Cardiovascular Effects of a New Inotropic Agent, Denopamine (TA-064); with Reference to It’s Effects on Cardiac Hemodynamics and Metabolism

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A new inotropic agent, denopamine (TA-064) was shown to have a strong positive inotropic effect. Its effect on cardiac hemodynamics and metabolism was evaluated by using wall stress and direct measurement of myocardial oxygen consumption. With plasma concentration of denopamine (21–29 ng/ml on average), attainable by one single oral dose (10 mg), the positive inotropic effect was evident by the significant increase in peak (+)dp/dt (+15% increase from control), and shortening velocity of the left ventricle (+39%), when heart rate or blood pressure was not altered significantly. End-diastolic stress and endsystolic stress of the left ventricle, defined as indices of preload and afterload, respectively, were reduced significantly. The reduction of preload (−51%) was the result of improved left ventricular filling, and the reduction of afterload (−23%) was due to the increased contractility. Neither coronary sinus blood flow nor aortocoronary AV O₂ difference was changed. Consequently, myocardial oxygen consumption remained unaltered. When the dose is chosen properly, denopamine is able to exert salutary effects in patients with severe heart failure.

CONGESTIVE heart failure (CHF) is a syndrome characterized by venous congestion and low cardiac output. Although CHF is the result of complex interaction of the cardiac, renal, neurohumoral and peripheral vascular systems, depression of myocardial contractility is playing the key role in the production of heart failure. In the treatment of heart failure, digitalis and various forms of afterload- or preload-reducing agents have been used with some success. However, the clinical use of digitalis is limited because of its narrow therapeutic range and serious arrhythmogenic effects in patients with severe heart failure.

At this time, only a limited number of inotropic agents are available for ambulatory use. Thus, a new class of orally effective inotropic agents is necessary.

Denopamine (TA-064) was synthesized recently at Tanabe Seiyaku Co., Ltd, Osaka, Japan. In previous reports, we have shown that denopamine has a strong positive inotropic effect that is orally effective as well. Furthermore, this agent was shown to exert salutary effects on patients with severe heart failure. However, any inotropic agent such as this would be expected to increase myocardial oxygen consumption, which makes it prolonged use questionable. In this study, we have tried to explore clinical usefulness of this agent by analyzing its effect upon myocardial oxygen consumption and cardiac hemodynamics.

Key Words:
TA-064
Denopamine
Cardiac hemodynamics
Metabolism

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SUBJECTS AND METHODS

1. Effects of Oral Denopamine: Echocardiographic Study

It is not our intention to demonstrate the maximal effect of denopamine, since the positive inotropic effect was previously shown to be dose dependent! We chose to use M-mode echocardiograms to assess left ventricular function. Therefore, nine patients with diseased hearts (age, 51 ± 11 years, MEAN ± SD) were selected on the basis of uniform hypokontraction of the left ventricle without any abnormality of the segmental wall motion seen on two dimensional echocardiographic study. All had CHF (New York Heart Association functional class II to IV) after full medical treatment with bed rest, low sodium diet, diurals, diuretics, and other preload- and afterload-reducing agents. The causes of CHF were peripartum cardiomyopathy, terminal stage of syphilitic aortic regurgitation, and ischemic cardiomyopathy, one case each; the other six patients had dilated cardiomyopathy of unknown etiology. After informed consent was obtained, the patients were evaluated in the postabsorptive state, 3 to 5 hours after receiving their daily oral dose of digitalis, diuretics, or other conventional regimens. Bed rest of at least 30 minutes stabilized blood pressure and heart rate. Echocardiogram was recorded with electronic sector scanners (Toshiba SSH-11A, Toshiba SSH-40A), with 2.5 MHz and 3.5 MHz transducers. M-mode echocardiograms were derived from two dimensional images. Echocardiographic measurements were performed according to the standard method12 End-diastole was set at the initial deflection of the q wave in lead II of the electrocardiogram and end systole at the initiation of the aortic component of the second heart sound recorded at the apex. The following parameters were obtained:

\[
\text{Dd} = \text{internal dimension of the left ventricle at end-diastole,} \\
\text{Ds} = \text{internal dimension of the left ventricle at end systole,} \\
\text{IVSs} = \text{thickness of the interventricular septum at end systole,} \\
\text{PWTs} = \text{posterior wall thickness at end systole,} \\
\text{WTs} = (\text{IVSs} + \text{PWTs})/2, \\
\text{FS} = \text{fractional shortening of the internal} \\
\text{dimension of the left ventricle obtained as } \text{FS} = (\text{Dd} - \text{Ds})/\text{Dd} \times 100 \% , \\
\text{mVcf} = \text{mean velocity of circumferential fiber} \\
\]

TABLE I EFFECTS OF A SINGLE ORAL DOSE (10 mg) OF DENOPAMINE ON CARDIAC FUNCTION AND WALL STRESS. (N = 9) (PLASMA CONCENTRATION OF DENOPAMINE 21 ± 23 ng/ml)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Denopamine</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>73 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>107 ± 27</td>
<td>116 ± 33</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59 ± 17</td>
<td>60 ± 13</td>
</tr>
<tr>
<td>Dd (cm)</td>
<td>5.6 ± 0.6</td>
<td>5.7 ± 0.6</td>
</tr>
<tr>
<td>Ds (cm)</td>
<td>4.6 ± 0.8</td>
<td>4.3 ± 0.8*</td>
</tr>
<tr>
<td>FS (%)</td>
<td>18.3 ± 7.4</td>
<td>24.5 ± 8.5**</td>
</tr>
<tr>
<td>mVcf (circ/sec)</td>
<td>0.67 ± 0.24</td>
<td>0.93 ± 0.27**</td>
</tr>
<tr>
<td>ESP (mmHg)</td>
<td>73 ± 8</td>
<td>75 ± 7</td>
</tr>
<tr>
<td>aes (g/cm²)</td>
<td>89 ± 31</td>
<td>71 ± 23*</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; ESP = endystolic pressure. *p < 0.01; **p < 0.001. "the number of cases is eight. One case with severe aortic regurgitation was deleted because reliable ESP could not be obtained noninvasively.

shortening of the left ventricle obtained from carotid pulse tracing simultaneously recorded with the left ventricular echocardiogram.

After baseline echocardiogram was obtained, one single dose (10 mg) of denopamine was given orally. Echocardiographic examination was repeated 30, 45, 60, 90, 120, and 180 minutes later. Five consecutive beats in cases of normal sinus rhythm and 7 consecutive beats in cases of atrial fibrillation were averaged for the determination of echocardiographic variables. Premature and post-premature beats were disregarded. Blood pressure was automatically measured by cuff method (sphygmanometer BP-203x, Nihon Kohrin, Tokyo) throughout this study11

Noninvasive Estimation of Endystolic Pessure and Stress

We determined afterload to the left ventricle noninvasively using meridional wall stress of the left ventricle at end systole (aes) according to the method of Grossman et al., as aes = [ESP x Ds x 1.35/4 x Wts x (1 + Wts/Ds)] (g/cm²), where ESP = endystolic pressure of the left ventricle13 We defined endystole at the point of end-ejection of the left ventricle, which is easily identified at the initial deflection of the aortic

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Fig. 1. The effects of one single oral dose of denopamine (10 mg). The representative case is shown. LV wall motion is clearly improved in a 45 year old female with idiopathic dilated cardiomyopathy at the plasma concentration of denopamine of 24.2 ng/ml. Heart rate was not changed when systolic blood pressure was changed modestly. Because of improved contractility, calculated wall stress (oes) was reduced significantly.

component of the second heart sound. Thus, dicrotic pressure of the central aorta was equated with endystolic pressure of the left ventricle, and noninvasively estimated from the brachial blood pressure obtained by cuff method and relative height of the dicrotic notch of the carotid pulse tracing, as ESP = b/a (SBP - DBP) + DBP, where b = height of the dicrotic notch, a = total amplitude of the carotid pulse tracing, SBP = systolic blood pressure, and DBP = diastolic blood pressure.

In order to validate this method, the dicrotic pressure of the central aorta was measured in 60 patients (aged 16 to 66 years) during routine cardiac catheterization study simultaneously with carotid pulse tracing and blood pressure measurements by cuff method. Dicrotic pressure was estimated noninvasively by the method described above and compared with direct measurements. In the range of 62 to 152 mmHg, both methods were found to have a high correlation (r = 0.963) with a mean difference of 5.3 ± 5.0 mmHg. The noninvasive method tends to underestimate dicrotic pressure by 5 mmHg on the average.

2. Effects on Myocardial Blood Flow and Metabolism; with Reference to Their Interaction with

*Japanese Circulation Journal Vol. 50, July 1986*
Acute hemodynamic effects of TA-064
(29±12 ng/ml)

Fig.2. With continuous intravenous infusion of denopamine, plasma concentration reached 29 ng/ml on average. Neither heart rate nor LV systolic pressure was changed. However, LV end-diastolic pressure was markedly reduced. Peak (+)dp/dt and peak (-)dp/dt were both significantly increased. (N = 7)

Cardiac Hemodynamics
The subjects of this study were eight patients with a history of severe CHF (age, 53 ± 10 years). The cause of CHF was aortic and mitral regurgitations in one, and coronary artery disease in two cases. The rest of five cases had dilated cardiomyopathy. The catheterization was performed by a brachial approach with the patient in the fasting state under mild sedation. All medications except digitalis were withheld for 12 to 18 hours before the procedure. Cardiac output was measured by the thermodilution method. Left-sided cardiac pressures were recorded with Mikro-tip® angiocatheters (PC-471 or 481, Millar Instruments). Left ventricular (LV) cineangio-grams were recorded in a 30° right anterior oblique projection. LV volume was calculated by the area-length method. Midwall circumferential stress (τ) was obtained at end-diastole and endsystole from the instantaneous volume,
Fig. 3. Although cardiac index or ejection fraction was not changed significantly, end-diastolic stress and end-systolic stress were markedly reduced. Cardiac output was obtained in six patients.

axes, wall thickness and pressure using the thick walled ellipsoid model of Mirsky as \( \sigma = \frac{P}{h/2B - B^2/2A^2} \), where \( P \) = pressure, \( h \) = wall thickness, and \( A \) and \( B \) = long and short radii to the midwall, respectively.\(^\text{14}\) Midwall circumferential wall stresses at end-diastole and endsystole were defined as the indices of preload and afterload. Details of this procedure were reported previously.\(^\text{15}\)

The multithermister flow catheter was introduced from the left antecubital vein and advanced into the coronary sinus. Thermodilution coronary sinus blood flow was measured in triplicate according to the method by Ganz et al.\(^\text{16}\) Blood samples were obtained from the central aorta and the coronary sinus for the measurements of oxygen, lactate, pyruvate, free fatty acid, and blood sugar content, and denopamine concentration, respectively. Myocardial extraction of each substrate was determined by the ratio of arterio-venous difference to the arterial content of the substrate in the coronary circulation. Myocardial oxygen consumption was estimated from the product of the thermodilution coronary


\(^{16}\) Ganz, W., et al., Catheterization of the heart, 1978, 1, 159-164.
TABLE II  EFFECTS OF DENOPAMINE ON CARDIAC METABOLISM (PLASMA CONCENTRATION OF DENOPAMINE 29 ± 12 ng/ml) (N = 6)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Denopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV O₂ diff (vol%)</td>
<td>11.67 ± 1.62</td>
<td>11.63 ± 1.89</td>
</tr>
<tr>
<td>O₂ ext. ratio</td>
<td>0.70 ± 0.04</td>
<td>0.68 ± 0.06</td>
</tr>
<tr>
<td>CSF (ml/min)</td>
<td>121 ± 40</td>
<td>111 ± 24</td>
</tr>
<tr>
<td>MVO₂ (ml/min)</td>
<td>14.3 ± 5.2</td>
<td>13.4 ± 3.4</td>
</tr>
<tr>
<td>BS ext. ratio</td>
<td>0.07 ± 0.17</td>
<td>-0.02 ± 0.08</td>
</tr>
<tr>
<td>pyruvate ext. ratio</td>
<td>0.15 ± 0.31</td>
<td>-0.02 ± 0.64</td>
</tr>
<tr>
<td>lactate ext. ratio</td>
<td>0.29 ± 0.17</td>
<td>0.21 ± 0.26</td>
</tr>
<tr>
<td>FFA ext. ratio*</td>
<td>0.12 ± 0.10</td>
<td>0.14 ± 0.14</td>
</tr>
</tbody>
</table>

Abbreviations: AV O₂ diff = aortocoronary sinus oxygen content difference; ext. ratio = extraction ratio; CSF = coronary sinus blood flow; MVO₂ = myocardial oxygen consumption; BS = blood sugar; FFA = free fatty acid. None of the changes shown above is statistically significant.

* N = 7, ** N = 6

sinus blood flow and the aortocoronary sinus oxygen content (AV O₂) difference.

Cardiac hemodynamic and metabolic studies, and LV gram were performed without significant time-delay. After baseline measurements were obtained, the patients were given denopamine at 2 µg/kg/min for 10 minutes and above procedures were repeated. The plasma concentration of denopamine was measured using selected ion monitoring technique by gas chromatography mass spectrometry. Significance of difference of the variables from their control values was evaluated using Student paired t-test.

RESULTS

1. Effects of Oral Denopamine

The control values and the peak effects after 10 mg of oral denopamine were shown in Table I. Denopamine concentration varies among individuals and reached its peak (20.7 ± 13.4 ng/ml, MEAN ± SD) at 30 to 180 minutes (87 ± 44 minutes). The representative case is shown in Fig. 1. Heart rate, blood pressures or internal dimension of the left ventricle at end-diastole was not changed significantly. Left ventricular dimension at end-systole, however, was significantly reduced. As a consequence, fractional shortening (FS) or shortening velocity of the left ventricle (mVcf) was increased significantly (FS +34%, mVcf +39%) increases from their controls). Endsystolic stress of the left ventricle, index of afterload, was significantly reduced (20% reduction).

2. Effects on Cardiac Metabolism and Hemodynamics

Plasma concentration of denopamine reached 28.8 ± 12.4 ng/ml with continuous intravenous infusion at a rate of 2 µg/kg/min for 10 minutes. Hemodynamic data were obtained in seven patients. Neither heart rate nor LV systolic pressures was changed significantly at this plasma concentration of denopamine. However, LV end-diastolic pressure was significantly reduced (12 ± 4 ± 6 ± 3 mmHg, p < 0.01). Peak (+)dp/dt and peak (−)dp/dt were significantly increased from their controls (Fig. 2). Cardiac output, LV volumes or ejection fraction was not altered significantly. End-diastolic stress and endsystolic stress were significantly reduced (p < 0.01; oes, 248 ± 77 + 192 ± 62 g/cm², p < 0.05) (Fig. 3).

Coronary sinus blood flow, AV O₂ difference in the coronary circulation or myocardial oxygen extraction ratio was not changed (Table II). Calculated myocardial oxygen consumption, thus, remained unaltered. The myocardial extraction ratio of blood sugar, pyruvate, lactate or free fatty acid was not changed significantly.

DISCUSSION

Denopamine was shown to have a strong positive inotropic effect at the concentration with minimal or no chronotrophic effect. Furthermore, we have shown that the increase in left ventricular contractility could result in reduction of preload and afterload. Myocardial oxygen consumption remained unaltered, as did several indices of cardiac metabolism. The reduction of preload was shown to be the result of fall in LV end-diastolic pressure and the reduction of afterload was the result of increased contractility.

Neither blood pressure nor cardiac output was altered in this study, negating the significant effect of this agent on the peripheral vascular system. This has been shown in experimental animals using canine arterial strips17 and the measurement of femoral blood flow in anesthetized dogs18. Therefore, the fall in LV end-diastolic pressure is considered to be the result of increased LV emptying and probably improved LV filling, as suggested by increased rate of LV pressure fall. Likewise, a strong
positive inotropic effect is evident by the significant increase in peak \((+dp/dt(+15\%))\) and shortening velocity of the left ventricle \((+39\%)) because the heart rate and blood pressure were not changed appreciably.

Whether or not denopamine exerts its favorable effects via "myocardial wasting" is a serious question to be answered, since any increase in LV contractility would be expected to increase myocardial oxygen consumption. Indeed, Bing et al. demonstrated that denopamine increased heart rate and myocardial oxygen consumption in the failing heart preparation. However, the concentration of denopamine used in Bing's experiment reached 400 ng/ml, which is 5 to 20 times higher concentration observed in our studies. The measurement of indirect myocardial oxygen consumption by Thomann et al. clearly demonstrated that oxygen consumption increases as the serum concentration of denopamine rises. However, of clinical importance is that the increase in myocardial oxygen consumption was more prominent in the group with normal LV contractility. In the group with depressed contractility, however, the increase in myocardial oxygen consumption was modest, even with large dose of denopamine \((153 \text{ ng/ml})\). At the concentration comparable to ours \((16 \text{ to } 42 \text{ ng/ml on average})\), myocardial oxygen consumption was not altered but rather reduced. The coronary AV \(O_2\) difference, coronary blood flow, thus, myocardial oxygen consumption were not altered significantly in our study. Likewise, several indices of myocardial metabolism were not changed. Furthermore, denopamine even with the highest concentration did not influence high energy phosphate or glycolytic intermediates in Bing's experiment. Therefore, "myocardial wasting" is not considered to have played a major role for the improvement of LV performance by denopamine.

Myocardial oxygen consumption is governed by several variables; heart rate, contractility and loading conditions of the heart, particularly afterload. We chose to use systolic and diastolic wall stresses as the indices of afterload and preload because wall stress is shown to be a useful index for the evaluation of muscle function and successfully applied by noninvasive means as well. There is a strong relation between changes in the afterload imposed on the heart and its oxygen consumption; acute reduction in afterload proportionally decreases myocardial oxygen consumption. Therefore, the significant reduction of wall stress observed in this study could explain the lack of change in myocardial oxygen consumption; the reduction of wall stress may have offset the increase in myocardial oxygen consumption induced by the positive inotropic effect of denopamine.

The lack of significant increase in cardiac output and ejection fraction is probably due to the marked reduction in preload \((51\% \text{ reduction on average})\), which lessened the ability of augmentation in cardiac performance. More importantly, however, the reduction of preload would alleviate the symptoms of heart failure, and lend a beneficial effect to the diseased muscle itself, since the increase in preload forms the basis of "afterload mismatch" and heart failure. Indeed, a multicenter trial on the chronic effects of denopamine showed that this agent reduced the symptoms of congestion and improved the sense of well-being up to one year in the patients with severe heart failure.

We should not be satisfied, however, by merely demonstrating hemodynamic improvement. It is our goal to improve the quality of life and hopefully prolong life. Since our experience is still limited, we must solve several important issues before we start its clinical use. Clinical effectiveness should be demonstrated by use of a totally objective method without any observer bias using a double-blind controlled study design. The absence of significant untoward effects should be documented on a large scale clinical study. We felt that this agent is promising and need more critical evaluation.

In summary, a new inotropic agent \((\text{denopamine})\) was shown to have a strong positive inotropic effect. Neither coronary blood flow nor myocardial oxygen consumption was not altered. Increase in contractility resulted in marked reduction in preload and afterload, which could explain the lack of significant increase in myocardial oxygen consumption. When the dose of denopamine is chosen properly, the salutary effects can be expected in the patients with severe heart failure.

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