A Clinical Study of Intravenous Cibenzoline in Selected Patients with Recent-onset Atrial Tachyarrhythmia

Pierre Andrivet, M.D.; Valérie Mach, M.D.; and Canh Vu Gnoc, M.D.

Twenty-five adult patients with sustained atrial tachyarrhythmia (ATA) and without heart failure were treated by intravenous cibenzoline, 1 mg/kg, as a slow bolus infusion, followed by a 8 mg/kg/24 h continuous infusion. Sinus rhythm conversion was observed in 18 patients (72 percent success rate). Severe adverse cardiac events were observed in only one patient (4 percent occurrence rate), as a wide QRS complex tachycardia finally requiring a semiemergency direct-current cardioversion. Two minor side effects were additionally observed. A similar population of 21 patients was conventionally treated with amiodarone, either given intravenously, 15 to 20 mg/kg/24 h, or orally, 30 mg/kg/24 h as a single dose. An identical success rate (15/21; 71 percent) was observed. Our results indicate that in selected patients with ATA, cibenzoline and amiodarone are highly effective for producing sinus rhythm conversion. We suggest that the former drug may be used as a first-line treatment. In case of failure, the latter may constitute an alternative to transthoracic electrical countershock.

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AF = atrial fbrillation; AFI = atrial flutter; AT = atrial tachycardia; ATA = atrial tachyarrhythmia

Atrial tachyarrhythmias (ATA), including atrial fibrillation (AF), atrial flutter (AFI), and atrial tachycardia (AT) are observed in a variety of underlying diseases, including valvular cardiopathies, ischemic and dilated cardiomyopathies, cor pulmonale, and hyperthyroidism. They also may occur in the absence of detectable underlying heart disease or thyroid dysfunction. Obviously, the ATA-related risks of both thromboembolic events and heart failure are at best minimized by treatments that restore sinus rhythm. Electrical transthoracic countershock remains the reference treatment, but needs general anesthesia and prolonged anticoagulation before it could be performed. Thus, several medical protocols using various drugs either intravenously (IV) or orally administered have been proposed in the past 10 years. Successful sinus rhythm conversion rates, ranging from 6 percent to 81 percent have been reported, but some of the best results were seemingly accompanied by a high rate of adverse reactions.

We report in the present prospective study our own experience with the use of cibenzoline, a compound included in the Ic subgroup of the Millar and Vaughan-Williams classification, having additional class 3 and 4 properties, and with the use of amiodarone, a widely used antiarrhythmic agent in our country.

**METHODS**

**Patients**

Cibenzoline Group (C Group): From October 1990 to April 1992, adult patients younger than 80 years, admitted in our ICU for ATA were considered for cibenzoline administration if they met the following requirements: sustained atrial tachyarrhythmia, lasting for at least 3 h; absence of acute myocardial infarction; absence of heart failure; absence of recent (3 months) cardiac surgery; and absence of impaired renal function, appreciated on the basis of a plasma creatinine concentration less than 120 μg/L.

Twenty-five patients fulfilled these inclusion criteria. Cibenzoline was administered as follows: loading dose of 1 mg/kg of body weight as a slow (2 min) bolus infusion, and maintenance dose of 8 mg/kg of body weight for 24 h.

Amiodarone Group (A Group): During the study period, 21 other patients fulfilling the same inclusion criteria were conventionally treated with amiodarone. Amiodarone was given either orally, with a single dose of 30 mg/kg of body weight during the first 24 h or IV with a loading dose of 5 to 7.5 mg/kg of body weight in 30 min, followed by continuous infusion of 10 to 15 mg/kg of body weight for 24 h.

In addition to these 46 patients, 5 subjects with the same inclusion criteria were admitted to the intensive coronary care unit, but they spontaneously returned to sinus rhythm before any therapeutic intervention.

The patients were observed for 30 min at rest before drug administration to allow clinical stabilization. In all groups, anticoagulation was ensured by IV heparin, at a rate adjusted to obtain an activated partial thromboplastin test 2 to 2.5 times control, except in three patients (two in the A group and one in the C group) already receiving antivitamin K regimen. In both C and A groups, digoxin administration (0.5 mg IV) was allowed, at the discretion of the attending physician.

In all these patients, 2D echocardiographic examination was performed within 7 days from hospital admission (usually within 48 h) to evaluate ventricular and atrial diameters and to ensure that left ventricular function was normal or near normal. Normal thyroid function was also verified in all of them.

The primary end-point of the study was the efficacy of the therapeutic regimen (ie, sinus conversion) after 24 h of treatment. The secondary end-point was the tolerance of the drug administration and the occurrence of adverse side effects.

Informed consent was obtained from each patient before therapy was begun.

**RESULTS**

Quantitative values are given as mean ± SEM. The
studied populations are described in Table 1. Atrial fibrillation was the most frequently observed ATA, but its association with AFL or AT was not uncommon. Previous episodes of ATA have been observed in 31 of our patients (70 percent), and 24 of them were treated with various long-term antiarrhythmic regimens. In both groups, echocardiographic findings confirmed the clinical evaluation by showing in each patient normal or near-normal atrial and ventricular diameters, as well as shortening fraction.

**Cibenzoline Group**

Five patients in this group (20 percent) had valvular heart disease. Another patient was treated for asymmetric septal hypertrophy without intraventricular obstruction, and an additional patient was followed for systemic hypertension.

Conversion to sinus rhythm was observed in 18 of these 25 patients, leading to an overall success rate of 72 percent. Table 2 shows the different success rates observed in subgroups of patients subdivided according to the type of arrhythmia and the duration of the ATA episode.

After 24 h of treatment, mean heart rate was 75 ± 5 beats/min in patients converted to sinus rhythm, and 106 ± 5 beats/min in patients with persistent atrial arrhythmia. After sinus conversion, no PR interval was greater than 0.20 s. There was no clinically relevant alteration of the QRS interval. The local venous tolerance of cibenzoline was excellent, and no extracardiac effect was observed with this drug.

Adverse cardiac events were noted in three patients: the first patient, a 62-year-old woman admitted to the hospital for AT with a ventricular rate of 145 beats/min, exhibited a quickening of the same ATA to a heart rate of 216 beats/min after bolus infusion of cibenzoline (0.5 mg IV) was added to slow the ventricular response, and sinus conversion occurred 1 h later. The second patient, a 64-year-old man admitted to the hospital for recurrence of AF despite long-term treatment with β-blockers, experienced during bolus infusion a transient bradyarrhythmia with narrow QRS complexes, which rapidly resolved after atropine, 1 mg IV. Conversion to sinus rhythm occurred 2 h later. The third patient, a 59-year-old man admitted to the hospital for AFL with a ventricular rate of 136 beats/min, exhibited after 18 h of continuous infusion a brisk quickening of his ventricular rate to 180 beats/min, with widened QRS complexes. Cibenzoline therapy was stopped. The tachycardia was not responsive to vagal maneuvers, and an electrical countershock was performed 30 min later, which finally restored sinus rhythm.

**Amiodarone Group**

Three patients in the A group (14 percent) had valvular heart disease. One patient was followed for systemic hypertension, and another patient was

<table>
<thead>
<tr>
<th>Type of Arrhythmia</th>
<th>Cibenzoline</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>Success Rate (%)</td>
<td>Failure</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>18</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Atrial Flutter and Atrial Tachycardia</td>
<td>7</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Duration of ATA, h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24</td>
<td>17</td>
<td>13 (77)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>8</td>
<td>5 (62)</td>
</tr>
</tbody>
</table>

*Isolated atrial fibrillations have been separated from atrial flutters and atrial tachycardias. Because of the small number of observations, patients with the two latter types of arrhythmias were combined. ATA = atrial tachycardia.
treated for acute idiopathic pericarditis.

Seven patients received the drug orally; the 14 remaining patients received IV amiodarone. Conversion to sinus rhythm was observed in 15 of these 21 patients, leading to an overall success rate of 71 percent. There was no difference between the two amiodarone regimens in terms of conversion to sinus rhythm (6/7 vs 9/14; Fisher's exact test, p = 0.70). Table 2 shows the different success rates observed with amiodarone in subgroups of patients subdivided according to the type of arrhythmia and the duration of the ATA episode.

After 24 h of treatment, mean heart rate was 72 ± 2.5 beats/min in patients converted to sinus rhythm, and 103 ± 4 beats/min in patients with persistent atrial arrhythmia.

Adverse cardiac events were noted in two patients who showed after sinus conversion a first-degree auriculoventricular block, with PR intervals, respectively, of 0.26 and 0.28 s. Difficulty in swallowing a large number of pills was also observed in two other patients. Local venous tolerance was fair.

**DISCUSSION**

The present prospective open-label study was primarily aimed to evaluate the efficacy and the safety of cibenzoline, a class 1c antiarrhythmic agent with additional class 3 and class 4 properties, in patients admitted to the hospital for sustained ATA. Patients with atrioventricular or atrioventricular nodal reentrant tachycardias were excluded from this study, because these supraventricular tachycardias are highly responsive to IV adenosine or adenosine triphosphate. Because the occurrence of a rapid ATA usually requires medical treatment, at least aimed to slow the ventricular rate, a placebo control group seemed to us unethical. Besides, this study was not designed to directly compare the respective efficacy of cibenzoline and amiodarone. Thus, we did not perform a double-blind, randomized protocol, but we thought that results obtained with amiodarone in a comparable population could bring additional, useful, and clinically relevant information.

The ability of cibenzoline to convert paroxysmal ATA in sinus rhythm is of particular interest in the present study. Although criteria for treatment efficacy could have been variously defined in previous studies, our results compare favorably with those obtained with other drugs (Table 3). However, it must be noticed that our 72 percent success rate was observed in a selected population of patients with no apparent sign of heart failure who were supposed to have normal or near-normal ventricular and atrial diameters, and assumption secondarily verified by echocardiography. Such success rates may not be observed in other categories of patients, particularly in patients with dilated atria. Moreover, it is also possible that some patients in the C group (as well as in the A group) could have spontaneously returned to sinus rhythm, as suggested by the observation of five additional patients in whom regularization occurred without any drug intervention. Thus, because 10 percent (5 of 51 patients) of sinus conversions may not be related to drug administration, the real efficacy of cibenzoline (as well as of amiodarone) likely ranges from 65 percent to 72 percent.

Attention has been drawn recently to the proarrhythmic effects of class 1c antiarrhythmic agents. In the present study, three patients experienced adverse cardiac effects while receiving cibenzoline. In the first patient, transient quickening of the ATA after bolus infusion may be due to the additional vagolytic property of cibenzoline and should be considered as a minor adverse event of the drug. Despite this atropine-like property of cibenzoline, the second patient exhibited a transient bradyarrhythmia during bolus infusion.

Cibenzoline has been shown to increase the intranodal conduction time in man. Thus, we cannot exclude that this bradycardia could be, at least partly, related to an adverse effect of cibenzoline, possibly potentiated by the associated long-term β-blocker treatment. Because bradyarrhythmia rapidly responded to atropine, this could also be considered as a minor adverse effect of the drug. In the last patient, a wide QRS complex tachycardia was observed after 18 h of IV infusion. Although we could not precisely determine if this rhythm was a new ventricular tachy-

**Table 3—Comparison of Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Antiarrhythmic Agent</th>
<th>Success Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faniel et al</td>
<td>26</td>
<td>Amiodarone</td>
<td>81</td>
</tr>
<tr>
<td>Fenster et al</td>
<td>26</td>
<td>Procainamide</td>
<td>58</td>
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<tr>
<td>To et al</td>
<td>29†</td>
<td>Sotalol</td>
<td>52</td>
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<tr>
<td>Esmolol MSRC*</td>
<td>50</td>
<td>Esmolol</td>
<td>30†</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>Propranolol</td>
<td>36‡</td>
</tr>
<tr>
<td>Borgest et al</td>
<td>30</td>
<td>Flecainide</td>
<td>67</td>
</tr>
<tr>
<td>Suttrop et al</td>
<td>39</td>
<td>Flecainide</td>
<td>59‡</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Verapamil</td>
<td>6</td>
</tr>
<tr>
<td>Biancoi et al</td>
<td>83</td>
<td>Propafenone</td>
<td>57</td>
</tr>
<tr>
<td>Suttrop et al</td>
<td>25</td>
<td>Flecainide</td>
<td>76‡</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Propafenone</td>
<td>52</td>
</tr>
<tr>
<td>Donovan et al</td>
<td>51</td>
<td>Flecainide</td>
<td>67</td>
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<tr>
<td>Present study</td>
<td>25</td>
<td>Cibenzoline</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>Amiodarone</td>
<td>71</td>
</tr>
</tbody>
</table>

*Summary of nine previous studies using various intravenous antiarrhythmic regimens in the treatment of paroxysmal atrial tachyarrhythmias and the present study. Success rate indicates the percentage of patients converted to sinus rhythm.
†Seven among these 29 patients were treated for supraventricular tachycardia, two of them having a Wolff-Parkinson-White syndrome.
‡Overall success rates are calculated by pooling the given results for atrial fibrillation and atrial flutter, which are presented separately.
cardia induced by cibenzoline or the preexistent ATA with aberrant intraventricular conduction, its treatment required electrical countershock. Thus, this event should be classified as a major adverse effect of the drug, leading in this short series to a rate of 4 percent. Donovan et al11 recently reported an episode of torsades de pointes after bolus infusion of flecainide, 2 mg/kg IV, in one among 51 patients treated for atrial fibrillation. Otherwise, proarrhythmic effects of oral cibenzoline seldom have been reported. Indeed, pooling four studies in patients treated long term for ventricular arrhythmias26-28 indicates an overall 6 percent rate, in good accordance with the 4 percent rate observed in the present report. In view of the potential benefit resulting from IV cibenzoline administration, this rate seems acceptable, at least within the conditions of our protocol, ie, short time drug infusion and continuous electrocardiographic monitoring in an ICU. However, adverse cardiac effects of class 1c may be more frequent and more severe in patients with advanced heart disease.34 Intravenous cibenzoline (1 mg/kg as a slow bolus) has been shown to decrease cardiac output transiently by 22 percent in man,25 with a peak effect 5 min after bolus infusion. Although cardiac output returned to control values 1 h later,25 caution must be exercised in patients with depressed ventricular function in whom the present protocol may not be suitable.

No other adverse effect was observed with cibenzoline. In two studies by Suttrop et al,8,16 transient, mild adverse effects were noted, respectively, in 26 percent and 42 percent of patients treated with flecainide. In the study by Donovan et al,11 severe hypotension was reported to occur in 22 percent of patients given flecainide, 2 mg/kg IV. Special attention must be given to sotalol, which seems both effective in treating AFL or AT and well tolerated,6 but whose efficacy rate on AF, the most common form of ATA, is only 27 percent. Because all these reports studied similar patients (ie, patients with ATA and without heart failure), the balance between efficacy and adverse effects seems to favor cibenzoline. However, only double-blind randomized studies could bring definitive conclusions on this particular point.

Finally, our study confirms the efficacy of amiodarone in treating ATA of selected patients.3,34 Because of its numerous pulmonary, hepatic, ocular, or thyroid side effects, amiodarone is not recommended as a first-line treatment,39,40 but it remains an alternative to electrical countershock after failure of other antiarrhythmic agents to convert paroxysmal ATA in sinus rhythm.

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Intravenous Cibenzoline in Recent-onset Supraventricular Tachycardia (Andrieh, Mach, Gncc)