Treatment of Variant Angina with Drugs: A Survey of 11 Cardiology Institutes in Japan

EICHI KIMURA, M.D., AND HIROSHI KISHIDA, M.D.

SUMMARY  Data from 11 cardiology institutes in Japan were examined to determine the effectiveness of drug therapy, especially with calcium antagonists, on variant angina. The subjects were 243 males and 43 females, most of whom were 40–59 years old. Coronary artery lesions were found in 92 of 162 patients (56.7%) in whom cinecoronary arteriograms were done. The efficacy rates of nifedipine, diltiazem and verapamil were 94.0%, 90.8% and 85.7%, respectively. Regardless of the presence or absence of organic coronary artery lesions, the drugs were effective in 92.3% of the patients with normal or nearly normal coronary arteries and in 82.6% of those with stenosis of more than 50% of the luminal diameter. These findings suggest that the drugs are effective through their antispasmodic actions.

VARIANT ANGINA pectoris, as described by Prinzmetal et al.1 was considered to be a rather rare syndrome. However, with the introduction of devices such as the long-term continuous recording electrocardiograph4 and the pocket electrocardiograph,5 it has become easier to record ECGs during anginal attacks and the prevalence of this disease has been found to be higher than was once thought.

As to the pathogenesis of the disease, coronary arteriography has revealed that, in addition to cases where there are definite organic obstructive lesions in coronary arteries, there are also cases with normal or nearly normal coronary arteries. According to current views,4,6 attacks of variant angina are caused by coronary spasm.

The effectiveness of nitroglycerin and other nitrates in relieving anginal pain has been confirmed empirically, but it is also important to prevent anginal episodes that might be accompanied by life-threatening arrhythmias.

Kimura et al.4 and Muller and Gunther7 reported that calcium antagonists, such as nifedipine, diltiazem and verapamil, are effective in suppressing anginal attacks and the results of a systematic study have been

8. Adverse reaction to Inocor™ (brand of amrinone). Summary, product information. Sterling-Winthrop Research Institute, October 23, 1979

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reported by Waters et al., but no comparative analysis of the effectiveness of the three calcium antagonists, anticoagulants and \( \beta \) blockers has been made in a large number of patients with variant angina.

In Japan variant angina is a common syndrome and many cases have been treated with these agents. With these considerations in mind, this report examines and discusses the effectiveness of these drugs in treating variant angina on the basis of the results obtained from a large number of patients.

**Subjects and Methods**

Usually, double-blind tests are required to evaluate the effectiveness of a drug. However, double-blind tests are difficult to perform in variant angina, not only because of the serious ethical problems involved, but also because the frequency of the attacks is not always constant and the risk of severe arrhythmias and myocardial infarction cannot be avoided. Moreover, because it is almost impossible to randomize the cases, it is possible that inappropriate conclusions would be obtained.

For this reason, we did not attempt any double-blind tests and examined the effectiveness of the drugs in 286 cases, 243 males and 43 females. The data for this large number of cases were obtained from the institutes listed in the Appendix. Most of the subjects were 40-59 years old. Variant angina was diagnosed when reversible ST-segment elevations of more than 0.1 mV were confirmed by ECGs recorded during spontaneous attacks at rest. Patients with a history of myocardial infarction were excluded from the study. The positive ergonovine test was not included among the diagnostic criteria for variant angina.

The drugs were evaluated and ranked as follows: markedly effective — complete elimination of anginal attacks within 2 days; effective — complete elimination of attacks after 2 days or a reduction in the number of attacks to less than half during the periods of drug administration in the hospital; ineffective — no reduction to less than half during the periods of drug administration. In 21 cases, the active drugs were replaced by inactive placebos to reconfirm the effectiveness of the drugs.

However, the effectiveness of anticoagulants and \( \beta \) blockers is difficult to assess because their effects only appear after a considerable time. Therefore, we did not apply the same criteria as for calcium antagonists, and evaluated anticoagulants and \( \beta \) blockers as effective when the number of attacks was reduced by more than half.

Long-acting nitrates were excluded from the survey because they were already known to be useful in the suppression of attacks of variant angina. The daily dosages of the six drugs used in this study were as follows: nifedipine 30-60 mg (average 39 mg) diltiazem 90-240 mg (average 160 mg); verapamil 120-320 mg (average 228 mg); a combination of 30-40 mg of nifedipine (average 32 mg) and 90-120 mg of diltiazem (average 100 mg); \( \beta \) blockers (propranolol) 30-90 mg (average 50 mg); an anticoagulant (warfarin) was given in varied doses according to its effectiveness in individual cases.

In 141 of the 286 patients, multiple drugs were used, including 15 patients who were given a combination of nifedipine and diltiazem. In the latter cases, when either nifedipine or diltiazem was found to be ineffective, the other drug was added. In the remaining cases, anticoagulants or \( \beta \) blockers were considered ineffective and were replaced by nifedipine or diltiazem.

Cinecoronary arteriography was carried out in 162 patients. Organic narrowing of the coronary artery was considered significant when it was more than 50% of the luminal diameter. Normal or nearly normal coronary arteries were found in 70 cases and stenosis greater than 50% was found in 92 patients — one-vessel disease in 55, two-vessel disease in seven and three-vessel disease in five. In the 25 remaining patients, the number of coronary arteries with stenosis was not described in the reports from the institutes. The relationships between the effectiveness of the drugs and the severity of the organic coronary lesions were analyzed using data from the 49 patients admitted to the authors' institute (Nippon Medical School Hospital).

**Results**

The number of spontaneous attacks in the 286 patients studied was 11.7 ± 1.0 per week before the administration of the drugs, with no significant differences between patients before the six treatment regimens. There was no deviation in the number of attacks between the markedly effective, effective and ineffective cases in any of regimens before treatment. Drugs were administered for 3-129 days, with a mean of 24.8 ± 1.4 days. The shortest mean duration was 12.9 ± 3.1 days for \( \beta \) blockers, probably because these drugs were replaced by some other drugs because of ineffectiveness in the early period. The longest mean duration was 30.7 ± 7.1 days for a combination of nifedipine and diltiazem.

Table 1 shows the effects of the drugs on variant angina. Of the 149 patients treated with nifedipine, anginal attacks disappeared completely in 115 (77.2%) and decreased to less than half in 25 (16.8%); because it was ineffective in only nine patients (6.0%), its beneficial effects were obtained in 94.0% of the patients. Similar results were obtained in the 87 patients treated with diltiazem and its rate of effectiveness was 90.8%. A combination of both drugs was effective in all 15 patients to whom it was administered.

When the drugs were replaced by inactive placebos in 21 cases in which either nifedipine or diltiazem was effective, the number of attacks increased from 0.4 ± 0.1 per week when the patients were on the active drugs for treatment periods of 35.8 ± 6.0 days, to 13.9 ± 2.0 when they were on the inactive placebos for periods of 4.9 ± 0.7 days.

In contrast, verapamil was effective in 85.7% of the patients to whom it was administered, but complete
disappearance of anginal attacks was observed in only 10.7%. The anticoagulants had an efficacy rate of 40.4%, much lower than that obtained with nifedipine, diltiazem and verapamil. There was a significant difference between the anticoagulants and the three other drugs (p < 0.001). Beta blockers were effective in only 11.1% of the patients.

We anticipated that the effectiveness of the antianginal drugs would depend upon the presence or absence of organic coronary artery lesions. An analysis of the results was available in 49 cases (table 2). Effectiveness compared with those with normal or no distinct lesions was a little lower in cases with coronary artery narrowing greater than 50%, but the difference was not significant, probably because of the small sample. Nifedipine and diltiazem were both effective, regardless of the presence or absence of coronary artery lesions.

There was only a small difference between the number of cases with coronary artery lesions and those without. Kimura et al.8 pointed out a similar relationship in Japanese patients. In contrast, reports from the United States9-13 France14 and Italy15 indicate that a majority of the patients had organic coronary artery disease, and that patients with normal or nearly normal coronary arteries accounted for only 16.3% of the total (table 3). The difference in the prevalence of the disease between Japan and Western countries was considered significant (p < 0.001).

**Discussion**

These results show that calcium antagonists such as nifedipine and diltiazem are effective in treating variant angina.

Usually, double-blind tests are necessary to

**Table 3. A Comparison of the Severity of Coronary Lesions between Cases in Japan and Western Countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases with coronary stenosis n</th>
<th>Cases without coronary stenosis n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy, France and U.S.A.</td>
<td>270 (83.7%)</td>
<td>226 (16.3%)</td>
</tr>
<tr>
<td>Japan (in this survey)</td>
<td>162 (56.7%)</td>
<td>92 (43.3%)</td>
</tr>
</tbody>
</table>

*p < 0.001 (chi-square test).
evaluate the effects of certain drugs on certain diseases. In the case of variant angina, Parodi et al.\textsuperscript{16} described the effectiveness of verapamil in cases in whom continuous electrocardiographic recording was used to compare verapamil with an inactive placebo by the crossover method. However, problems are involved in carrying out double-blind tests in variant angina. Our survey was carried out because we thought it essential to analyze the effects of medical treatment in a large number of patients before conducting a double-blind study. This is probably the first report of its kind, and the data obtained showed the marked effectiveness of the drugs on anginal attacks in most of the cases, although these results do not apply to patients treated with verapamil.

Nifedipine, diltiazem and verapamil were included among the calcium antagonists in a recent pharmacologic view, as first proposed by Fleckenstein.\textsuperscript{17} The action of these drugs on ordinary angina pectoris is explained by coronary vasodilation accompanied by the depression of myocardial oxygen consumption. We used calcium antagonists to treat variant angina because we considered this disease to be no more than a type of angina pectoris.

Formerly, anticoagulants were used to prevent attacks of variant angina. In this survey, we found their efficacy rate to be 40.4%. Although anticoagulants have some effect on variant angina, we cannot place much reliance on them. There are some reports that \( \beta \) blockers are effective; Guazzi et al.\textsuperscript{18} for example, described how propranolol was effective on variant angina, while Practolol was not. The most commonly used \( \beta \) blocker in this survey was propranolol, but the effectiveness of \( \beta \) blockers was only 11.1%. Yasue et al.\textsuperscript{19} and Hansen and Sandle\textsuperscript{20} reported that \( \beta \) blockers aggravated the disease.

Our findings that nifedipine and diltiazem were dramatically effective in cases of variant angina suggest that their mode of action on variant angina must be different from that on classic angina pectoris.

Guazzi et al.\textsuperscript{21} observed that, unlike angina of effort, anginal attacks in variant angina were not preceded by increases in blood pressure and heart rate. The inhibitory action of these drugs on myocardial oxygen consumption does not seem to play an important role in the prevention of attacks of variant angina.

The etiology of variant angina is generally ascribed to coronary spasm on the basis of cinecoronary angiographic findings and the ergonovine maleate provocation test for anginal attacks of Heupler et al.\textsuperscript{22} In addition, the fact that calcium antagonists are effective whether or not organic coronary lesions are present suggests that variant angina may result from a functional rather than an organic event.

Provided all of these results are accepted, the effectiveness of calcium antagonists may be regarded as residing in their antispasmodic action. There is an increasing body of evidence to support this view.\textsuperscript{8, 23}

Although ergonovine maleate, which is known to have an \( \alpha \)-adrenergic action, induces coronary spasm, there are very few reports of the effectiveness on variant angina of \( \alpha \)-blocking agents, such as phen tolamine and phenoxybenzamine.\textsuperscript{24} According to Hansen and Sandle\textsuperscript{20} \( \alpha \)-blocking agents were ineffective.

Some investigators have suggested that the aggregation of platelets plays an important role in coronary spasm.\textsuperscript{25, 26} According to Foltz et al.,\textsuperscript{27} coronary blood flow showed cyclical reductions to near zero in coronary stenosis of 60–80% of the luminal diameter in experimental animals. This reduction in flow was eliminated by aspirin, probably because of its ability to reduce platelet aggregation, an effect that is observable in vitro. If so, aspirin would appear to inhibit the spasm that may be produced by the release from platelet aggregates of vasoconstrictive substances, such as serotonin, prostaglandin \( G_2 \) and thromboxane, at least in experimental animals.

Oliva and Breckinridge\textsuperscript{28} described how platelet aggregation may occur with spasms produced by vasoconstrictive substances released through transient sympathetic discharge related to cigarette smoking and the rapid-eye-movement phase of sleep. According to Levine,\textsuperscript{29} whilebishydroxycoumarin dilates the coronary arteries, leading to an increase in coronary blood flow in experimental animals, platelet adhesive ness decreases during bishydroxycoumarin therapy. He also stated that warfarin may increase the duration of platelet aggregation in response to ADP. Some of the effectiveness attributed by us to warfarin may be explained by these actions.

The prevalence of atherosclerotic coronary artery disease is lower in Japan than in the United States.\textsuperscript{28, 29} Robertson et al.,\textsuperscript{30, 31} reported that the prevalence of myocardial infarction is higher in Japanese people who migrated to the United States than in those living in Japan. There was no significant difference between the two groups in terms of the risk factors of blood pressure, serum cholesterol, relative weight and age, although there was a significant difference in cigarette smoking, the percentage being higher in Japanese living in the United States.

Although the prevalence of variant angina has been said to be much higher in the Japanese than in Occidentals, the large number of papers on the subject published recently in the Unite States\textsuperscript{10, 12, 32} and Europe\textsuperscript{14, 15} suggests that there is, in fact, no significant difference.

Coronary angiographic findings in cases of variant angina in Japan and in Western countries show that the differences exist in the prevalence of variant angina without organic coronary stenosis; there is a higher prevalence in Japan than in the Western countries. The reasons for this difference may be explained, in part, by such facts as the higher prevalence of coronary atherosclerosis in Japanese who had migrated to the United States than in those living in Japan. However, it is extremely difficult to determine why spasm in patients without marked coronary stenosis is more frequently observed in Japanese than in Western people. Further investigation is necessary to solve this problem.
References


Appendix

The following cardiology institutes and cardiologists participated in the study: Third Department of Internal Medicine, Kurume University (Hironori Toshima, M.D.); Research Institute of Angiocardiology, Kyushu University (Motoomi Nakamura, M.D.); Institute of Bulneotherapeutics, Kyushu University (Takashi Yanaga, M.D.); Surgical Department, Kobe University (Sakae Asada, M.D.); Division of Internal Medicine, Shizuoka City Hospital (Hirofumi Yasue, M.D.); Second Department of Internal Medicine, University of Tokyo (Satoru Murao, M.D.); Third Department of Internal Medicine, Showa University (Hirokazu Niitani, M.D.); Department of Cardiovascular Disease, Toranomon Hospital (Hiroshi Yamaguchi, M.D.); The Cardiovascular Institute, Tokyo (Kazuzo Katoh, M.D.); Department of Internal Medicine, Jichi Medical School (Saichi Hosoda, M.D.); First Department of Internal Medicine, Nippon Medical School (Eiichi Kimura, M.D.).
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