EFFICACY OF DENOPAMINE, A $\beta_1$ ADRENOCEPTOR AGONIST, IN PREVENTING CORONARY ARTERY SPASM

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The selective $\beta_1$ adrenoceptor agonist denopamine was studied for its effectiveness in abolishing active vasospastic angina in 10 patients without obstructive coronary artery stenosis. All patients had anginal attacks at least once a day during the 3-day placebo period. Denopamine, 40 mg/day, completely abolished the attacks in 7 patients (efficacy 70%). Denopamine reduced the mean daily number of anginal attacks and nitroglycerin consumption in comparison with placebo (0.56 ± 1.23 vs 2.20 ± 1.27; p < 0.005 and 0.10 ± 0.24 vs 1.60 ± 1.93; p < 0.05, respectively). Aggravation of anginal attacks was not seen in any patient. During placebo period, anginal attacks were provoked in 6 of the 10 patients who received exercise stress test, and in 6 of the 7 patients who received the cold pressor test in combination with hyperventilation. Denopamine prevented anginal attacks induced by exercise stress tests in 4 of the 6 patients (67%) and that induced by the cold pressor test in 4 of the 6 patients (67%). There were no severe adverse effects during denopamine therapy. These results suggest that 1) denopamine is a safe and effective medication for vasospastic angina; 2) $\beta_1$ adrenoceptors may play an important role in the prevention of coronary artery spasm.

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DENOPAMINE is an orally active, positive inotropic agent. It has no catechol moiety in its structure, but it has been characterized as a selective $\beta_1$ adrenoceptor agonist by pharmacodynamic and receptor-binding studies. Denopamine was recently introduced to clinical use for treatment of patients with congestive heart failure and has been reported as effective in improving cardiac performance of such patients. Since $\beta$ adrenoceptor agonists lead to increases in heart rate, blood pressure, and myocardial contractility, and myocardial oxygen demand, the drug has been considered to be contraindicated for the treatment of classic angina pectoris.

Although nitrates and calcium antagonists have been reported to be very effective for vasospastic angina; numbers of patients are refractory to those drugs. It has been reported that the use of prazosin, trihexyphenidyl hydrochloride guanethidine and clonidine were occasionally effective in such patients. We reported the first case in which denopamine dramatically abolished the anginal attacks of a patient with active variant angina who was refractory to conventional treatment (nifedipine 80 mg or diltiazem 240 mg daily and isosorbide nitrate 185 mg daily) or prazosin, trihex-

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TABLE I SUMMARY OF CLINICAL AND ANGIOGRAPHIC FINDINGS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>ECG during spontaneous attack</th>
<th>Coronary angiography during attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>ST(↑): II, III, aVF, or ST(↓): V₂-V₆</td>
<td>normal</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>ST(↑): II, III, aVF</td>
<td>diffuse RCA</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>ST(↑): II, III, aVF</td>
<td>50% RCA</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>ST(↑): II, III, aVF, V₄₋₆</td>
<td>50% LAD</td>
</tr>
<tr>
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<tr>
<td>6</td>
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<td>M</td>
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</tr>
<tr>
<td>7</td>
<td>51</td>
<td>M</td>
<td>ST(↑): V₁₋₅</td>
<td>100% LAD</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>M</td>
<td>ST(↑): II, III, aVF, or ST(↓): V₂₋₆</td>
<td>normal</td>
</tr>
<tr>
<td>9</td>
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<td>M</td>
<td>ST(↑): V₂₋₆</td>
<td>25% LAD</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>M</td>
<td>ST(↑): II, III, aVF</td>
<td>100% LAD</td>
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LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; ST\(↑\) = ST elevation; ST\(↓\) = ST depression;

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yphenidyl hydrochloride. Since the patient's spasm in the right coronary artery which developed during cardiac catheterization did not disappear after intracoronary administration of nitroglycerin but disappeared promptly after the administration of noradrenaline, we administered denopamine in order to suppress the coronary artery spasm. To our knowledge, however, no quantitative data have been reported on the clinical effectiveness of \( \beta \) adrenoceptor agonists in suppressing coronary artery spasm.

It is generally accepted that the stimulation of \( \alpha \) adrenoceptors, or enhanced activity of the parasympathetic nervous system, plays an important role in coronary spasms. \(^9,\,10\) However, the precise mechanism by which coronary spasms occur still remains unknown. \( \beta \) adrenoceptor blocking agents have been reported to aggravate coronary artery spasms, since the blockade of coronary \( \beta \) adrenoceptors unmask \( \alpha \) adrenergic activity in large coronary arteries. \(^11,\,12\) However, Ozaki et al. \(^13\) reported that denopamine caused markedly significant concentration-related relaxations mediated by \( \beta_1 \) adrenoceptors in isolated canine coronary arterial strips contracted with prostaglandin F₂α. Therefore, it is possible that the blockade of coronary vasodilation via \( \beta_1 \) adrenoceptors may trigger or facilitate spasm in highly sensitized coronary segments.

The present study was performed in 10 patients with vasospastic angina without obstructive coronary artery stenosis in order to assess the effectiveness of denopamine for the prevention of coronary artery spasm.

**METHODS**

**Patients**

Ten male patients aged 48 to 66 years with vasospastic angina were enrolled in a comparison trial of placebo and denopamine (Table I). All patients had recurrent episodes of angina at rest, usually in the early morning or at night, associated with transient ST-segment elevation of at least 0.2 mV (8 patients) or depression of at least 0.1 mV (2 patients) on a standard 12-lead ECG. Seven patients had angina of effort as well. All patients were in an active phase of their disease at the time of our study. Selective coronary angiography was performed on all patients prior to entry into the study. No patient had significant organic coronary artery stenosis (defined as \( \geq 70\% \) reduction of luminal diameter after administration of nitroglycerin). In 6 patients, coronary artery spasm, defined as total or subtotal coronary occlusion associated with chest pain and ischemic ST-segment deviations, was induced by intracoronary injection of acetylcholine. \(^14\) Coronary artery spasm developed spontaneously during angiography.
in the other 4 patients. During the study, no patient received other cardioactive medication, including long-acting nitrates, calcium antagonists, or α or β adrenoeceptor blocking agents. Sublingual nitroglycerin for relief of angina was given.

Study Design
After the diagnosis of vasospastic angina was established, the study was initiated by entering a 3 day trial of the placebo period. All patients had at least 3 episodes of angina during this 3 day period. Next, denopamine, 40 mg/day divided into 4 doses, was administered orally for 7 days (the denopamine period). Informed consent was obtained from all patients before the study. The study was in agreement with the guidelines approved by our institution’s review committee.

Clinical Response to Therapy
Each patient was seen at least once a day by 1 of the investigators, and the following variables were measured: the number of episodes of angina (recorded daily by the patient in a diary), the amount of sublingual nitroglycerin consumed (recorded daily by the patient in a diary), and the number of adverse effects.

Electrocardiographic Response to Therapy
Electrocardiographic examinations were performed during the placebo and denopamine periods. Ischemic ST-segment deviations from baseline were considered to have occurred if ST elevation of at least 0.2 mV or depression of at least 0.1 mV was present.

1) Ambulatory ECG recording
Two-channel, calibrated, 24 h ambulatory ECG recordings were performed at the end of the placebo and denopamine periods. Two bipolar leads corresponded to V5 and inferior lead in each patient. From each tape, the following variables were measured; episodes of ischemic ST-segment deviation, episodes of chest pain concomitant with ST segment deviation, the number of ventricular premature contractions (VPCs) per day, and the highest grade of ventricular ectopic activity (according to the modified Lown grading system). Episodes of ST-segment deviation were defined as ischemic if a horizontal or downsloping ST depression or ST elevation of at least 0.1 mV was present for at least 1 min; ST-segment deviation was measured 80 ms after R wave.

2) Treadmill exercise stress test
A treadmill exercise stress test using the Bruce protocol was performed in the morning during the placebo and denopamine periods in all patients.

3) Cold pressor test in combination with hyperventilation
In 7 patients, the cold pressor test in which the patient’s right hand was submerged in ice water for 2 min immediately after vigorous hyperventilation for 6 min was performed in the early morning during the placebo and denopamine periods. If chest pain or ischemic ST-segment deviations on a standard 12-lead ECG appeared, the test was terminated immediately. The cold pressor test in combination with hyperventilation was considered positive if both chest pain and ischemic ST-segment deviations were induced.

Follow-up Study
After completion of the trial, 2 patients who had been protected from anginal attacks by denopamine continued to receive treatment with denopamine 40 mg per day (patient No. 2 and 6). They were followed clinically for 12 months and 18 months.

Data Analysis
The efficacy of denopamine was assessed by analyses of the reduction of the frequency of angina and of nitroglycerin consumption during the denopamine period in comparison with the placebo period. In addition, if the treadmill exercise stress test or the cold pressor test failed to produce chest pain or ST-segment deviations during the denopamine period in spite of a positive test during the placebo period, the administration of denopamine was considered effective.

The average number of episodes of angina, the amount of nitroglycerin consumption per day and the mean daily heart rate from ambulatory ECG recording during the denopamine period were compared with the placebo period using paired t tests. A p value of 0.05 or less was considered significant.
RESULTS

Clinical Response to Therapy

The mean daily number of anginal attacks and the amount of nitroglycerin consumption during the placebo period and the denopamine period are shown in Fig. 1. Denopamine reduced the number of anginal attacks and the amount of nitroglycerin consumption per day compared with placebo (0.56±1.23 versus 2.20±1.27; p<0.005 and 0.10±0.24 tablets versus 1.60±1.93 tablets; p<.05, respectively). Complete abolition of anginal attacks was seen in 7 of the 10 patients (70%). Anginal attacks were not accelerated in any case. It should be note that denopamine completely abolished anginal attacks in patients No. 1 and 6, who had been refractory to large doses of conventional treatment with calcium antagonists before the study (patient 1; nifedipine 40 mg, diltiazem 120 mg daily, patient 6, nifedipine 80 mg, diltiazem 240 mg daily) and isosorbide dinitrate (patient 1; 185 mg, patient 6; 120 mg daily). In the other 8 patients, a calcium antagonist and isosorbide dinitrate suppressed anginal attacks.

Complications and Adverse Effect

There were no complications during the study. No adverse effects were ascertained except in 1 patient who complained of slight palpitation during the denopamine period. There was no need for this patient to withdraw from the study. No patient's blood pressure changed after denopamine administration.

Electrocardiographic Response to Therapy

1) Ambulatory ECG recording

For the 10 patients, a total of 480 h of ambulatory ECG recording was analyzed. The average of mean daily heart rate in 10 patients was 66±10 beats/min during the placebo period and 77±6 beats/min during the denopamine period (p<0.01). A total of 15 episodes of ischemic ST-segment deviations were seen during the placebo period. Two of the 15 episodes were asymptomatic ST segment deviations. Denopamine reduced the overall episodes of ischemic ST segment deviations from 15 to 2.

No patient had a couplet of VPCs or ventricular tachycardia (VT) during the placebo period except during some episodes of ST-segment elevation. During the denopamine period, there were no signifi-
Fig. 2. Lown's grading system during the placebo period versus the denopamine period.
Denopamine did not deteriorate the grade of Lown's classification in any case. Although ventricular tachycardias were observed during some episodes of ST segment elevation in 2 patients during the placebo period, denopamine completely abolished all anginal attacks and ventricular premature contraction (VPCs). Lown's grading system was as follows: Grade 0, no VPCs; I, occasional isolated VPCs; II, frequent VPCs (more than 30 per hour); III, multiformal VPCs; IV A, repetitive VPCs (couple); IV B, repetitive VPCs (salvos); V, early VPCs ("R on T" phenomenon).

TABLE II INDIVIDUAL RESULTS OF PROVOCATIVE TESTS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Placebo period</th>
<th>Exercise stress test</th>
<th>Cold pressor test</th>
<th>ECG changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Placebo period</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Significant changes in the daily number of VPCs, and the grade of Lown's classification did not progress in any case (Fig. 2). Although VT was observed during some episodes of ST segment elevation in 2 patients (patient 1, patient 6) during the placebo period, denopamine completely abolished all anginal attacks and VPCs. Thus, denopamine did not appear to have significant arrhythmogenic potential in these patients.

2) Treadmill exercise stress test (Table II)
During the placebo period, anginal attacks and ischemic ST-segment deviations were provoked by a treadmill exercise stress test.

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in 6 of the 10 patients who received the test. The test turned negative in 4 of those 6 patients (67%) during the denopamine period. The test remained negative in the other 4 patients during the denopamine period.

3) Cold pressor test in combination with hyperventilation (Table II)
Anginal attacks accompanied by ST-segment elevations (at least 0.2 mV) were provoked by the cold pressor test in combination with hyperventilation in 6 of the 7 patients who received the test during the placebo period. Administration of denopamine prevented anginal attacks in 4 of the 6 patients (67%). Although patient NO. 1 had no spontaneous attacks during the denopamine period, an anginal attack was provoked by the cold pressor test in combination with hyperventilation.

Follow-up study
Two patients (no. 2 and 6) remained pain-free during the follow-up period for 12 months and 18 months respectively. Thus, the development of tolerance to the preventive effect of coronary artery spasm was not observed even when long-term treatment was carried out. In addition, no adverse effects were observed.

DISCUSSION
In the present study, denopamine completely abolished anginal attacks in 7 of the 10 patients with vasospastic angina without obstructive coronary artery stenosis (efficacy 70%). In addition, denopamine appeared to prevent anginal attacks induced by exercise stress tests in 4 of the 6 patients (67%) and the cold pressor test in combination with hyperventilation in 4 of the 6 patients (67%). These results suggest that denopamine can be another therapeutic agent for vasospastic angina. In particular, denopamine may be very useful for patients who cannot have Ca antagonists or nitrates because of side effects such as hypotension. This is the first study which has suggested that denopamine prevents coronary artery spasms, including exercise-induced spasms. It suggests that $\beta_1$ adrenoceptors might play an important role in preventing coronary artery spasms.

It is unlikely that the decrease of anginal attacks resulted from spontaneous remission of the disease. The present study was performed for 10 days to limit potential bias due to spontaneous changes in disease activity. In addition, we evaluated denopamine as effective only when it completely abolished anginal attacks, even though similar clinical trials have often reported it as successful if the number of ischemic episodes were reduced by 50% from control. Moreover, we performed the exercise stress test and the cold pressor test in combination with hyperventilation for the evaluation of coronary spasms during the placebo period and the denopamine period. Girotti et al. recommended the hyperventilation test as a useful procedure for selecting the best possible drug for the long-term treatment of variant angina. In their experience, the reproducibility was 100 percent when the test was performed under the same conditions, and 17 of 18 negative tests performed under the influence of a long-acting drug coincided with total remission of the patient's anginal episodes when this drug was administrated on a short-term or long-term basis. We performed the cold pressor test immediately after hyperventilation to enhance the sensitivity as a provocative test. Also, in the present study, the percentage of patients in whom denopamine made the test negative coincided with the percentage of patients in whom complete abolition of anginal attacks were seen during the denopamine period.

Yasue et al. reported that in only 1 of 13 patients with variant angina, isoproterenol infusion (10–15 μg/min for 1–3 min) provoked angina with ST elevations. However, the patient concerned had an 80% stenosis of the left descending coronary artery. Similarly, Kawashima et al. reported that isoproterenol infusion (0.01–0.08 μg/kg/min) provoked angina or ST segment deviations in 7 of 10 patients with variant angina who had at least 70% stenosis of the coronary artery corresponding to the area of ST segment changes. Conversely, in none of 8 patients with coronary artery stenosis less than 70%, were angina or ST segment changes precipitated by isoproterenol. Thus, it has not been reported that isoproterenol causes coronary spasm in patients with variant angina without obstructive coronary artery stenosis. Furthermore, Hillis and Braunwald said that
in theory β adrenoceptor agonists that cause β-mediated coronary artery vasodilation might be beneficial in relieving coronary artery spasm. However, no quantitative studies that examine whether or no β adrenoceptor agonists such as isoproterenol may relieve attacks due to coronary spasm have been reported. Our results clearly suggest that β₁ adrenergic stimulation prevents coronary artery spasm in patients with variant angina.

Stimulation of coronary α adrenoceptors has been repeatedly implicated as a mechanism potentially responsible for coronary spasm. The evidence for this hypothesis is mainly based on the observations reporting that spasm can be precipitated by both pharmacologic9,10 and reflex24 α adrenergic stimulation, and can be prevented or reversed by α adrenoceptor blocking agents5,10,21 On the other hand, several reports11,12 have shown that β adrenoceptor blocking agents may exacerbate variant angina, presumably by allowing α adrenergic stimulation of the large coronary arteries to occur unopposed. However, Chierchia et al25 reported that phenylephrine infusion or norepinephrine infusion with β adrenoceptor blocking agent failed to produce spasm in 12 patients with vasospastic angina, and high-dosage phentolamine infusion did not reduce the frequency of spontaneous ischemic episodes. Moreover, 2 placebo-controlled, double-blind studies of specific α adrenoceptor blocking agent with prazosin showed no obvious beneficial effects in patients with variant angina26,27 These results do not support the hypothesis that α adrenergic activation plays an important role in the genesis of coronary artery spasm. The blockade of β₁ adrenoceptors itself with β adrenoceptor blocking agents could have exacerbated variant angina from the view to our results that a β₁ adrenoceptor agonist prevented coronary artery spasm.

Several β adrenoceptor agonists such as isoproterenol and dobutamine have been shown to cause the development of tolerance to the hemodynamic effect. This is due to desensitization of positive inotropy and adenylate cyclase activity, accompanied by down-regulation of adrenoceptors and/or uncoupling of the receptor-adenylate cyclase complex28,29 It has been reported that chronic administration of denopamine at the effective doses does not produce desensitization of positive inotropy or down-regulation30 probably because agonist-promoted desensitization is mediated by phosphorylation of β adrenoceptors via cyclic AMP.31 It has been suggested that denopamine hardly results in desensitization of positive inotropy because the degree of elevation in cardiac cyclic AMP with denopamine is smaller than that with isoproterenol.30 In this study, 2 patients (No. 2 and 6) who had been treated with denopamine remained pain-free for more than 12 months. These results suggest that denopamine does not cause the development of tolerance to the preventive effect of coronary artery spasm, even when long-term treatment is carried out.

In conclusion, denopamine appears to be a safe and effective agent for preventing angina due to coronary artery spasm in patients without obstructive coronary artery stenosis. Long term, randomized and double-blind trials in larger groups of patients with vasospastic angina are required in future studies.

REFERENCES


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