Effects of Thromboxane Synthetase Inhibitors on Cyclical Reduction of Coronary Blood Flow in Dogs

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SUMMARY

Effects of new inhibitors of thromboxane synthetase, (E)-3-[(1-imidazolmethyl)phenyl]-2-propenoic acid and (E)-3-[4-(pyridylmethyl)phenyl]-2-methyl-2-propenoic acid on cyclical reduction of flow in the partially constricted coronary artery were examined in anesthetized beagle dogs. Intravenous injections of both agents with a dose of 20 mg/Kg eliminated the cyclical reduction induced by constriction in the majority of experiments. However, they failed to eliminate the cyclical reduction induced by indomethacin. Indomethacin-induced reduction was eliminated by prostaglandin I$_2$ in all experiments. It is suggested that thromboxane A$_2$ acted as an accelerator in the cyclical reduction of coronary flow induced by coronary constriction, but did not in the reduction induced by indomethacin.

Additional Indexing Words:
Thromboxane A$_2$  Prostaglandin I$_2$  Indomethacin

PATHOGENESIS of cyclical reduction of blood pressure and flow in a partially constricted coronary artery of anesthetized dogs has been studied by Uchida and co-workers. The previous studies suggested participation of vasospasm and platelet aggregation in the cyclical reduction. In addition, it was suggested that prostaglandin (PG) I$_2$ acted as an inhibitor of the reduction. On the other hand, thromboxane (TX) A$_2$ failed to induce and the inhibitors of TX synthetase such as imidazole and 1-methyl-imidazole failed to eliminate the reduction. This study was performed to examine the effects of new inhibitors of TX synthetase, (E)-3-[(1-imidazolmethyl)phenyl]-2-propenoic acid (OKY 046) and (E)-3-[4-(pyridylmethyl)phenyl]-2-methyl-2-propenoic acid (OKY 1580) on cyclical reduction of flow in the partially constricted coronary artery, in order to clarify whether or not TX A$_2$ participates as an inducer in the cyclical reduction.
METHODS

Experimental preparations
Twenty-nine beagle dogs were anesthetized with intravenously administered pentobarbital sodium (35–40 mg/Kg). The trachea was intubated for artificial positive pressure respiration with air. The upper 7 ribs on the left side were removed. After pericardiotomy, the proximal segment of the left circumflex artery was dissected free of surrounding tissues and a magnetic flowmeter (Nihonkoden, MF-2) was placed on it for measurement of coronary blood flow. Zero level of flow was determined by occluding a coronary segment distal to the flowmeter. A segment of the artery 1–1.5 cm distal to the flowmeter was also dissected free and a cylindrical constrictor was placed on it to reduce the flow to 40 to 70% of the control value. A catheter of 1 mm in internal diameter was introduced in retrograde fashion into a small branch of the artery to monitor the peripheral coronary blood pressure. Another catheter was introduced into the right femoral artery to monitor systemic blood pressure. Heart rate was obtained by a pulse-integrator triggered by femoral arterial pulse. A monopolar electrode was fixed on the left ventricular wall to monitor surface electrogram.

The 14 dogs in which cyclical reduction of coronary flow occurred within 1 hour, were then given the TX synthetase inhibitors. The agents were dissolved in distilled water and were given intravenously. During the cyclical changes in peripheral coronary blood pressure and flow, the pressure and flow usually decreased gradually and increased abruptly, and the changes were repeated. The cycle length of the changes was fairly constant at least from the first to 13th cycle in the previous study. Therefore, successive 3 cycles were timed, and the agents were injected 1–2 min after the fourth abrupt increase in pressure and flow in the majority of preparations, and the time required for reappearance of the cyclical reduction was compared to the average value of the preceding 3 cycles. When the time required for reappearance was significantly (Student’s t test, p<0.05) longer than the preceding cycle, the agents injected were considered to have eliminated the cyclical reduction.

The 10 dogs in which the cyclical reduction did not occur within 1 hour of observation and 5 dogs in which the reduction appeared but disappeared after a few cycles, were given 10 mg/Kg of indomethacin which could induce the reduction in the preliminary study. In these dogs, the TX inhibitors and PG I₂ were injected intravenously to examine whether they could suppress the indomethacin-induced cyclical reduction.

RESULTS

1. Effects of TX synthetase inhibitors on cyclical reduction of coronary blood flow

Fig. 1 shows the effect of intravenous injection of OKY 046 on cyclical reduction of coronary blood pressure and flow, and on the associated cyclical changes in surface electrogram. Following the injection of this agent, the cyclical reduction disappeared and did not reappear for more than 2 hours.
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Fig. 1. From top: coronary blood flow (CBF), peripheral coronary blood pressure (CBP), surface electrogram (ECG), systemic blood pressure (SBP), and heart rate (HR). A: before coronary constriction. B: during coronary constriction. C and D: 80 and 120 min after injection of OKY 046, respectively.

Table I. Effects of OKY 046 and 1580 on Cyclical Reduction of Coronary Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>dose (mg/Kg)</th>
<th>n</th>
<th>control cycle length (min)</th>
<th>reappearance time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OKY 046</td>
<td>20</td>
<td>7</td>
<td>7.1±1.6</td>
<td>70.3±16.5**</td>
</tr>
<tr>
<td>OKY 1580</td>
<td>20</td>
<td>7</td>
<td>9.0±2.0</td>
<td>63.3±15.8**</td>
</tr>
</tbody>
</table>

** p<0.01

Thereafter, small reduction of flow reappeared and then the magnitude of the reduction gradually returned to that of before the injection. Similarly, the reappearance time became longer than the control cycle length in the other 4 preparations. On the other hand, the reappearance time was not longer than the control cycle length in the remaining 2 preparations. As a whole, however, the reappearance time was significantly longer than the control cycle length (Table I). Following the injection of OKY 1580, the reappearance time also became longer than the control cycle length (Table I).

2. Effects of TX synthetase inhibitors and PG I₂ on indomethacin-induced cyclical reduction of coronary blood flow

Intravenous injection of 10 mg/Kg of indomethacin sodium resulted in cyclical reduction of coronary blood flow in 7 of 10 preparations in which the reduction did not appear within 1 hour after constriction. The time required for appearance of the reduction ranged from 3 to 48 (20.3±5.1, mean±SD) min. Also, the injection of the same dose resulted in cyclical...
reduction in all 5 preparations in which the reduction disappeared spontaneously. In these preparations, the time required for appearance of the reduction ranged from 2 to 25 (8.8±3.5) min. The indomethacin-induced cyclical reduction was little influenced by the TX synthetase inhibitors although the dose (20 mg/Kg) used was sufficient for elimination of the reduction in the preparations in which the reduction appeared without indomethacin. On the other hand, the indomethacin-induced cyclical reduction was always eliminated by intravenous injection of 1 μg/Kg of PG I₂ (Fig. 2).

Fig. 2. Effect of OKY 046 and PG I₂ on indomethacin-induced cyclical reduction of coronary blood flow.

**DISCUSSION**

The result in this study indicates that the TX synthetase inhibitors can eliminate the cyclical reduction of blood pressure and flow in the partially constricted coronary artery. It is known that these agents suppress synthesis of TX A₂ and augment synthesis of PG I₂ through inhibition of TX synthetase.⁷ Therefore, there are at least 2 possible mechanisms by which the agents eliminated the cyclical reduction: elimination of the reduction through inhibition of TX A₂ synthesis and through increased PG I₂ synthesis secondary to inhibition of TX A₂ synthesis. In the previous study,⁴¹ the cyclical reduction was not eliminated by imidazole and 1-methylimidazole that inhibit synthesis of TX A₂. Probably, they could not eliminate the reduction since their inhibitory action on TX synthetase is much weaker than those of the agents used in this study.⁷⁻⁹)

In this study, the cyclical reduction was induced by indomethacin which inhibits cyclooxygenase, and accordingly inhibits synthesis of both TX A₂ and PG I₂ in vitro.⁹ Therefore, we considered that indomethacin
inhibited synthesis of both TX A\textsubscript{2} and PG I\textsubscript{2} in this study. Probably, circulating PG I\textsubscript{2}\textsuperscript{10}) and that in the vascular wall\textsuperscript{11}) were suppressed by indomethacin leading to recurrent vasospasm and platelet aggregation,\textsuperscript{11)-13}) and resulting in cyclical reduction of coronary blood flow. Indomethacin-induced cyclical reduction was little influenced by the TX synthetase inhibitors. It is likely that TX A\textsubscript{2} synthesis was already suppressed by indomethacin and therefore the inhibitors could not play their role. Differing from TX synthetase inhibitors, PG I\textsubscript{2} always eliminated indomethacin-induced cyclical reduction. The fact supports the possibility that indomethacin induced the cyclical reduction mainly through inhibition of PG I\textsubscript{2} synthesis.

**REFERENCES**