a 2-fold increase in sudden cardiac death.5 A reduction in QT dispersion is observed after successful thrombolytic therapy in acute myocardial infarction and parallels a decreased risk of arrhythmic cardiac death.6 QTc dispersion is increased in left ventricular hypertrophy (LVH)7 and in hypertension.8,9 and abnormal QT dispersion may be an early indicator of end-organ damage involving the heart in hypertension. Since angiotensin II and aldosterone have been implicated in myocyte hypertrophy10 and cellular matrix modification,11 respectively, we hypothesized that an angiotensin II antagonist would reduce QT dispersion. The aim of the present study was to test the hypothesis that irbesartan would favorably reduce indexes of QT dispersion compared with amlodipine, a highly selective vasodilator.

Methods

Subjects

Males and postmenopausal females aged 65 years or older with established or newly diagnosed mild to moderate essential hypertension (diastolic blood pressure [DBP] 95 to 110 mm Hg) were recruited. Exclusion criteria included seated systolic BP (SBP) >200 mm Hg and known or suspected secondary hypertension. Seated BP was measured with a standard mercury sphygmomanom-
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eter, with 3 readings taken 1 minute apart averaged. Subjects underwent assessment to exclude those with significant cardiovascular, neurological, endocrinologic, renal, pulmonary, or gastrointestinal disease or malignancy. This study had the approval of local ethical committees, and informed written consent was given by all subjects at the time of enrollment.

Study Design

This was a randomized, multinational, multicenter, double-blind study in elderly ($\geq 65$ years of age) subjects with mild-to-moderate essential hypertension (seated DBP, 95 to 110 mm Hg). This trial was conducted in 32 centers (Australia, 8; Canada, 4; New Zealand, 2; United Kingdom, 18). Subjects recruited into the study initially underwent a single-blind placebo lead-in period of 4 to 5 weeks. Subjects with DBP 95 to 110 mm Hg at the end of this period were then randomized to either irbesartan or amlodipine. The starting dose of irbesartan was 75 mg and of amlopidine, 5 mg. The doses of the respective agents were doubled (irbesartan, 150 mg; amlopidine, 10 mg) at week 6 or anytime thereafter to week 24 for seated trough DBP $\geq$90 mm Hg. If DBP remained elevated during use of the study drug, open-label hydrochlorothiazide (12.5 mg titrated to 25 mg) followed by open-label atenolol (50 mg titrated to 100 mg) was added at week 12 or thereafter. The therapeutic response at the end of the treatment period was defined as normalized if trough DBP was $<$90 mm Hg.

Electrocardiography

Standard 12-lead ECGs were recorded using a paper speed of 25 mm/s. These were obtained at baseline and after completion of the study, generally after 24 weeks of therapy. A single observer (A.A.O.N.) blinded to other measurements and treatment groups analyzed all ECGs. The methodology used in measuring QT intervals (QT dispersion, QTc dispersion, and QTc max), which has intraobserver coefficients of variation of $<8\%$, has been described elsewhere.5,15,18

Statistical Analysis

Descriptive statistics are expressed as mean (SD). Within-treatment regimen changes from baseline in the QT indexes (QT dispersion, QTc dispersion, and QTc max) were analyzed using paired t tests. Analysis of covariance (ANCOVA) was used to compare the regimens with regard to changes from baseline in the QT indexes. The ANCOVA models included terms for treatment group, baseline DBP, and the corresponding QT index. Model and distributional assumptions inherent in the ANCOVA analyses were assessed. The Pearson correlation coefficients between changes from baseline in the above QT indexes and the change from baseline in BP were calculated. All statistical tests were two-tailed, and a probability value $\leq 0.05$ was considered significant.

Results

Of a total enrollment of 352 subjects, 188 were randomized to receive the double-blind treatment regimen. Thirty-six subjects with unsuitable ECGs were excluded (poor-quality ECG tracings, 25; atrial fibrillation, 2; significant ST abnormalities, 6; multiple ventricular ectopies, 1; and left bundle branch block, 2). A total of 118 subjects had good-quality baseline ECGs, and within this group, 104 also had ECGs performed at week 24. There were no statistically significant treatment differences in demographic characteristics or in baseline efficacy characteristics, apart from a slight imbalance in DBP (Table 1). At the end of the treatment period, BP response rates were similar ($P=0.378$), but there was a reduction in resting heart rate in the irbesartan group, this being statistically significant when the entire study population was considered ($n=138$) (Table 2).

### Table 1. Baseline Demographic Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Irbesartan (n=53)</th>
<th>Amlodipine (n=51)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>23</td>
<td>0.327</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51</td>
<td>51</td>
<td>0.495</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>70.7 (4.6)</td>
<td>70.4 (4.9)</td>
<td>0.776</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.8 (13.2)</td>
<td>77.8 (14.8)</td>
<td>0.275</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.7 (10.6)</td>
<td>167.1 (9.8)</td>
<td>0.480</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>10.9 (9.7)</td>
<td>9.0 (8.0)</td>
<td>0.270</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>167.3 (17.2)</td>
<td>171.4 (15.5)</td>
<td>0.208</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>99.2 (3.6)</td>
<td>100.8 (3.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.3 (10.3)</td>
<td>78.5 (11.1)</td>
<td>0.287</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>74.1 (27.8)</td>
<td>73.5 (28.4)</td>
<td>0.911</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>77.0 (27.2)</td>
<td>78.0 (30.4)</td>
<td>0.869</td>
</tr>
<tr>
<td>QTc max, ms</td>
<td>509.1 (37.2)</td>
<td>510.1 (37.0)</td>
<td>0.888</td>
</tr>
</tbody>
</table>

Values are mean (SD). *P<0.05.

The use of adjunctive therapy (Table 2) was not significantly different with respect to $\beta$-blockade, which may potentially confound this study. As for diuretic use, a third of subjects in the irbesartan group and a quarter of those on amlopidine were on this additional therapy. Diuretic use may cause hypokalemia, which may increase QT dispersion.19 Serum potassium levels were unchanged in the irbesartan group. This cannot be explained by altered renal handling of potassium20 in the short term, although irbesartan may conserve potassium in the long term by modulating aldosterone.

### Table 2. Hemodynamic Profile, Serum Potassium, and Need for Adjunctive Therapy at End of the Study Period

<table>
<thead>
<tr>
<th>Hemodynamic Profile</th>
<th>Irbesartan (n=53)</th>
<th>Amlodipine (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>145.2 (17.2)</td>
<td>144.6 (12.7)</td>
</tr>
<tr>
<td>$\Delta$SBP, mm Hg</td>
<td>$-22.1 (17.3)^*$</td>
<td>$-26.2 (15.2)^*$</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>86.5 (5.4)</td>
<td>83.7 (5.9)</td>
</tr>
<tr>
<td>$\Delta$DBP, mm Hg</td>
<td>$-13.0 (6.5)^*$</td>
<td>$-16.9 (7.6)^*$</td>
</tr>
<tr>
<td>Percentage of responders†</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>72.1 (10.5)</td>
<td>76.8 (9.1)</td>
</tr>
<tr>
<td>$\Delta$HR, bpm‡</td>
<td>$-2.3 (9.4)$</td>
<td>$-1.5 (8.4)$</td>
</tr>
<tr>
<td>$\Delta$Serum potassium, mmol/L</td>
<td>0.02 (0.41)</td>
<td>$-0.25 (0.43)^*$</td>
</tr>
</tbody>
</table>

Adjuvative therapy§

| Hydrochlorothiazide, n (%)   | 18/49 (37%)       | 12/47 (26%)       |
| Atenolol, n (%)             | 1/49 (2%)         | 2/47 (4%)         |

Values are mean (SD). End of the study period was week 24. HR indicates heart rate.

*P<0.05, compared with baseline.
†Responder: DBP $<90$ mm Hg.
‡Data from the entire study population, adjunctive $\beta$-blockade: irbesartan group (3 [4%]) vs amlopidine group (2 [3%]).
§Data not available for 8 subjects.
secretion. There was, however, a small but significant reduction in serum potassium in the amlodipine group. This level of change is unlikely to be of any consequence. Therefore, adjunctive therapy does not contribute to the overall interpretation of the results of the present study.

There were statistically significant reductions in QT indexes in the irbesartan group, but in the amlodipine group, these reductions did not quite reach statistical significance (Table 3). Changes in QT indexes did not differ significantly between the treatments, but there was a consistent trend toward greater reduction in the irbesartan group. There was a significant and consistent positive correlation between the change in QT dispersion and SBP in the amlodipine group that was not seen in the irbesartan group (Table 4 and the Figure).

Discussion
This multicenter, randomized, double-blind study demonstrated a significant reduction in QT indexes with irbesartan. As for the amlodipine group, the reduction in QT indexes did not quite reach statistical significance. Changes in QT dispersion in the irbesartan group did not relate to BP lowering, suggesting that at least some of this effect may be independent of the antihypertensive effect. However, there was an associated reduction in heart rate with treatment. Correcting for heart rate and controlling for BP did not alter this effect of irbesartan. In contrast, although amlodipine failed to significantly reduce QT indexes, the changes in QT indexes correlated positively with the corresponding reduction in SBP. Any agent that reduces BP may also reduce QT dispersion to some degree because of a mechanoelectrical feedback mechanism. The fact that BP reduction and QT dispersion reduction were well-correlated in the amlodipine group suggests that BP reduction per se played a large part in its effect on QT dispersion. Although it is well-established that QT dispersion correlates with baseline BP level, the relationship between the change in BP due to therapeutic intervention and the associated change in QT dispersion has not been previously demonstrated.

Mayet and colleagues studied 24 hypertensive subjects treated over 6 months with a combination of ramipril and felodipine. In their uncontrolled study, heart rate after treatment was significantly reduced even following drug washout. Since their study was uncontrolled, this may have represented habituation to an initial alerting response. The alerting response may be partly due to sympathetic activation, which may have increased QT dispersion at baseline. After repeated clinic visits, this effect may be diminished, as may QT dispersion. Mayet’s group failed to find a significant correlation between changes from baseline in QT indexes with the change from baseline in BP. In another study, Gonzalez-Juanatey and colleagues followed 24 hypertensive subjects treated with long-term enalapril and reported a significant reduction in QT dispersion with treatment. Again, this was an uncontrolled study. The positive result in their study may be partly explained by the significant increase in serum potassium that occurred, which has been shown to reduce QT dispersion.

The effect of hypotensive therapy on QT dispersion is not known, as few studies have addressed this issue. There are, however, several possible mechanisms as to how irbesartan may reduce QT dispersion. One is through modulation of the autonomic nervous system, in particular, a reduction in sympathetic activity, as reflected by the reduced heart rate in our study. Angiotensin II alters autonomic function through multiple pathways, including the release of catecholamines from the adrenal glands, stimulation of the cardiac and peripheral sympathetic nervous systems, and centrally mediated reduction of vagal tone. Blocking these effects of angiotensin II reduces overall sympathoadrenal activity. A previous study from our group suggested a positive link between sympathetic activity and QT dispersion. Furthermore, survivors of ventricular fibrillation after myocardial infarction have increased QT dispersion with associated low heart rate variability, indicative of autonomic imbalance in favor of sympathetic overactivity. Reducing sympathetic tone may therefore reduce QT dispersion. Also, although

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### Table 3. Treatment Group Comparison of Mean Changes From Baseline QT Indexes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Irbesartan (n=53)</th>
<th>Amlodipine (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT dispersion, ms</td>
<td>-9.3 (34.9); CI, -18.9 to 0.3</td>
<td>-8.9 (34.0); CI, -18.5 to 0.7</td>
</tr>
<tr>
<td>P</td>
<td>0.058</td>
<td>0.067</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>-11.4 (34.5); CI, -20.9 to -1.8*</td>
<td>-9.7 (35.4); CI, -19.7 to 0.2</td>
</tr>
<tr>
<td>P</td>
<td>0.02</td>
<td>0.055</td>
</tr>
<tr>
<td>QTc max, ms</td>
<td>-12.8 (35.5); CI, -22.6 to -3.0*</td>
<td>-8.6 (33.2); CI, -18.0 to 0.7</td>
</tr>
<tr>
<td>P</td>
<td>0.011</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Values are mean (SD), with confidence interval (CI).

*P<0.05 compared with baseline.

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### Table 4. Pearson Correlation Coefficients Between Change in QT Dispersion Parameters and Change in BP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BP Change From Baseline With Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QT Dispersion</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
</tr>
<tr>
<td>∆SBP</td>
<td>-0.072</td>
</tr>
<tr>
<td>∆DBP</td>
<td>-0.248</td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
</tr>
<tr>
<td>∆SBP</td>
<td>0.373*</td>
</tr>
<tr>
<td>∆DBP</td>
<td>0.105</td>
</tr>
</tbody>
</table>

*P<0.01; †P<0.001.
cardiac ischemia/infarction is associated with an increase in QT dispersion, this effect may be largely due to sympathetic overactivity associated with a stress response. In support of this, β-blockade normalizes QT dispersion related to exercise in subjects with ischemic heart disease. If ischemia plays a significant role in increased QT dispersion, amlodipine should decrease QT dispersion. This is because hypertensive individuals, especially those with increased left ventricular mass, have reduced coronary reserve and may have occult ischemia. Amlodipine is known to release nitric oxide into coronary microvessels, as do angiotensin-converting enzyme inhibitors, and it has coronary vasodilator capacity. It is likely that modulation of the sympathetic nervous system by angiotensin-converting enzymes also contributes to the reduction in QT dispersion seen in heart failure and in hypertension.

It is tempting to suggest that LVH regression related to BP lowering plays a part in reducing QT dispersion. Certainly, animal experiments have demonstrated a dominant role of angiotensin II, where subpressor doses may lead to LVH and cardiac fibrosis. These experiments have consistently demonstrated the presence of angiotensin II type 1 (AT₁) receptor subtype within the myocardium and cardiac conduction systems. The blockade of this receptor prevents the development of LVH and reduces left ventricular mass in animal models of hypertension. AT₁ blockade also reduces heart rate. Blocking AT₁ receptors should thus retard the pathological processes that lead to increased QT dispersion. QT dispersion has been shown to be increased in LVH. Whether this effect is related to myocyte hypertrophy or cardiac fibrosis has not been established. The relationship between the change in QT dispersion and change in left ventricular mass attributable to treatment remains unproven in humans. Unlike in the rat heart, the AT₂ receptor is the predominant receptor subtype found in the human heart. Although angiotensin II has a positive inotropic effect on human atria, it has no noticeable mechanical effect on human ventricles, in contrast to its positive inotropic effect on animal

Correlations between change in QTc dispersion and SBP in irbesartan and amlodipine treatment groups. The correlation between SBP reduction and QTc dispersion reduction remains robust even after the 2 points in the bottom left hand corner of the graph are taken out in the amlodipine group; $R^2=14.6\%, P=0.007$. 

Irbesartan

\[ R^2 = 0.1\% \]

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(hamster, cat, rabbit, and rat) ventricles. The myocardial effects of AT$_1$ blockade thus may be different between animals and humans. As yet, there are no firm data characterizing the long-term effect of AT$_1$ blockade on the human heart, although early results suggest that irbesartan is more effective in reducing left ventricular mass than atenolol.

Our study was primarily designed to assess the efficacy of BP lowering comparing irbesartan and amlopidine. The effect of treatment on QT dispersion was a secondary objective. Although irbesartan reduced QT dispersion significantly within the treatment group, a differential treatment effect between irbesartan and amlopidine on the change in QT dispersion could not be demonstrated. Despite this limitation, to date our study represents the single largest randomized, controlled trial assessing the effect of BP treatment and QT dispersion in hypertension.

Hypertensive individuals have an increased risk of sudden cardiac death. A follow-up study of 214 apparently healthy hypertensive subjects (mean age, 59 years) over a mean period of 2 years reported by Galinier and colleagues suggested that 1 in 20 of these subjects died suddenly. Subjects with increased QT dispersion (>80 milliseconds) were 5 times more likely to die suddenly. Treating hypertension with an agent that reduces QT dispersion as well as BP may potentially reverse or reduce this excess risk of sudden death. However, further studies are needed to study the effect of treatment of hypertension on QT dispersion and to determine whether this reduction is related to myocyte hypertrophy or cardiac fibrosis. In addition, it is important to discover whether a reduction in QT dispersion parallels an improved prognosis.

Conclusion
In conclusion, irbesartan reduced QT dispersion in elderly hypertensive subjects after 6 months of treatment. This effect was not related to the lowering of BP alone. In contrast, the reduction in QT dispersion with amlopidine did not quite reach statistical significance. This favorable effect of irbesartan may reduce sudden cardiac death in at-risk hypertensive individuals.

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