Initial Experience With Nifekalant Hydrochloride (MS-551), A Novel Class III Antiarrhythmic Agent, in Patients With Acute Extensive Infarction and Severe Ventricular Dysfunction

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Nifekalant hydrochloride, a novel class III antiarrhythmic agent, was used as the treatment in 4 patients with extensive anterior infarction and severe ventricular dysfunction. The malignant ventricular tachyarrhythmia was effectively suppressed at a relatively low dose, without compromising the hemodynamics, indicating that this potent K+ channel blocker has therapeutic potential for acute myocardial infarction. (Jpn Circ J 2001; 65: 60–62)

Key Words: Antiarrhythmia agents; Electrocardiography; Myocardial infarction

Nifekalant hydrochloride (NIF) (Shinbit®, Mitsui Pharmaceuticals Inc, Japan), formally known as MS-551, is a novel class III antiarrhythmic agent that was developed in Japan and has recently become commercially available! It has the unique characteristic of potent, nonselective K+ channel blocking without inhibiting either the Na+ channels or the β-adrenergic receptors. In canine models of myocardial infarction, NIF effectively suppressed ventricular tachyarrhythmia, without compromising hemodynamics.2,3

We report our initial experience of using NIF in patients with acute extensive infarction and severe ventricular dysfunction.

Four male patients (age, 67±10 [mean±SD] years) were referred because of extensive anterior acute myocardial infarction (AMI). All patients had single-vessel disease (the proximal left anterior descending artery) for which percutaneous transluminal coronary angioplasty was performed. The peak level of creatine kinase was 8,102±5,552 U/L. Echocardiography revealed severely depressed left ventricular function with 16±4% fractional shortening. In 2 of 4 patients (cases 1 and 3), intra-aortic balloon pumping was introduced for circulatory support. The patients’ characteristics are summarized in Table 1.

Despite successful reperfusion therapy, ventricular tachyarrhythmia (sustained ventricular tachycardia or fibrillation) developed 48–72 h following the AMI. None of the patients responded to therapy with lidocaine and/or procainamide under the correction of electrolyte (potassium and magnesium) and acid–base disturbance. We decided to use NIF intravenously, infusing a loading dose of 0.05–0.15 mg/kg and a maintenance dose of 0.05–0.20 mg·kg⁻¹·h⁻¹, which were much lower doses than those used in a previous study (loading dose: 0.30 mg/kg; maintenance dose: 0.60 mg·kg⁻¹·h⁻¹). The ventricular tachyarrhythmia, which was refractory to class IA and IB drugs, was effectively suppressed by NIF; the corrected QT interval (QTC) was extended to 0.58±0.03, from 0.46±0.05 s of the baseline. During the NIF infusion, the hemodynamics did not appear to deteriorate; rather, they were stabilized in conjunction with the controlling of the malignant ventricular tachyarrhythmia. None of the patients needed additional antiarrhythmic therapy when NIF was discontinued after 1–19 days.

Fig 1 shows the ECG recordings from case 1, a 59-year-old man who was supported by intra-aortic balloon pumping. The drug-refractive ventricular tachyarrhythmia (Fig 1B) was successfully treated with NIF at a loading dose of 0.15 mg/kg and a maintenance dose of 0.1 mg·kg⁻¹·h⁻¹, which extended the QTC to 0.51 s (Fig 1C). Neither the pulmonary capillary wedge pressure (from 19 to 16 mmHg) nor the cardiac index (from 1.9 to 1.9 L·min⁻¹·m⁻²) changed significantly following NIF treatment.

Fig 2 shows the ECG recordings from case 2, a 78-year-old man with a 24% left ventricular ejection fraction. His monomorphic sustained ventricular tachycardia (Fig 2B) was initially treated with NIF at a loading dose of 0.15 mg/kg and a maintenance dose of 0.1 mg·kg⁻¹·h⁻¹. Although the original arrhythmia disappeared, torsade de pointes (Fig 2D) newly developed when the QTC exceeded 0.60 s (Fig 2C). After NIF was decreased to 0.05 mg·kg⁻¹·h⁻¹, the QTC decreased to 0.56 s, so this patient was effectively treated by preventing proarrhythmia (Fig 2E).

The ventricular tachyarrhythmia associated with AMI is a difficult problem to prevent and treat. Patients with an extensive infarction and severe ventricular dysfunction have an especially high risk of sudden or arrhythmic death. In these patients, class I antiarrhythmic agents depress cardiac function, compromising hemodynamics and this negative inotropic action, as well as a proarrhythmic action, may explain the disappointing results (ie, increased mortality) of the Cardiac Arrhythmias Suppression Trials. There-
Table 1 Patients' Characteristics

<table>
<thead>
<tr>
<th>Case no.</th>
<th>On admission</th>
<th>Reperfusion therapy/ circulatory support</th>
<th>Pre QTc (s)</th>
<th>NIF dose</th>
<th>Post QTc (s)</th>
<th>No. days of treatment</th>
<th>Abnormal Q in ECG</th>
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<tr>
<td></td>
<td>PCWP (mmHg)</td>
<td>CI (L·min⁻¹·m⁻²)</td>
<td>SVI (ml/m²)</td>
<td></td>
<td>Loading (mg/kg)</td>
<td>Maintenance (mg·kg⁻¹·h⁻¹)</td>
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<td>19</td>
<td>PTCA, CA, IABP</td>
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<td>0.15</td>
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<td>29</td>
<td>1.8</td>
<td>PTCA, CA</td>
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<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>33</td>
<td>1.8</td>
<td>PTCA, CA, IABP</td>
<td>0.44</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>15</td>
<td>2.9</td>
<td>PTCA</td>
<td>0.53</td>
<td>0.15</td>
<td>–</td>
</tr>
</tbody>
</table>

PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; PTCA, percutaneous transluminal coronary angioplasty; CA, catecholamines; IABP, intra-aortic balloon pumping; QTc, corrected QT interval; NIF, nifekalant hydrochloride (MS-551).
fore, more attention has been focused on class III agents, which prolong the action potential duration and effective refractory period.

NIF (MS-551; N-substituted 6-[(2-aminoethyl)amino]-1,3-dimethyl-2,4(1H,3H)-pyrimidinedione), is a novel class III antiarrhythmic agent that blocks the delayed rectifier K⁺ current, the transient outward K⁺ current, the inward rectifier K⁺ current, and ATP-sensitive K⁺ current, without affecting the Na⁺ current or β-adrenergic activity. Previous experimental studies have shown that NIF suppresses ventricular tachyarrhythmia in myocardial ischemia and infarction; in conditions in which the K⁺ channels play a key role. It is noteworthy that NIF did not significantly alter cardiac function in dogs with myocardial infarction or in normal dogs. It was on the basis of these experimental findings, that we sought to determine the therapeutic implications of this drug for the treatment of complications associated with AMI in a clinical setting.

In the present study, taking into account the presence of extensive anterior AMI and severe ventricular dysfunction, we administered NIF at doses less than half of those previously used in patients with stable hemodynamics. Even at such low doses, NIF effectively suppressed the malignant ventricular tachyarrhythmia following AMI that is refractory to class IA and IB drugs.

Using NIF at low doses may significantly prevent deterioration of hemodynamics, as was shown in case 1 who required mechanical circulatory support for cardiogenic shock. NIF neither altered the cardiac index nor the pulmonary capillary wedge pressure.

Low doses of NIF may also minimize proarrhythmia, as was shown in case 2 in whom torsade de pointes was transiently induced when the QTc was extended beyond 0.60 s. The dose of NIF was halved and there was no recurrence of either torsade de pointes or the original ventricular tachycardia.

NIF was also used successfully in case 4 in whom the QTc at baseline was already prolonged to 0.53 s. Because a bolus injection of NIF (0.15 mg/kg) extended the QTc beyond 0.60 s, we did not add the maintenance dose. In this particular case, the QTc fluctuated between 0.55 and 0.60 s after the NIF loading. Therefore, from the current data, it can be seen that the optimal dose of NIF is the one at which QTc is maintained below 0.60 s, which is important to prevent the adverse effects of proarrhythmia.

In conclusion, despite the small number of patients in this study, short-term intravenous administration of NIF appears to be an effective and safe treatment for malignant ventricular tachyarrhythmias refractory to class IA and IB drugs. This finding indicates the therapeutic potential of this new class III antiarrhythmic drug in the treatment of AMI.

References