Effects of Antiarrhythmic Drugs on Inappropriate Shocks in Patients With Implantable Cardioverter Defibrillators

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Background Patients with atrial fibrillation (AF) or congestive heart failure (CHF) are more vulnerable to inappropriate shocks from implantable cardioverter-defibrillators (ICDs), but the effect of antiarrhythmic drugs in these patients remains unknown.

Methods and Results A total of 55 patients with AF and/or CHF (New York Heart Association functional class ≥II) who had ICDs were divided into 3 groups [amiodarone (n=24), sotalol (n=12), β-blocker (n=19)] and the cumulative rates of inappropriate shocks were compared. The baseline characteristics of the 3 groups were not significantly different. The 4-year event rate of inappropriate shocks was 27.3% in the amiodarone group, 54.3% in the sotalol group, and 70.6% in the β-blocker group (amiodarone vs β-blocker: log-rank p=0.003; sotalol vs β-blocker: log-rank p=0.16; amiodarone vs sotalol: log-rank p=0.29). Amiodarone reduced the risk of inappropriate shocks significantly as compared with β-blockers (hazard ratio (HR) 0.17; 95% confidence interval (CI) 0.05–0.64; p=0.008), whereas sotalol did not (HR 0.57; 95%CI 0.19–1.68; p=0.3). Amiodarone was discontinued in 4 patients (16.7%) because of pulmonary toxicity and the dose was reduced in 4 patients (16.7%) because of a thyroid function abnormality.

Conclusions Amiodarone is more effective than sotalol or β-blockers in preventing inappropriate ICD shocks in patients with AF or CHF, but it has a significant risk of drug-related adverse effects. (Circ J 2008; 72: 102–105)

Key Words: Amiodarone; Implantable cardioverter-defibrillator

Previous clinical trials have reported the efficiency of implantable cardioverter-defibrillators (ICDs) for the primary and secondary prevention of sudden cardiac death.1,2 Despite their proven effect, inappropriate shocks remain a problem in a significant number of patients. In addition to being painful, inappropriate ICD shocks can potentially induce dangerous arrhythmias and can lead to premature battery depletion.3,4 For these reasons, antiarrhythmic drugs are necessary in up to 70% of patients with ICDs.5 Although class III antiarrhythmic drugs are generally considered to be effective in preventing frequent shocks, there are few studies that demonstrate their efficacy.6,7 It has been suggested that advanced heart failure (HF) or a history of atrial fibrillation (AF) predicts an increased risk for inappropriate shocks,8,9 so our retrospective study was undertaken to compare the effect of amiodarone, sotalol and β-blockers on the prevention of inappropriate shocks in patients with an increased risk of this.

Methods

Patient Population
From April 1996 to February 2006, 137 patients underwent ICD implantation at Asan Medical Center and from them we selected 65 who had a history of AF and/or advanced HF symptoms (New York Heart Association (NYHA) functional class ≥III), because of their supposed high risk of inappropriate ICD shocks. Of the 65 patients, 10 were excluded because either they were taking antiarrhythmic drugs other than amiodarone, sotalol or β-blockers (5 patients), or the inappropriate ICD shocks were caused by extracardiac noise detection (5 patients). Finally, a total of 55 patients were enrolled and divided into 3 groups (amiodarone group: n=24, sotalol group: n=12, and β-blocker group: n=19). Nine patients in the amiodarone group were given amiodarone with β-blockers. All the antiarrhythmic drugs were prescribed to suppress frequent attacks of ventricular tachyarrhythmias or ICD shocks. The medical records were analyzed for baseline demographics, electrocardiographic data, clinical characteristics, and medications taken.

Implanted ICDs and Programming
The ICDs were Medtronic (GEM-VR, Marquis-VR; n=7) or St Jude Medical (Photon-VR, Photon-DR, Atlas-VR, Atlas-DR, Epic-VR, Epic-DR; n=48) and were programmed in the standard fashion. The rate of detection of ventricular tachycardia (VT) was set according to the patient’s VT characteristics; a feasible VT zone was from 102 to 214 beats/min. The slow and fast VT zones were divided according to the patient’s condition. The possible number of VT detection intervals was 8–100 and the usual setting was 12–16. The anti-tachycardia pacing scheme was programmed with 3 attempts of 8–10 stimuli with a cycle length 85% of the detected tachycardia cycle length. After ICD implantation, the patients were followed in the ICD clinic routinely every 3 months and whenever they...
Definition of Inappropriate ICD Shock

We followed the general guidelines of supraventricular tachycardia (SVT) discrimination based on the electrogram analysis. Nominal criteria for the discrimination (favoring AF or SVT against ventricular fibrillation) were: (1) morphology discrimination matching >60–70%, and (2) RR interval variability >50 ms. Based on these criteria, the sensitivity and specificity of the single-chamber ICD has been reported to exceed 90%. In addition to these electrographic features, additional clinical information at the time of the event was taken into consideration. If the patient remained stable during the shock with minimal symptoms, it was considered to strongly suggest against ventricular fibrillation. If the patient was symptomatic and visited the emergency room with documentation of AF, it was also considered to be an inappropriate shock. Electrograms were reviewed by at least 2 experienced electrophysiologists to confirm the accuracy of the diagnosis.

Statistical Analysis

The clinical outcome was the first episode of an inappropriate ICD shock. Continuous variables were described as the mean (SD) and categorical variables were described as the number (percentage). Differences in the frequency of the characteristics were assessed by the ANOVA for continuous variables. Chi-square statistics (or Fisher's exact test if applicable) were used for categorical variables. The comparison between antiarrhythmic drugs for the event-free survival was analyzed using the Kaplan-Meier method via a log-rank test. The hazard ratio (HR) and 95% confidence interval (CI) were calculated based on the Cox proportional hazards regression model. A 2-tailed p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 12.0 software (SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics

The mean follow-up was 2.6±2.0 years. The demographic and clinical characteristics of the 3 groups are presented in Table 1. Most patients were male (n=44, 80%) and 26 (47.3%) had a history of myocardial infarction. There were no significant differences among the groups with regard to the age, gender, implantation of dual-chamber ICDs, history of AF, underlying disease, NYHA functional class or left ventricular ejection fraction (Table 1).

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<th>Table 1 Demographics and Baseline Characteristics</th>
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<td>No. of patients</td>
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<td>NYHA class, mean (SD)</td>
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<td>Left ventricular ejection fraction, (SD), %</td>
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SD, standard deviation; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; VT, ventricular tachycardia; NYHA class, New York Heart Association functional classification.

Treatment Effects

A total of 82 inappropriate shocks were delivered in 18 (32.7%) patients: 6 received 2 each, 4 received 4 each and 1 patient each received 3, 6, 9 and 32 inappropriate shocks. The shocks were because of AF (n=67) and other SVT (n=15). After implantation of an ICD, the event rate of inappropriate shocks at 1-year intervals up to 4 years was 12.6±4.9%, 22.6±6.4%, 31.8±7.5% and 50.2±9.0%, respectively (Fig 1). The 4-year event rate of inappropriate shocks was 27.3±14.5% in the amiodarone group, 54.3±16.6% in the sotalol group, 70.6±13.3% in the ß-blocker group. The incidence of inappropriate shocks was significantly higher in the ß-blocker group than in the amiodarone group (log rank p=0.003). However, it did not significantly differ between the sotalol and ß-blocker groups (log-rank p=0.29), or between the amiodarone and sotalol groups (log-rank p=0.16).
relative to β-blockers, on appropriate and inappropriate shocks. Amiodarone decreased the incidence of inappropriate shocks by 83% as compared with β-blockers (HR 0.17; 95% CI 0.05–0.64; p=0.008). Sotalol only showed a tendency toward reducing the risk of inappropriate shocks as compared with β-blockers (HR 0.57; 95% CI 0.19–1.68; p=0.3). Also, there was no significant risk reduction of inappropriate shocks between amiodarone and sotalol (HR 0.57; 95% CI 0.19–1.68; p=0.3).

Adverse Effects of Amiodarone

Of the 24 patients on amiodarone, 8 (33.3%) developed amiodarone toxicity; pulmonary toxicity in 2 patients (8.3%) as drug-induced interstitial pulmonary infiltrations, 2 patients (8.3%) had an asymptomatic decrease in the lung diffusion capacity, and 4 patients (16.7%) had thyroid function abnormalities. Amiodarone was discontinued in the 4 patients with pulmonary toxicity and the dose was reduced in the 4 with hypothyroidism. The dosage of amiodarone in the patients with adverse effects ranged from 200 to 400 mg/day and the time between administration of amiodarone and the onset of adverse effects was 23.8±16.3 months (range 1.5–54.7 months).

Discussion

This study demonstrated that amiodarone can reduce the risk of inappropriate shocks, as compared with β-blockers, in patients with an ICD and an increased risk of inappropriate shocks. However, despite this beneficial effect, amiodarone has significant drawbacks because of pulmonary or thyroid toxicity.

In the Conventional versus Amiodarone Drug Evaluation (CASCADE) study, patients with ICDs who received amiodarone experienced fewer ICD shocks than the patients treated with class I antiarrhythmic drugs.12 In contrast, the Nippon ICD Plus Pharmacologic Option Necessity (NIPPON) study in ICD patients could not demonstrate any benefit of amiodarone as compared with the class I and control groups; however, the incidence of inappropriate shocks was significantly lower in the amiodarone group than in the class I and control groups.13 Although these studies suggest that amiodarone can reduce the incidence of inappropriate ICD shocks, it could not be determined whether amiodarone actually reduced the number of ICD shocks, or whether the class I drugs were more proarrhythmic.

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study showed that amiodarone in conjunction β-blockers significantly reduced the risk of any ICD shocks more than just β-blockers alone.14 However, that trial could not prove the effect of amiodarone alone on the risk reduction of inappropriate shocks. We found that amiodarone alone was an effective antiarrhythmic drug for the reduction of inappropriate shocks and was better than β-blockers in patients with ICDs and advanced HF or a history of AF.

In a placebo-controlled randomized trial, sotalol significantly reduced the risk of a first shock for all reasons, or death, compared with placebo.6 However, the OPTIC study demonstrated that sotalol, when compared with β-blockers, did not significantly reduce ICD shocks.14 Further, our study showed that sotalol did not significantly reduce the risk of inappropriate shocks as compared with β-blockers.

There appears to be high incidence of inappropriate ICD shock in the present study, but the patients had a history of either advanced HF or AF, which increases the risk of inappropriate ICD shocks. In the OPTIC study, the annual incidence of inappropriate shocks in the β-blocker alone group ranged from 15% to 16%. Considering the longer follow-up in our study (approximately 70% over 4 years), the incidence of inappropriate shocks does not seem to be exceedingly high.

Amiodarone is associated with many side-effects in-
volving the lungs, thyroid, skin and nervous system. We observed a high rate of thyroid function abnormalities and pulmonary events. The rate of adverse effects and drug discontinuation in our study was similar to the rates previously reported.²

Study Limitations
First, it was a retrospective, single-center study and lacked the clear advantage of a multicenter prospective, randomized study. Second, inappropriate anti-tachycardia therapy was not evaluated and third, the amiodarone group included 9 patients who received ß-blockers in conjunction with amiodarone. However, the ß-blockers used in those patients were small doses of carvedilol, which does not seem to have affected the outcome of the amiodarone group. Fifteen patients who received only amiodarone showed a lower risk of inappropriate shocks than the ß-blocker group (HR 0.19; 95% CI 0.04–0.89; p=0.034). Despite these limitations, this is the first study to evaluate the influence of antiarrhythmic drugs on inappropriate shocks in patients at risk for inappropriate shocks.

Conclusion
Amiodarone may be more effective than ß-blockers in reducing inappropriate ICD shocks in patients with AF or advanced HF. Compared with amiodarone and ß-blockers, sotalol did not show any efficacy in reducing inappropriate ICD shocks.

In summary, amiodarone could be recommended for patients with advanced HF or AF who receive an ICD. However, because of its significant risk of adverse effects, the dosage for prevention of inappropriate shocks should be carefully individualized.

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References