Intracoronary Administration of a Thromboxane A2 Synthase Inhibitor Relieves Acetylcholine-Induced Coronary Spasm

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This study sought to clarify the effectiveness of intracoronary administration of a thromboxane (TX) A2 synthase inhibitor, Ozagrel Na, to relieve coronary spasms induced by intracoronary injection of acetylcholine (ACh). An ACh spasm provocation test was performed in 92 consecutive patients with coronary spastic angina using incremental doses of 20, 50, and 80μg into the right coronary artery, and 20, 50, and 100μg into the left coronary artery within 20 s. A coronary spasm was defined as TIMI 0 or 1 flow and an intracoronary injection of 20mg Ozagrel Na was administered when it was provoked. Within 2 min of the administration of the TXA2 synthase inhibitor, ACh-induced coronary spasms were relieved (TIMI 3 flow) in 88.1% of procedures without complications. In only 4 cases (4.3%), it took more than 3 min to relieve the coronary spasms. Intracoronary administration of 20mg Ozagrel Na when ACh-induced spasms occurred, shortened the spasm relief time in all 7 patients (200±59 s vs 111±23 s, p<0.01), improved the maximal ST segment elevation in 5 of them (3.9±3.7 mm vs 0.7±1.5 mm, p<0.05), and stopped chest pain in 4 patients. In 4 patients who had ACh-induced coronary spasm of the left anterior descending artery, the TXB2 concentration in the coronary sinus decreased after intracoronary administration of Ozagrel Na into the left coronary artery (463±562 vs 96±45, p<0.01). In conclusion, intracoronary administration of a TXA2 synthase inhibitor can relieve ACh-induced coronary spasms by inhibiting TXA2 synthesis in the local coronary circulation. (Circ J 2002; 66: 826–830)

Key Words: Acetylcholine; Spasm relief; Thromboxane A2 synthase inhibitor

Thromboxane (TX) A2 and prostaglandin (PG) I2 are extremely labile substances, with half-lives of 30 s and 10 min, respectively. PGI2 and TXA2 have the opposite effects on platelet aggregation and vascular smooth muscle: PGI2 inhibits platelet aggregation1 and induces relaxation of vascular smooth muscle2 whereas TXA2 induces platelet aggregation3 and powerful contraction of vascular smooth muscle4,5. As a spasm provocation test, intracoronary injection of acetylcholine (ACh) is clinically used in the cardiac catheterization laboratory6,7 because ACh is superior to ergonovine for the induction of multiple spasms8. It is also known that coronary artery spasms can activate the coagulation system in the coronary circulation9 and that an increase in platelet aggregates in peripheral and coronary sinus blood occurs in patients with coronary spastic angina10. Moreover, elevation of TXB2 concentrations in patients with variant angina in peripheral and coronary sinus blood has been reported11,12. It is possible that a transient imbalance between TXA2 and PGI2 is temporally associated with the development of coronary spasms. Intravenous administration of PGI2 and aspirin failed to prevent attacks of vasospastic angina, despite decreasing the TXB2 concentration, when they were trialled approximately 20 years ago13–15 but it is still not known whether intracoronary administration of a TXA2 synthase inhibitor can relieve coronary spasms locally.

We sought to clarify the effectiveness of intracoronary administration of a TXA2 synthase inhibitor, Ozagrel Na, to relieve coronary spasms induced by the intracoronary injection of ACh.

**Methods**

**Study Patients**

From January 1996 to December 1998, we performed systematic ACh provocation tests in all patients who underwent diagnostic coronary arteriography. Subjects were excluded from the spasm provocation test if they had left main narrowing (>50%), 3-vessel disease, 2-vessel disease with total occlusion, heart failure (New York Heart Association functional class III or IV), renal failure, spontaneous spasms or if isosorbide dinitrate was initially used to relieve spasms in the coronary artery being tested. During
In this period, we performed the Ach spasm provocation tests in 212 consecutive patients (154 men, mean age: 63±10 years) undergoing coronary arteriography and without significant organic stenosis, and coronary artery spasms were observed in 92 (82 men, 63±10 years) (Table 1). The procedure was explained in detail to each patient, informed consent was obtained and the protocol of the study was in agreement with the guidelines of the institution’s ethical committee.

Ach Spasm Provocation Test

Coronary arteriography was carried out after injection of 8–10 ml of Iopamiron (Scherling) with the Sones technique in the morning and afternoon (from 10.00 h to 16.00 h) under no medication for at least 24 h. A USCI bipolar electrode catheter was inserted into the right ventricular apex through the femoral vein and connected to a temporary pacemaker set at a rate of 45 beats/min. As previously reported16–22 provocation of coronary vasospasms was performed with intracoronary injections of Ach at incremental doses of 20, 50 and 80 μg into the right coronary artery and 20, 50 and 100 μg into the left coronary artery over 20 s with at least a 3-min interval between each injection. Coronary arteriography was performed when ST-segment changes, chest pain or both occurred and there was a 1-min interval until spasm relief. When a coronary spasm was induced, a 20 mg intracoronary bolus of TXA2 synthase inhibitor, Ozagrel Na, was administered into the responsible vessel. Moreover, if the coronary spasm did not resolve within 3 min or if hemodynamic instability occurred, 2.5–5.0 mg of isosorbide dinitrate was injected into the responsible vessel. During the study, arterial blood pressure and heart rate were monitored on an oscilloscope with a Nihon-Kohden poly-electrocardiogram (ECG) lead (II) were continuously measured after intracoronary administration of isosorbide dinitrate (2.5–5.0 mg) to evaluate coronary atherosclerosis defined as >75% luminal narrowing. Coronary arteries were excluded from this study. Significant organic stenosis was defined as >99% vessel narrowing (>99%) localized in one major coronary artery and a diffuse spasm was diagnosed when transient vessel narrowing less than 99%, compared with the baseline coronary angiography, was observed from the proximal to distal segments in the 3 major coronary arteries. Coronary spasm relief was defined as TIMI 3 flow.

Spontaneous Relief vs Effect of Ozagrel Na in Ach-Induced Spasms

In 7 of the patients we compared serial coronary angiography with and without an intracoronary bolus injection of Ozagrel Na during Ach-induced spasms. Coronary spasms were provoked by Ach in 5 right coronary arteries and 2 left anterior descending arteries, and coronary arteriography was performed at 1-min intervals until TIMI 3 flow was achieved.23 All 7 patients had the same spasm configurations and sites on a second Ach test, which was performed 15 min after the first. Spasm relief time, maximal ST segment elevation and frequency of chest pain were compared between the 2 tests.

Table 2 Spasm Relief Time After Intracoronary Injection of Ozagrel Na

<table>
<thead>
<tr>
<th>Spasm relief time</th>
<th>Right coronary artery</th>
<th>Left coronary artery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1min</td>
<td>21</td>
<td>22</td>
<td>43 (46.8%)</td>
</tr>
<tr>
<td>1–2min</td>
<td>21</td>
<td>17</td>
<td>38 (41.3%)</td>
</tr>
<tr>
<td>2–3min</td>
<td>5</td>
<td>2</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td>&gt;3min</td>
<td>1</td>
<td>3</td>
<td>4 (4.3%)</td>
</tr>
</tbody>
</table>

Table 3 ECG Changes and Chest Pain (CP) During Spasm Provocation Tests With or Without Intracoronary Administration of 20 mg Ozagrel Na

<table>
<thead>
<tr>
<th>Case</th>
<th>Site</th>
<th>Ach dose (μg)</th>
<th>ST elevation</th>
<th>Max (mm)</th>
<th>Time (sec)</th>
<th>Spasm site</th>
<th>CP</th>
<th>ST elevation</th>
<th>Max (mm)</th>
<th>Time (sec)</th>
<th>Spasm site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LCA</td>
<td>20</td>
<td>V1–4</td>
<td>12</td>
<td>240</td>
<td>6 (f)</td>
<td>0/10</td>
<td>V1–2</td>
<td>4</td>
<td>120</td>
<td>6 (f)</td>
</tr>
<tr>
<td>2</td>
<td>LCA</td>
<td>50</td>
<td>V1–3</td>
<td>3</td>
<td>120</td>
<td>7 (f)</td>
<td>0/10</td>
<td>V1–2</td>
<td>1</td>
<td>120</td>
<td>7 (f)</td>
</tr>
<tr>
<td>3</td>
<td>RCA</td>
<td>50</td>
<td>II III aVF</td>
<td>1</td>
<td>150</td>
<td>3 (f)</td>
<td>1/10</td>
<td>no</td>
<td>0</td>
<td>120</td>
<td>3 (f)</td>
</tr>
<tr>
<td>4</td>
<td>RCA</td>
<td>50</td>
<td>10/10 II II aVF</td>
<td>3</td>
<td>300</td>
<td>1 (d)</td>
<td>0/10</td>
<td>no</td>
<td>0</td>
<td>120</td>
<td>1 (d)</td>
</tr>
<tr>
<td>5</td>
<td>RCA</td>
<td>50</td>
<td>5/10 II III aVF</td>
<td>3</td>
<td>200</td>
<td>2 (f)</td>
<td>0/10</td>
<td>no</td>
<td>0</td>
<td>60</td>
<td>2 (f)</td>
</tr>
<tr>
<td>6</td>
<td>RCA</td>
<td>50</td>
<td>10/10 II II aVF</td>
<td>2</td>
<td>180</td>
<td>4 (f)</td>
<td>6/10</td>
<td>no</td>
<td>0</td>
<td>120</td>
<td>4 (f)</td>
</tr>
<tr>
<td>7</td>
<td>RCA</td>
<td>20</td>
<td>10/10 II II aVF</td>
<td>3</td>
<td>210</td>
<td>2 (f)</td>
<td>5/10</td>
<td>no</td>
<td>0</td>
<td>120</td>
<td>2 (f)</td>
</tr>
</tbody>
</table>

Ach, acetylcholine; RCA, right coronary artery; LCA, left coronary artery; (f), focal spasm; (d), diffuse spasm.
demonstrated during and/or after the pharmacologic tests: (1) ST-segment elevation of $>0.1$ mV in at least 2 related leads or (2) ST-segment depression of $>0.1$ mV of a horizontal or downsloping type or $>0.2$ mV of a junctional type. During the study, the arterial blood pressure and 1 ECG lead (II) were continuously monitored on an oscilloscope with a Nihon-Kohden polygraph and a standard 12-lead ECG was recorded every 30 s with a radiolucent carbon electrode used as the chest lead electrode.

Statistical Analysis
All values are expressed as the mean±SD. Differences among proportions were analyzed by the chi-square test with correction or the ANOVA test. $P<0.05$ was considered significant.

Results

Effectiveness of Ozagrel Na in ACh-Induced Spasms

Table 2

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>ACh dose (µg)</th>
<th>Spasm site</th>
<th>ST elevation</th>
<th>TX B2 concentration before</th>
<th>2 min</th>
<th>8 min</th>
<th>6-keto PGF1 concentration before</th>
<th>2 min</th>
<th>8 min</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>100</td>
<td>V1-V5</td>
<td>V1-V6 (5)</td>
<td>1270</td>
<td>137</td>
<td>2090</td>
<td>35</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>100</td>
<td>V1-V6</td>
<td>V1-V6 (6)</td>
<td>417</td>
<td>121</td>
<td>244</td>
<td>39</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>M</td>
<td>100</td>
<td>V1-V4</td>
<td>V1-V4 (3)</td>
<td>124</td>
<td>90</td>
<td>140</td>
<td>55</td>
<td>41</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>20</td>
<td>V1-V5</td>
<td>V1-V6 (6)</td>
<td>40</td>
<td>36</td>
<td>41</td>
<td>22</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

TXB2 and 6-keto PGF1 Concentrations in the Coronary Sinus During ACh-Induced Spasms and After Ozagrel Na

All 4 patients had coronary spasm of the left anterior descending artery during ACh-induced spasms. Intracoronary injection of 20 mg Ozagrel Na at 1 min was achieved TIMI 3 flow with 1 min. In addition, 2 min after Ozagrel Na, the right coronary artery was dilated.

Comparison Between Natural Spasm Relief and the Effect of Ozagrel Na

After intracoronary administration of 20 mg Ozagrel Na, the relief time of ACh-induced spasms was significantly shortened (200±59 s vs 111±23 s, $P<0.01$), ST elevation disappeared in 5 of the 7 patients and chest pain disappeared in 4 patients (Table 3). Representative cases are shown in Figs 1 and 2. The maximal ST segment elevation was markedly suppressed after intracoronary Ozagrel Na during ACh-induced spasms (Fig 1). Moreover, coronary spasms were not relieved naturally within 2 min, but intracoronary injection of 20 mg Ozagrel Na achieved TIMI 3 flow with 1 min. In addition, 2 min after Ozagrel Na, the right coronary artery was dilated (Fig 2).

TXB2 and 6-keto PGF1 Concentrations in the Coronary Sinus During ACh-Induced Spasms and After Ozagrel Na

All 4 patients had coronary spasm of the left anterior descending artery during ACh-induced spasms. Intracoronary injection of 20 mg Ozagrel Na at 1 min was achieved TIMI 3 flow with 1 min. In addition, 2 min after Ozagrel Na, the right coronary artery was dilated.

Fig 1. Maximal ST segment elevation was 12 mm on anterior precordial leads when 20 mg of acetylcholine induced a spasm in segment 6 (Upper). In contrast, intracoronary injection of 20 mg of Ozagrel Na decreased the maximal ST segment elevation (4 mm) when coronary spasm was observed in segment 6 after intracoronary injection of 20 mg of acetylcholine (Lower).

Fig 2. Coronary spasm was not relieved after 4 min of intracoronary injection of acetylcholine (Upper), but TIMI 3 flow was obtained 1 min after intracoronary administration of Ozagrel Na (Lower). Coronary spasm disappeared 2 min after intracoronary administration of 20 mg Ozagrel Na.
descending artery and intracoronary administration of Ozagrel Na was performed in all cases (Table 4). TXB2 concentration decreased after spasm relief (463±562 pg/ml vs 96±45 pg/ml, p<0.05) and returned to the baseline level after 10 min, administration of Ozagrel Na (628±978 pg/ml). The TXA2 synthase inhibitor prevented a significant increase in the coronary sinus concentration of TXB2 after ACh-induced spasm, but had little effect on the concentration of 6-keto-PGF2α.

Discussion
In previous reports, TXA2 synthase inhibitors have shown potential for reducing infarct size and in the treatment of angina pectoris25,26 but the administration of the TXA2 synthase inhibitor was systemic in the majority of the previous reports. Selective, intracoronary injection of a TXA2 synthase inhibitor has not been reported until now when we have shown that intracoronary TXA2 synthase inhibitor relieved coronary artery spasms induced by intracoronary injection of ACh. Therefore, we recommend that a TXA2 synthase inhibitor, as well as isosorbide dinitrate, should be administered for local relief of ACh-induced spasms.

Possible Mechanism of Selective Spasm Relief
Large doses of aspirin aggravate variant angina by blocking PG synthesis, although smaller doses have been reported as effective in reducing myocardial infarction.27 Shimokawa et al reported that in miniature pigs intravenous PG12 infusion failed to prevent histamine-induced coronary artery spasms, whereas intracoronary administration of thromboxane A2 markedly constricted all epicardial coronary arteries, but failed to provoke coronary artery spasms.28 Chierchia et al also reported that TXA2 blockade failed to prevent attacks of vasospastic angina, and that PG12 infusion also failed to block ergonovine-induced coronary vasospasms.29,30 In contrast, Szczeklik et al reported that infusion of PGH2 caused angina in 5 of 7 patients with angina at rest31 and Ohmori et al also reported that in 7 of 8 patients with ergonovine-induced spasms, intravenous infusion of TXA2 synthase inhibitor attenuated the increased spasticity with reduction of coronary sinus concentrations of TXB2.32 Thus from those reports, it remains controversial whether intracoronary administration of a TXA2 synthase inhibitor can relieve ACh-induced coronary artery spasms.

Intracoronary injection of ACh induces spasms via the muscarinic receptors.33 Endothelium-derived relaxing factors, such as NO, PG12, endothelium-derived hyperpolarizing factor and endothelium-derived constricting factors (TXA2 and PGH2), are released from the endothelium after intracoronary injection of ACh.34,35 The ACh-induced spasm stimulates the endothelium and platelet aggregation, and accelerates the synthesis of TXA2 in the endothelium of the coronary artery. The increased TXA2 and PGH2 concentrations lead to constriction of the coronary artery and in this situation, intracoronary administration of plenty of a TXA2 synthase inhibitor may inhibit TXA2 synthesis in the coronary circulation, thus playing a major role in coronary spasm relief.

The spontaneous release of TXB2 from the cerebral artery is approximately 10-fold higher than that of the coronary, mesenteric and saphenous arteries.36 It has been reported that a TXA2 synthase inhibitor was effective in the cerebral circulation, and if the local concentration of TXB2 is high in ACh-induced spasms, a large amount of TXA2 synthase inhibitor could block TXB2 synthesis in the coronary circulation and give spasm relief. However, because not only PG but other factors as well are involved in causing the coronary spasm, the effectiveness of intracoronary injection of a TXA2 synthase inhibitor to relieve ACh-induced spasms has critical limitations in the clinical situation.

Clinical Implications
Peripheral administration of a TXA2 synthase inhibitor and PG12 did not relieve coronary spasms clinically. However, the present study proved there is a clinical possibility for selective and local administration of a TXA2 synthase inhibitor for relief of ACh-induced spasms. Intracoronary administration of a TXA2 synthase inhibitor may reduce the amount of isosorbide dinitrate needed, and may lead to the diagnosis of spasms strictly according to whether or not there are other coronary artery spasms. If a TXA2 synthase inhibitor relieves ACh-induced spasms without the need to wait for spontaneous relief, we can perform ACh spasm provocation tests more safely. Because the pathogenesis of coronary artery spasms involves multiple factors in the clinical situation, intracoronary administration of a TXA2 synthase inhibitor may be useful for spasms that are refractory to isosorbide dinitrate.

Study Limitations
We did not have a placebo control for the effects of the TXA2 synthase inhibitor, so possible preconditioning effects cannot be excluded. However, spontaneous spasm relief was often observed in the ACh tests within a few minutes. We performed ACh tests with and without administration of a TXA2 synthase inhibitor in only 7 patients (7.6%), not in all 92 patients. All 7 patients had spasm relief after 20 mg of Ozagrel Na, but further study is necessary to investigate the TXA2 effect in relieving coronary spasms in many patients, including those with ergonovine-induced spasms.

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References


