Clinical Effects of Nitrendipine on Variant Angina Pectoris

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SUMMARY

The clinical effects of nitrendipine, a new calcium antagonist, were investigated in a single-blind test on 21 patients with variant angina pectoris. The efficacy of the drug was evaluated on the basis of frequency of anginal attacks and Holter electrocardiographic findings during different treatment periods at doses of 10 mg once a day (period I) and 20 mg once a day (period II). The number of anginal attacks decreased significantly from a pretreatment level of 2.1 ± 0.3 per day to 0.7 ± 0.2 per day in treatment period I and 0.3 ± 0.1 per day in treatment period II ($p < 0.01$, $p < 0.001$, respectively). The consumption of sublingual nitroglycerin tablets decreased significantly in both treatment periods in comparison with the observation period before treatment ($p < 0.01$, $p < 0.001$, respectively). In 20 patients with continuous ECG monitoring, the frequency of ST-segment elevation was 4.5 ± 1.0 per day during the pretreatment period; it decreased significantly to 0.9 ± 0.6 per day in treatment period I and 0.5 ± 0.3 per day in treatment period II ($p < 0.01$, $p < 0.001$, respectively). The duration and the maximum magnitude of ST-segment elevation also improved significantly in both treatment periods. These results demonstrate the efficacy of nitrendipine in the treatment of variant angina at a single daily dose of 10 mg.

Additional Indexing Words:

Nitrendipine Variant angina pectoris Holter monitoring Calcium antagonist

SEVERAL recent studies have shown¹⁾⁻³⁾ that calcium antagonists are extremely effective in the prevention of coronary artery spasms. Nitrendi-

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pine,⁴⁾ a long-acting calcium antagonist, is chemically related to nifedipine, a well-characterized calcium channel blocker. The initial pharmacologic studies with nitrendipine indicated that this drug is a highly effective vasodilator⁵⁾; its antihypertensive activity has also been confirmed in humans.⁶⁾ Recently, it was reported⁷⁾ that nitrendipine inhibits prostaglandin F_{2α} (PGF_{2α})-induced rhythmic contraction in isolated human coronary arteries. Therefore, nitrendipine is expected to be effective in the treatment of variant angina pectoris. The present study assessed the efficacy of nitrendipine on variant angina pectoris so that the appropriate dosage and administration schedule could be established on the basis of symptoms and the results of Holter monitoring.

SUBJECTS AND METHODS

1. Patient selection and baseline characteristics

Patients were admitted to the study if they (1) were hospitalized with a diagnosis of variant angina pectoris with a transient ischemic ST-segment elevation of more than 0.1 mV during anginal attacks, (2) had two or more anginal attacks during the 2-day pre-observation period, (3) responded with a relief of angina to sublingual nitroglycerin, (4) presented with no clinical findings indicative of acute myocardial infarction or a history of life-threatening arrhythmia with loss of consciousness, and (5) had given informed consent for participation in the study. Excluded from the study were patients with: 1) anemia or valvular heart disease, and 2) conduction disorders such as left bundle branch block or WPW syndrome.

Table I. Baseline Characteristics of 21 Patients Treated with Nitrendipine

	Patients or frequency
No. of patients (Male : Female)	21 (20 : 1)
Mean age (year)	58 ± 2
Mean duration of angina (months)	16 ± 5
Patterns of angina provocation (n/%)	
Rest angina only	14/67%
Exertional angina only	2/ 9%
Rest & exertional angina	5/24%
History of previous infarction (n/%)	1/ 5%
Diseased coronary arteries (n/%)	
Normal or nearly normal	7/39%
Single-vessel	7/39%
Multi-vessel	4/22%
Anginal attacks (/day)	2.1 ± 0.3

A total of 21 patients (20 males and 1 female, 58 ± 2 years, mean $\pm$ SE) were entered in the study and treated at the medical institutions listed in the Appendix. Table I shows the backgrounds of the 21 patients used in the evaluation of the drug efficacy. The mean duration of angina pectoris was 16 ± 5 months. Fourteen patients had rest angina alone, 2 patients exertional angina alone and 5 patients rest and exertional angina. Only one patient had a history of myocardial infarction. Coronary arteriography was performed in 18 of the 21 patients. Significant organic coronary stenosis was defined as a luminal narrowing of more than 50%. The 7 patients had normal or nearly normal coronary arteries and the remaining 11 had significant organic coronary stenosis. The frequency of anginal attacks was 2.1 ± 0.3 /day in the pretreatment observation period.

2. *Clinical trial procedure*

A placebo control period (for a minimum of 2 days) was followed by two treatment periods, which lasted at least 3 days. During the first dose period, the patients received a single daily dose of 10 mg nitrendipine. During the second dose period, a single 20 mg daily dose was administered. The times of drug administration were selected at the discretion of the attending physician. The duration of administration in either treatment period did not exceed 1 week. Other antianginal drugs were not allowed during the study. The efficacy of the drug was evaluated on the basis of frequency of anginal attacks and Holter electrocardiographic findings. Twenty-four hour continuous Holter monitoring was performed in 20 patients during the control (placebo) and second treatment periods and in 15 patients during the first treatment period. The mean times of dosing were 8.4 p.m. (8 p.m. to 9 p.m.) during the first and the second treatment periods in a majority of cases.

3. *Evaluation of therapeutic response*

Each patient's therapeutic response was evaluated according to changes in both the number of anginal attacks and the frequency, duration and magnitude of occurrence of ST-segment elevation following treatment. In order to evaluate the effects of nitrendipine on the number of anginal attacks, the responses were rated on a four-grade scale as follows:

- 1) Markedly effective: complete disappearance of angina.
- 2) Moderately effective: $\geq 75\%$ reduction in number of attacks.
- 3) Mildly effective: $\geq 50\%$ reduction in number of attacks.
- 4) Ineffective: $< 50\%$ reduction or no change in number of attacks.

The frequency and duration of ST-segment elevation and the magnitude of maximum ST-segment elevation were compared from Holter ECG record-

ings before and after treatment. To further delineate the pharmacologic effects of nitrendipine, data were analyzed according to the relationship of the time of onset of ST-segment elevation and the time of drug administration before and after treatment.

4. Twenty-four hour Holter electrocardiograph

Twenty-four hour ECG was recorded at most study sites with an Avionics Holter electrocardiograph. The ECG was recorded through 2 channels, one of them where the maximum ST-segment elevations were observed. The same leads were used in the control and treatment periods. The time of attacks and their relationship to daily activities were recorded by the patients. A positive ST-segment elevation was defined as an elevation of this segment of 1 mm (0.1 mV) or more lasting at least 60 sec.

5. Statistical analysis

The Wilcoxon sign rank test was used to compare control and treatment period data concerning the ST-segment elevation in the ECG, the frequency of anginal attacks and the consumption of sublingual nitroglycerin tablets. All significance levels were calculated for two-tailed tests.

RESULTS

Effects on subjective symptoms:

Figure 1 shows the frequency of anginal attacks and the consumption of sublingual nitroglycerin before and after administration of nitrendipine.

Fig. 1. Effects of nitrendipine on the frequency of anginal episodes and consumption of nitroglycerin tablets. ** $p < 0.01$, *** $p < 0.001$.

The mean number of anginal attacks was 2.1 ± 0.3 per day before treatment with nitrendipine; it was reduced significantly to 0.7 ± 0.2 per day during treatment period I (10 mg nitrendipine) and 0.3 ± 0.1 per day during treatment period II with 20 mg nitrendipine ($p < 0.01$, $p < 0.001$, respectively, compared to pretreatment). The consumption of sublingual nitroglycerin tablets was significantly reduced during both treatment periods ($p < 0.01$, $p < 0.001$ versus pretreatment, respectively). As shown in Table II, anginal attacks disappeared completely in 50% of the patients receiving 10 mg nitrendipine and 85% of patients receiving a 20 mg daily dose. The effectiveness rates, inclusive of marked or moderate response, were 72.2% in the former and 90% in the latter treatment conditions.

Results of Holter monitoring:

Figure 2 shows the frequency, duration and magnitude of ST-segment elevation before and after treatment. The mean frequency of ST-segment elevation per patient was 4.5 ± 1.0 per day in the pretreatment period, 0.9 ± 0.6 per day in treatment period I and 0.5 ± 0.3 per day in treatment

Table II. Effectiveness of Nitrendipine: Reduction in Number of Anginal Attacks

	Effect (%)				
	Markedly	Moderately	Mildly	No change	Worsening
Treatment period I	50	22.2	16.7	11.1	0
Treatment period II	85	5	5	5	0

Fig. 2. Results of Holter monitoring after administration of nitrendipine.

** $p < 0.01$, *** $p < 0.001$.

period II (both significant decreases, $p < 0.01$, $p < 0.001$, respectively). The duration of periods of ST-segment elevation was 695.3 ± 136.0 sec per day before treatment; it was reduced significantly to 181.3 ± 111.1 sec per day during treatment period I and 68.5 ± 34.7 sec per day during treatment period II (both $p < 0.001$). The maximum ST-segment elevation was also reduced significantly during the treatment period, decreasing from 3.3 ± 0.4 mm before treatment to 1.0 ± 0.5 mm during treatment period I and to 0.7 ± 0.4 mm during treatment period II ($p < 0.01$, $p < 0.001$, respectively).

Figure 3 shows the frequencies of symptomatic and asymptomatic ST-segment elevation during pretreatment and treatment periods I and II. The hourly frequencies of ST-segment elevation tended to be high at midnight and in the early morning during the pretreatment period, but were reduced throughout the day during treatment periods I and II. The treatment with nitrendipine was effective for both symptomatic and asymptomatic ST-segment elevation. Thus, nitrendipine can be expected to provide prolonged antianginal and anti-ischemic effects. No side effects were encountered in any of the 21 patients.

Fig. 3. Relationship between the time of occurrence of ST-segment elevation and the time of nitrendipine administration.

DISCUSSION

Drug efficacy evaluation method:

In variant angina pectoris the angina is often unstable. Since the frequency of attacks is inconsistent, patients may die suddenly of acute myocardial infarction or arrhythmias. Thus, patients with either an impending infarction or life-threatening arrhythmias associated with syncope must be excluded from the clinical trials and observation periods must be minimized. Since few cases satisfy criteria for patient selection necessary to assay the therapeutic effect of new antianginal agents,⁸⁾ this study involved multiple centers (see Appendix).

In variant angina pectoris, the incidence of ST-segment elevation is independent of anginal symptoms.^{9)–11)} In our study ST-segment elevation was not accompanied by anginal symptoms in 45.6% of cases. Therefore, continuous ECG recording over many hours is essential for evaluating responses to therapy in variant angina pectoris. Holter monitoring is a simple method for evaluating ST-segment elevation in such a patient.¹²⁾

Efficacy of nitrendipine:

The mean number of anginal attacks in this study was 2.1 per day and the mean frequency of ST-segment elevation was 4.5 per day. Eleven of the 18 patients undergoing coronary angiography had significant organic coronary stenosis and the other 7 had normal or nearly normal coronary arteries. This group of patients was not considered to be biased toward less severe cases on the basis of reports of coronary artery lesions published in Japan.^{1),13)}

The frequency of anginal attacks and amount of sublingual nitroglycerin consumed decreased significantly during treatment periods I and II. The nitrendipine treatment produced a marked decrease in anginal attacks in 50% of the 21 patients in treatment period I and in 85% of cases in treatment period II. The efficacy of nitrendipine was 72.2% in the former and 90.0% in the latter period. Our previous trials of nifedipine, diltiazem and verapamil in variant angina pectoris showed an efficacy rate of 92.5% with a marked improvement in 71.3% of those patients. This is comparable with the published efficacy rates of nicorandil (87.5%)⁸⁾ and nilvadipine (92.5%).¹⁴⁾

The frequency, duration and magnitude of ST-segment elevation were reduced or shortened during nitrendipine therapy. Nifedipine, nicorandil and nilvadipine require t.i.d. or b.i.d. administration. By contrast, nitrendipine is a long-acting drug that is administered only once daily and that suppresses ST-segment elevation for at least 10 hours. The plasma concentra-

tion of nitrendipine in healthy adults peaked at 3 to 4 hours after dosing, and the half-life of the disappearance phase ($T_{1/2\beta}$) was about 10 hours.¹⁵⁾ These findings were compatible with the actions of nitrendipine in this study.

Anginal attacks in patients with variant angina pectoris are frequent at night and in the early morning.¹⁶⁾ Conventional calcium antagonists or oral nitrates do not suppress morning attacks in many cases because of their short times of action. These drugs are used at night and in the early morning. However, nitrendipine suppressed early morning anginal attacks in patients given the drug at 8 p.m. to 9 p.m. Therefore, the drug may be useful for the treatment of anginal attacks because its less frequent dosing schedule is more convenient for patients. Moreover, the marked efficacy in the present study may also reflect a prophylactic effect of nitrendipine on coronary vasospasm, through mechanisms demonstrated experimentally by Miyazawa et al.⁷⁾

APPENDIX

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