Prospective Comparative Study of Intravenous Cibenzoline and Disopyramide Therapy in the Treatment of Paroxysmal Atrial Fibrillation After Cardiovascular Surgery

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Background: It has been reported that approximately one-third of patients undergoing cardiovascular surgery experience paroxysmal atrial fibrillation (AF) during the postoperative period. There is, however, little information on the selection of anti-arrhythmic drugs for terminating postoperative paroxysmal AF.

Methods and Results: Between April 2007 and March 2009, 118 patients (76 men, 42 women, mean age 68±10 years) who had postoperative paroxysmal AF lasting ≥30 min were randomly assigned to receive either iv cibenzoline (70 mg, n=60) or disopyramide (50 mg, n=58) for terminating postoperative paroxysmal AF. The success rate of iv cibenzoline therapy (47%) was significantly greater than that of iv disopyramide therapy (24%; P<0.05). To identify clinical factors to increase the termination efficacy of iv cibenzoline, multivariate logistic regression was used to adjust for several covariates and to generate adjusted odds ratios (OR). The significant variables for the termination of paroxysmal AF after iv cibenzoline therapy were pretreatment with oral β-adrenergic blockers (OR=8.224, P=0.030) and smaller left atrial dimensions (OR=0.879, P=0.039).

Conclusions: The efficacy of iv cibenzoline for the termination of postoperative paroxysmal AF was significantly better than that of disopyramide, especially in patients with pre-administration of oral β-adrenergic blockers and those with smaller left atrium. (Circ J 2010; 74: 1859–1865)

Key Words: Cardiac surgery; Cibenzoline; Circadian rhythm; Disopyramide; Paroxysmal atrial fibrillation

It has been reported that 27–39% of patients undergoing open-heart surgery experience paroxysmal atrial fibrillation (AF) during the postoperative period. Because postoperative AF may induce deterioration of cardiac hemodynamics, increase the incidence of serious complications such as ventricular tachyarrhythmia and ischemic stroke, prolong hospitalization and thereby increase health-care costs, and worsen the clinical course after surgery, prompt treatment of postoperative AF would decrease health-care costs during hospitalization and improve the prognosis of patients following cardiovascular surgery. But although there have been many reports published on the efficacy of prevention of paroxysmal AF with anti-arrhythmics in patients after cardiovascular surgery, few reports have been published on pharmacological termination of postoperative AF. It has been reported that AF recurs in approximately 25% of patients with paroxysmal AF within a few minutes after sinus rhythm has been restored with electrical cardioversion. Because it is difficult in some patients to maintain sinus rhythm with cardioversion alone, anti-arrhythmic drugs are added or cardiac pacing is used before and after cardioversion.

The aim of the present study was therefore to carry out a prospective comparative study of the efficacy and safety of cibenzoline and disopyramide in controlling paroxysmal AF after cardiovascular surgery.

Methods

A total of 428 consecutive patients (279 men and 149 women; mean age 65±13 years; range 20–88 years) who were due to undergo heart/aortic surgery at Iwate Medical University...
Hospital between April 2007 and March 2009 and in whom continuous sinus rhythm was confirmed preoperatively, participated in the present study after exclusion of 31 patients with chronic AF from among 459 candidate subjects. Prior to surgery, all patients were evaluated on chest X-ray, 12-lead electrocardiogram (ECG), transthoracic echocardiography, pulmonary function testing, and other non-invasive examinations. When the attending physicians considered it necessary, patients underwent additional assessments such as exercise tolerance testing, transesophageal echocardiography and cardiac catheterization. Patients were interviewed for history of paroxysmal AF and history of heart/aortic disease, and medical records were reviewed for types of drugs that had been used before surgery, C-reactive protein level, hepatic/renal function, and operative category.

The following patients were excluded from the study: those with serious bradyarrhythmia (eg, sick sinus syndrome, atrioventricular block, or intraventricular conduction defect); those with ejection fraction ≤50% on transthoracic echocardiography; those with abnormal hepatic/renal function test results; those who might be pregnant; those with urinary retention or glaucoma; and those with a history of drug allergy.

### Anti-Arrhythmic Therapy

When AF was detected on continuous 12-lead ECG monitoring in each participant during the observation period following surgery, the investigators confirmed that the patient had a preoperative ejection fraction ≥50% and randomized the patient to treatment with cibenzoline 70 mg or disopyramide 50 mg using the envelope method. The drugs were dissolved in 50–100 ml physiological saline and infused iv over 5–10 min. The treatment was considered to be effective when sinus rhythm was restored within 60 min after termination of iv infusion, and the patient was followed for adverse events. When AF lasted after the treatment, the patient underwent cardioversion under iv anesthesia with thiopental. Under this treatment, patients were observed closely for presence or absence of AF recurrence. Prior to the initiation of test treatment with cibenzoline or disopyramide, we explained the necessity for use of an anti-arrhythmic drug and possible adverse effects before obtaining oral or written informed consent from each subject.

### Definitions

Postoperative paroxysmal AF was defined as ECG findings consistent with AF that continued for at least 5 min during hospitalization. Transient ischemic attack was defined as the occurrence of neurological signs/symptoms that disappeared spontaneously within 24 h after onset. Ischemic stroke was diagnosed on the basis of occurrence of neurological signs/symptoms and detection of an ischemic lesion 3 mm in size on brain computed tomography or magnetic resonance imaging. Patients with paroxysmal AF were classified into the following 3 categories according to when episodes of palpitations developed: diurnal type (episodes occurred from 07:00 hours to 17:00 hours); nocturnal type (episodes occurred from 17:00 hours to 07:00 hours); and mixed type (episodes occurred both diurnally and nocturnally). Hypertension was defined according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009).

### Statistical Analysis

Continuous data are expressed as mean ± SD. Between-group comparisons were performed using Mann–Whitney U-test for continuous variables and the chi-square test for non-continuous variables. The independent predictors for terminating postoperative paroxysmal AF were analyzed on multivariate logistic regression. In all of these tests, P<0.05 was taken as indicating a significant difference.

### Results

#### Incidence of Postoperative Paroxysmal AF vs Patient Characteristics

Postoperative paroxysmal AF developed in 118 of the 428 participants (27.6%; 76 men and 42 women; mean age 68±10 years). A comparison between patients in the cibenzoline...
Atrial Fibrillation After Cardiac Aortic Surgery

Table 2. Patient Characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>Cibenzoline group</th>
<th>Disopyramide group</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>58</td>
<td></td>
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<tr>
<td>Duration of paroxysmal AF (min)</td>
<td>85±103</td>
<td>81±97</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative RAAS inhibitors</td>
<td>27 (45)</td>
<td>24 (41)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative β-blockers</td>
<td>27 (45)</td>
<td>27 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative statins</td>
<td>18 (30)</td>
<td>18 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative AADs</td>
<td>13 (22)</td>
<td>16 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Days of occurrence of postoperative AF</td>
<td>4.5±3.8</td>
<td>4.4±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative complication</td>
<td>6 (10)</td>
<td>9 (16)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Surgical procedure

- Coronary artery bypass grafting: Cibenzoline group 18 (30), Disopyramide group 11 (19), NS
- Aortic valve replacement: Cibenzoline group 18 (30), Disopyramide group 14 (24), NS
- Mitral valve replacement: Cibenzoline group 15 (25), Disopyramide group 18 (31), NS
- Resection of cardiac tumors: Cibenzoline group 1 (2), Disopyramide group 0 (0), NS
- Closure of atrial septal defect: Cibenzoline group 3 (5), Disopyramide group 5 (9), NS
- Thoracic aortic surgery: Cibenzoline group 10 (17), Disopyramide group 11 (19), NS
- Abdominal aortic surgery and peripheral arterial surgery: Cibenzoline group 8 (13), Disopyramide group 13 (22), NS

Table 3. Patient Characteristics (3)

<table>
<thead>
<tr>
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<th>Cibenzoline group</th>
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<th>P value</th>
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<tr>
<td>N</td>
<td>60</td>
<td>58</td>
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Preoperative findings

- LVDd (mm): Cibenzoline group 48.0±7.6, Disopyramide group 48.1±7.8, NS
- LAD (mm): Cibenzoline group 43.1±8.4, Disopyramide group 43.8±8.5, NS
- LVEF (%): Cibenzoline group 64.0±7.8, Disopyramide group 64.6±7.5, NS
- IVS (mm): Cibenzoline group 12.6±2.4, Disopyramide group 12.5±2.3, NS
- LVPW (mm): Cibenzoline group 12.7±2.4, Disopyramide group 12.6±2.2, NS
- E/A ratio: Cibenzoline group 1.07±0.64, Disopyramide group 1.10±0.61, NS
- Deceleration time (ms): Cibenzoline group 262.0±91.0, Disopyramide group 254.9±83.2, NS

Postoperative findings

- LVDd (mm): Cibenzoline group 43.4±5.8, Disopyramide group 43.7±6.0, NS
- LAD (mm): Cibenzoline group 40.8±7.7, Disopyramide group 41.3±7.8, NS
- LVEF (%): Cibenzoline group 61.8±9.8, Disopyramide group 62.0±10.0, NS
- IVS (mm): Cibenzoline group 12.8±2.2, Disopyramide group 12.6±2.1, NS
- LVPW (mm): Cibenzoline group 12.5±2.1, Disopyramide group 12.5±2.0, NS
- E/A ratio: Cibenzoline group 1.33±0.77, Disopyramide group 1.36±0.81, NS
- Deceleration time (ms): Cibenzoline group 213.4±71.0, Disopyramide group 212.3±74.7, NS

Data given as mean±SD or n (%).
RAAS, renin-angiotensin-aldosterone system; AAD, anti-arrhythmic drug. Other abbreviation see in Table 1.

group (n=60) and those in the disopyramide group (n=58) indicated no significant differences in demographic clinical characteristics, drug treatment before surgery, surgical procedure, and several pre- or postoperative findings (operative findings, or postoperative findings; Tables 1–3).

Efficacy and Safety in Controlling AF With iv Anti-Arrhythmic Therapy

AF was terminated in 28 of the 60 patients receiving cibenzoline (47%) and in 14 of the 58 patients receiving disopyramide (24%). The success rate of pharmacological cardioversion was significantly higher in the cibenzoline group than in the disopyramide group (P=0.0291; Figure). Electrical cardioversion for patients with AF that persisted after anti-arrhythmic treatment terminated AF in all patients except 1 in the disopyramide group. Among patients who underwent coronary artery bypass grafting (CABG), AF disappeared in 12 of 18 patients receiving cibenzoline (67%), and in 5 of 11 patients receiving disopyramide (45%); there was no significant difference between the 2 groups. Among patients who underwent surgery other than CABG, AF disappeared in 12 of 18 patients receiving cibenzoline (67%), and in 5 of 11 patients receiving disopyramide (45%); there was no significant difference between the 2 groups. No patients experienced serious adverse drug effects requiring discontinuation of anti-arrhythmic therapy.
Successful termination of atrial fibrillation by iv cibenzoline vs disopyramide.

**Figure.**

| Table 4. Multivariate Predictors for Termination of AF on iv Cibenzoline |
|-------------------------------------------------|-----------------|-------|
| OR (95%CI)                                      | P value         |
| Preoperative β-blockers                         | 8.224 (1.229–55.01) | 0.030 |
| LAD (mm)                                        | 0.879 (0.777–0.993) | 0.039 |
| Diabetes mellitus                               | 3.094 (0.575–16.65) | 0.188 |
| Preoperative RAAS inhibitors                     | 2.802 (0.601–13.05) | 0.189 |
| Ischemic heart disease                          | 3.289 (0.472–22.91) | 0.229 |
| Body weight (kg)                                | 0.951 (0.870–1.039) | 0.267 |
| Duration of paroxysmal AF (min)                 | 1.004 (0.997–1.011) | 0.294 |
| LVPW (mm)                                       | 1.350 (0.706–2.579) | 0.364 |
| LVEF (%)                                        | 0.957 (0.865–1.059) | 0.392 |
| IVS (mm)                                        | 0.760 (0.384–1.504) | 0.431 |
| LVDd (mm)                                       | 0.964 (0.849–1.093) | 0.565 |
| Hypertension                                    | 0.733 (0.185–2.897) | 0.658 |
| Valvular disease                                | 1.456 (0.225–9.429) | 0.694 |
| Preoperative statins                            | 1.078 (0.222–5.250) | 0.926 |
| Days of occurrence of postoperative AF          | 0.959 (0.779–1.182) | 0.959 |

Abbreviations see in Tables 1–3.

| Table 5. Multivariate Predictors for Termination of AF on iv Disopyramide |
|-------------------------------------------------|-----------------|-------|
| OR (95%CI)                                      | P value         |
| LAD (mm)                                        | 0.845 (0.722–0.971) | 0.030 |
| Preoperative β-blockers                         | 6.184 (1.107–38.36) | 0.046 |
| LVEF (%)                                        | 1.045 (0.999–1.124) | 0.137 |
| Preoperative RAAS inhibitors                     | 2.022 (0.452–9.034) | 0.357 |
| Ischemic heart disease                          | 2.056 (0.390–10.84) | 0.395 |
| Body weight (kg)                                | 0.951 (0.870–1.039) | 0.398 |
| Duration of paroxysmal AF (min)                 | 1.003 (0.998–1.009) | 0.436 |
| LVPW (mm)                                       | 1.278 (0.773–2.349) | 0.412 |
| IVS (mm)                                        | 0.806 (0.422–1.418) | 0.501 |
| Preoperative statins                            | 0.678 (0.059–7.817) | 0.755 |
| Valvular disease                                | 0.794 (0.038–9.468) | 0.773 |
| Diabetes mellitus                               | 0.835 (0.198–3.525) | 0.806 |
| Hypertension                                    | 0.973 (0.298–3.178) | 0.964 |
| Days of occurrence of postoperative AF          | 0.979 (0.782–1.159) | 0.972 |
| LVDd (mm)                                       | 1.001 (0.909–1.102) | 0.991 |

Abbreviations see in Tables 1–4.
Predictors of Successful Pharmacological Cardioversion With iv Cibenzoline and Disopyramide

On multivariate logistic analysis adjusted for differences in baseline confounding factors, independent predictors of successful pharmacological cardioversion with iv cibenzoline therapy were concomitant use of oral β-adrenergic blockers (odds ratio (OR)=8.224, 95% confidence interval (CI)=2.312–29.24; P=0.030) and left atrial dimension (OR=0.879, 95% CI=0.813–0.950; P=0.039; Table 4). Independent predictors of successful pharmacological cardioversion with iv disopyramide therapy were also left atrial dimension (OR=0.845, 95% CI=0.722–0.971; P=0.030) and concomitant use of oral β-adrenergic blockers (OR=6.184, 95% CI=1.107–38.36; P=0.046; Table 5).

Discussion

According to the 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, it has been reported that the administration of β-blockers prior to surgery decreases perioperative cardiovascular events and improves the prognosis among patients with moderate or severe cardiovascular risk as well as those in vascular surgery with moderate or severe invasive operations.17 In particular, pretreatment with β-blockers limits the onset of paroxysmal AF after cardiovascular surgery:18 meta analysis also confirmed these effects of preventing postoperative AF (36–39%),18 and they are classified under class I indications.19 Increases in exogenous and endogenous catecholamine levels are cited as one of the causes of postoperative AF,20 and β-blockers are considered reasonable drugs of choice from the viewpoint of their pharmacological action. In Japan as well, pretreatment with β-blockers has been reported as an independent predictor of the prevention of AF after CABG20 and was an independent predictor that facilitated the terminating effects of class I anti-arrhythmic drugs in the present study.

Recently, detailed analysis of 24-h ambulatory ECG has shown that paroxysmal AF tends to develop at particular times of the day and that the autonomic nervous system plays an important role in inducing AF.21 We previously reported that development of postoperative paroxysmal AF peaked at around 03:00 hours and 15:00 hours and was more common during the daytime. Coumel suggested that development of paroxysmal AF may be related to activation of the sympathetic nervous system, on the basis of the finding that patients with heart disease tend to experience paroxysmal AF more often during sympathetic nervous system activation.22 It has also been reported that β-blockers are effective in preventing postoperative paroxysmal AF.1,7–10 These findings suggest the existence of a relationship between paroxysmal AF and activation of the sympathetic nervous system.

The 2006 ACC/AHA/European Society of Cardiology guidelines recommend oral amiodarone and sotalol to prevent paroxysmal AF after cardiovascular surgery and iv ibutilide to terminate it.23 It is known that some patients requiring cardiovascular surgery have impaired cardiac function resulting from underlying heart disease. Class I anti-arrhythmic drugs, causing possible deterioration of the cardiac function and/or inducing proarrhythmia, may lead to increased adverse drug reactions in these patients. Therefore, in the present study we investigated patients without impaired left ventricular contraction characterized by a left ventricular ejection fraction of ≥50% on preoperative transthoracic cardiac ultrasonography; no serious adverse drug reactions were observed at the standard dose for iv infusion of cibenzoline and disopyramide. Because class I anti-arrhythmic drugs have negative inotropic effects, these drugs should not be used iv in patients with an impaired left ventricular systolic function.

In contrast, according to studies conducted in Europe and the USA on the effects of disopyramide to terminate postoperative paroxysmal AF, all evaluations were made at 12 h after administration.24–27 The effects of a placebo to terminate paroxysmal AF, however, were reported to be 15% at 1 h28 and 48% at 8 h.29 In the present study we investigated the terminating effects of iv cibenzoline and disopyramide at 1 h after administration to exclude the placebo effect as much as possible.

The superior efficacy of cibenzoline for terminating postoperative paroxysmal AF compared with disopyramide might be due to differences in the channels blocked by cibenzoline and disopyramide: Cibenzoline inhibits the IKur channel, which is specifically distributed in atrial muscle cells, as well as sodium channels, the IKs channel, and calcium channels, while disopyramide does not inhibit these channels.30 But it is impossible at present to specify the most important pharmacological mechanism of termination of AF in individual patients in the clinical setting. Further investigation is needed to determine this.

In the present study, predictors of successful pharmacological cardioversion with iv cibenzoline and disopyramide therapy were smaller left atrial dimensions and use of oral β-adrenergic blockers. It has been reported that the period of AF,31 size of left atrial dimension,32 and presence of underlying heart disease33 may affect the efficacy of pharmacological cardioversion in patients with paroxysmal AF. In general, patients with a prolonged history of AF (months–years) may exhibit an increase in left atrial dimension due to progression of structural remodeling. Histopathology of patients with significant atrial dilatation indicated irreversible pathological findings such as degeneration and fibrillation of atrial muscle. It can be expected that the effects of anti-arrhythmic drugs on channels on the cell membrane decrease as atrial dilatation progresses.

It is well known that the underlying mechanisms involved in postoperative AF development are multifactorial.2,3,4,35 One of the causative mechanisms is thought to be neurohormonal activation.36 Increased sympathetic activation alter atrial refractoriness (eg, a shortening of the atrial effective refractory periods), thus possibly contributing to the arrhythmia substrate. It has been reported by Dimmer et al that a shift in the autonomic balance with a loss of vagal tone and a moderate increase in sympathetic tone are observed before the onset of postoperative AF.37 Several clinical trials have evaluated the efficacy of various β-adrenergic blockers on the incidence of postoperative AF, showing an overall reduction of this complication.1,8,10 A recent meta-analysis also reported that β-adrenergic blockers had the greatest magnitude of efficacy across 28 trials (OR=0.35, 95% CI=0.26–0.49).7

In the present study it was suggested that preoperative β-adrenergic blockers enhanced the efficacy for terminating paroxysmal AF treated with iv cibenzoline and disopyramide therapy. Thus, the present result is consistent with aforementioned reports, indicating the useful addition of oral β-adrenergic blockers to iv cibenzoline and disopyramide therapy.

Study Limitations

First, no placebo group was included in the present prospective clinical study. It has been reported that placebo can
terminate paroxysmal AF in 4–15% of patients within 60 min after administration. 38,39 We cannot rule out the possibility that postoperative paroxysmal AF terminated spontaneously in some patients. But we evaluated the efficacy of anti-arrhythmic treatment over a 60-min period, which is relatively brief, and assumed that the placebo effects of cibenzoline and disopyramide were similar. We therefore believe that, with regard to patients in whom AF terminated spontaneously, there was little effect on the results. Second, we may have overlooked asymptomatic AF, because ECG monitoring was not continued until discharge from the hospital, although the incidence of postoperative paroxysmal AF in the present study was similar to those in previous studies. 7,8 Third, we did not determine serum electrolyte concentrations at the time of onset of postoperative paroxysmal AF. We therefore cannot rule out the possibility that some patients experienced transient AF due to hypokalemia or hypocalcemia. Finally, the number of subjects in the present study was limited, especially including only patients with normal or minimally impaired left ventricular function.

Conclusion

The efficacy for terminating paroxysmal AF after cardiovascular surgery in patients with normal or minimally impaired left ventricular function was significantly higher for iv cibenzoline therapy than for iv disopyramide one. Pharmacologically, cardioversion was achieved in approximately half of the patients receiving cibenzoline, and this therapy was considered particularly effective in patients with concomitant use of oral β-adrenergic blockers and those with smaller left atrial dimensions. Intravenous cibenzoline therapy may decrease the rate of adverse outcomes in a population at high risk for cardiovascular surgery and reduce utilization of medical resources.

Acknowledgments

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References


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Atrial Fibrillation After Cardiac Aortic Surgery


