Evaluation of a New Vasodilating β-Blocking Agent, Carvedilol, in Exertional Angina Using Holter Monitoring

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SUMMARY

Antianginal and antiischemic effects and clinical pharmacologic actions of carvedilol, a novel β-blocking agent with a vasodilator action, were determined by Holter electrocardiographic monitoring in 13 patients with exertional angina. The patients were observed for 1 week prior to entry into the study, followed by 1 to 2 weeks of treatment with carvedilol. During the observation period the patients received one placebo tablet daily, and during the treatment period one 20 mg tablet of carvedilol daily. Before and after the treatment 24-hour Holter electrocardiographic tracings were obtained. The mean interval of Holter monitoring was 11.2±4.5 days for the observation and treatment periods, and the mean time of drug administration was 8:25 a.m. (±30 min). The Holter electrocardiographic tracings which were obtained twice in 9 patients during the observation period showed a high degree of reproducibility with respect to the frequency, magnitude and duration of ST-segment depression. The total frequency of ST depression per patient was 4.5±3.4 events/day pre-drug and 2.1±2.1 events/day post-drug. There was a significant reduction in total frequency of ST depression post-drug (p<0.01). The frequency of asymptomatic ST depression was similarly decreased post-drug (p<0.01), and the total magnitude and duration of ST depression were significantly improved post-drug (p<0.01 and p<0.05, respectively). These effects of carvedilol lasted for 24 hours after administration. Considering that the heart rate was not excessively reduced during the night, and nocturnal myocardial ischemic episodes were not exacerbated, the mode of action of this drug seems to be based on not only a β-blocking action but also on a vasodilator action. Carvedilol benefits exertional angina when used in a 20 mg s.i.d. regimen.

Additional Indexing Words:
Carvedilol  Exertional angina  Holter monitoring  Antianginal agent
CARVEDILOL is a noncardioselective β-blocking agent with vasodilator activity\textsuperscript{11,12} which was developed in West Germany. Its mode of vasodilator action is presumed to be based on an α-blocking action and a direct action on vascular smooth muscle.\textsuperscript{31} The β-blocking action of carvedilol is more powerful and longer lasting than that of propranolol. Carvedilol has no intrinsic sympathomimetic action, but has a membrane-stabilizing action.

In Western countries several reports have been published which deal with the clinical effects of carvedilol on angina pectoris,\textsuperscript{4)-6} although in Japan little work has been done in this respect. It is, therefore, our purpose in this study to determine the usefulness of carvedilol as an antianginal drug used in a 20 mg s.i.d. regimen and characterize its clinical pharmacologic actions by Holter monitoring.

Materials and Methods

1. Subjects

The subjects of this study were chosen from among the outpatients and inpatients who were treated for stable angina pectoris of effort or angina pectoris of effort and at rest at the Nippon Medical School Hospital between December 1986 and October 1988. They were all males averaging in age 59.6±8.7 years, with a range of 45 to 70. Informed consent was obtained from the patients prior to entry in the study. All patients had at least one anginal episode a week which was relieved by sublingual nitroglycerin and also demonstrated a 0.1 mV or greater ischemic ST depression in the exercise test. However, patients with impending infarction, myocardial infarction within the previous 6 months, bradycardia and heart block under 55 beats/min, heart failure or bronchial asthma and those whom the attending physicians considered unfit for admission into the study were excluded. Concomitant use of other antianginal drugs was, in principle, prohibited during the study period except in 2 patients (one of whom received nicorandil and diltiazem in combination and the other who remained on a long-acting nitrate preparation, with no change in administration or dosage throughout the study period). Three patients had a history of myocardial infarction, and their mean frequency of anginal episodes was 5.3±5.3 events/week. Coronary angiography as performed on 12 of 13 patients revealed single-vessel and a double-vessel disease in 3 patients each and triple-vessel disease in 6 patients.
2. Test Medications
The test medications consisted of 20 mg tablets of carvedilol and inactive placebo.

3. Dosage Schedule and Test Methods
This study was designed as a single blind trial. During the observation period of 1 week each patient received one tablet of placebo once daily after breakfast, and during the treatment period of 1 to 2 weeks one 20 mg tablet of carvedilol was administered once daily after breakfast (between 7:00 and 9:00 a.m.). The actual duration of treatment was 1 week in 9 patients and 2 weeks in 4 patients. In 2 of the 4 patients, however, the treatment period had to be extended over 2 weeks for reasons of Holter monitoring. The mean time of drug administration was 8:25 (±30 min) a.m.

During the observation and treatment periods 24-hour tracings by Holter monitoring were obtained once or twice: twice in 9 patients and once in 4 patients during the observation period; twice in 4 patients and once in 9 patients during the treatment period. The patients were given instructions to keep a regular pattern of daily activity during the observation and treatment periods.

When comparing the results of Holter monitoring between the observation and the treatment periods, the findings obtained in the second session were adopted in both periods. The 2 patients who were monitored more than 2 weeks (days 19 and 21) after treatment, as noted earlier, were included in the analysis of data, for they presented no particular problem. The mean Holter monitoring interval was 11.2±4.5 days during both the observation and treatment periods, and the mean Holter monitoring interval in 9 patients where tracings were obtained twice was 4.3±1.6 days.

4. Holter Electrocardiograph and Items of Analysis
The Holter electrocardiograph used in this study was model 335B of Avionics Co. or model 8500 of Marquette Co., and the reproducing equipment was model 8000T Marquette Co. The tracings were obtained in 2 bipolar standard leads, and, in principle, recorded on leads C6 to C5R and modified lead II. The patients were given a log to keep and requested to enter such information as the time of occurrence of anginal pain and the major events in daily living, so that said information might be referred to when interpreting the tracings for ST deviation.

The trendgram was considered positive for ST deviation in cases where there was ischemic ST depression of 1 min or longer duration and the interval between the first and the second ischemic episodes was at least 1 min.
after the recovery of ST depression to baseline level. The duration of ST depression was defined as the time from onset of ST depression return baseline level.

The results of Holter monitoring were assessed regarding the following items of analysis.

1) Total frequency of ST depression (events/day) (each 0.1 mV or greater ST depression of 1 min or longer duration being considered one event)
2) Maximum ST depression (mm) (the greatest ST depression for the day)
3) Total magnitude of ST depression (mm/day)
4) Total duration of ST depression (min/day) (sum total of ST depression durations for the day)
5) Time relationship between ST depression and drug administration
6) Relationship between heart rate and time of drug administration
7) Relationship between heart rate and plasma levels of drug

Those items of analysis were compared before and after treatment.

5. Measurement of Plasma Levels of Drug

The plasma levels of carvedilol were determined by high-performance liquid chromatography (HPLC) on the last day of treatment. Blood was collected in 4 patients 24 hours before and 2, 4 and 7 hours after drug administration. The mean duration of treatment for the 4 patients was 6.0±1.0 days, and the mean time of administration was 8:00 a.m.±30 min.

6. Statistical Assessment of Data

The data on the frequency, magnitude and duration of ST depression were assessed by the paired t-test, and the data on the heart rate by the paired t-test and analysis of variance. Differences were considered significant when p<0.05. All values are represented by the mean±standard deviation.

RESULTS

1. Reproducibility of Items of Analysis

Table 1 shows the reproducibility of 24-hour Holter electrocardiographic tracings obtained twice in 9 patients. The total frequency, maximum degree, total magnitude and total duration of ST depression in the 9 individual patients were about the same in the first and second recordings. To wit, there was no significant difference in these parameters between the first and the second measurements.
Table I. Reproducibility of Transient Myocardial Ischemia Using Holter Monitoring

<table>
<thead>
<tr>
<th>Items</th>
<th>Observation period</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Holter</td>
<td>Second Holter</td>
</tr>
<tr>
<td></td>
<td>monitoring</td>
<td>monitoring</td>
</tr>
<tr>
<td>Total frequency of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (/day)</td>
<td>4.5±3.6</td>
<td>4.6±3.9</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>1.2±2.3</td>
<td>0.9±1.4</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3.3±2.3</td>
<td>3.7±2.9</td>
</tr>
<tr>
<td>Magnitude of maximum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (mm)</td>
<td>2.4±1.0</td>
<td>1.8±0.6</td>
</tr>
<tr>
<td>Total magnitude of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (mm/day)</td>
<td>7.3±5.2</td>
<td>6.1±5.8</td>
</tr>
<tr>
<td>Total duration of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (min/day)</td>
<td>86.1±69.6</td>
<td>81.2±86.2</td>
</tr>
</tbody>
</table>

The reproducibility was examined in 9 patients in whom two 24-hour Holter monitorings were recorded during the observation period. The mean interval between the two Holter monitorings was 4.3±1.6 days. NS=not significant.

Table II. Effect of Carvedilol on Transient Myocardial Ischemia Before and After Treatment Using Holter Monitoring

<table>
<thead>
<tr>
<th>Items</th>
<th>Carvedilol</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Total frequency of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (/day)</td>
<td>4.5±3.4</td>
<td>2.1±2.1</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0.9±1.3</td>
<td>0.3±0.4</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3.6±2.6</td>
<td>1.8±2.1</td>
</tr>
<tr>
<td>Magnitude of maximum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (mm)</td>
<td>2.0±0.9</td>
<td>1.3±1.1</td>
</tr>
<tr>
<td>Total magnitude of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (mm/day)</td>
<td>6.5±5.5</td>
<td>3.3±4.0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>1.9±3.0</td>
<td>0.6±0.9</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>4.6±3.7</td>
<td>2.7±3.6</td>
</tr>
<tr>
<td>Total duration of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment depression (min/day)</td>
<td>81.7±79.0</td>
<td>28.1±30.0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>24.5±42.2</td>
<td>5.3±8.9</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>57.2±48.4</td>
<td>22.6±28.1</td>
</tr>
</tbody>
</table>

2. Effects on ST Depression

Table II shows the post-drug changes in the frequency, magnitude and duration of ST depression. The total frequency of ST depression per patient was 4.5±3.4 events/day pre-drug and 2.1±2.1 events/day post-drug. The post-drug changes were statistically significant (p<0.01). The fre-
Fig. 1. Effects of carvedilol on frequency of ST-segment depression determined by Holter monitoring.

Fig. 2. Time of occurrence of ST-segment depression before and after carvedilol therapy. The mean time of carvedilol administration was at 8:25 (±30 min) a.m. The start of ST-segment depression measurement before treatment was consistent with the drug administration time.

Figures of both symptomatic and asymptomatic ST depressions were decreased post-drug, and the frequency of asymptomatic ST depression, in particular, was reduced to a significant extent (p<0.01).

Figure 1 compares the total frequency of ST depression per day in individual patients before and after treatment. Nine of 13 patients had 3 ST depressions/day or more before treatment, while after treatment this number decreased to 4 and 4 patients became negative for ST depression.

The maximum degree and total magnitude of ST depression were both
decreased post-drug, compared to the pre-drug values, and the change in the latter parameter, in particular, was statistically significant (p<0.01).

The total duration of ST depression was decreased from 81.7±79.0 min/day pre-drug to 28.1±30.0 min/day post-drug. The change was again significant (p<0.05). The duration of ST depression, be it symptomatic or asymptomatic, was reduced post-drug, and the change in asymptomatic ST depression, in particular, was significant (p<0.01).

3. Duration of Action of Carvedilol

1) Relationship between time of drug administration and ST depression

Figure 2 plots the frequency of ST depression against time after the administration of carvedilol. The upper panel indicates the frequency of ST depression which was determined at 4 hour intervals pre-drug, and the lower panel, the frequency of ST depression determined post-drug. The time of drug administration was the same for the placebo and carvedilol. Whereas ST depression was observed round the clock before treatment, the frequency of ST depression was markedly decreased at all times of measurement post-drug, especially at 0–4 hours, 12–16 hours and 20–24 hours post-drug. Furthermore, symptomatic ST depression was no longer observed 8 hours or more after treatment.
2) Effects of carvedilol on heart rate

The hourly changes in maximum, minimum and mean heart rates before and after the administration of carvedilol are plotted in Fig. 3. When the data were assessed by analysis of variance, all three parameters were significantly decreased post-drug (p<0.01 for the first two parameters and p<0.001 for the last). It should be noted, however, that the decrease in heart rate was less marked during the night than during the day.

4. Relationship between Plasma Levels of Drug and Reduction in Heart Rate

Figure 4 shows the hourly changes in heart rate before and after treatment. The maximum decrease in heart rate was $-20.5 \pm 13.2\%$ at 5 hours after treatment and the minimum decrease, $-8.4 \pm 10.9\%$ at 17 hours. The decrease at 24 hours was $-13.7 \pm 12.7\%$. As reflected in these changes, carvedilol down-regulated the heart rate around the clock. Plasma levels of drug were determined in 4 of 13 patients at $6 \pm 1$ days. The mean plasma level of drug was $25.2 \pm 23.8$ ng/ml at 2 hours, $21.8 \pm 11.1$ ng/ml at 4 hours, $12.8 \pm 3.3$ ng/ml at 7 hours and $3.2 \pm 2.8$ ng/ml at 24 hours. The heart rate was markedly decreased at times after drug administration when plasma levels of drug were still high, but an inhibitory effect on heart rate was still observed as late as 24 hours after drug administration, when plasma levels of drug were rather low.
DISCUSSION

1. Background Factors of Patients and Drug Efficacy Evaluation Method

Patients with anginal attacks on exertion were chosen as subjects of this study. Of the 13 patients so chosen, 12 had a history of angina pectoris, and the remaining 1 had recent onset of angina of effort, but anginal attacks had been stabilized. Coronary angiography revealed that all 12 patients examined had organic lesions in the coronary arteries. They were therefore considered to be in a condition pathologically stable enough to be appropriate as subjects of this study. Their qualification as study subjects is also supported by the fact that the frequency, magnitude and duration of symptomatic and asymptomatic ST depression determined during the observation period were highly reproducible.

Pointing out that transient myocardial ischemia experienced by patients with coronary artery disease in their daily activity has a rather high degree of spontaneous variability, Nabel et al^7^ suggest that due care be exercised in drug efficacy evaluation. For the reasons mentioned above the selection of subjects for this study may be considered justified.

2. Efficacy of Carvedilol

The frequency, magnitude and duration of ST depression were significantly decreased after treatment with carvedilol, and its effects lasted for 24 hours. Our results suggest that not only antianginal but also antiischemic actions may be expected of this drug used in a 20 mg s.i.d. regimen.

In recent years, the serious clinical implications of episodes of asymptomatic myocardial ischemia in patients with coronary artery disease have been underlined,^8^,^9^ and their presumed association with the onset of acute myocardial infarction^8^ and sudden cardiac death,^9^,^10^ in particular, has been the focus of attention. It has also been pointed out that angina pectoris or post-myocardial infarction patients who no longer have anginal attacks but still have episodes of asymptomatic myocardial ischemia have a high cardiac event rate and carry a poor prognosis.^10^–^13^)

As has been discussed, the improvement of myocardial ischemic episodes by antianginal agents is important. Thus far, the efficacy of such β-blocking agents as atenolol,^14^,^15^ propranolol^16^,^17^ and metoprolol^18^ and such calcium antagonists as verapamil,^19^ diltiazem^20^ and nifedipine^21^ in the treatment of episodes of asymptomatic myocardial ischemia has been evaluated by Holter monitoring.

Rodrigues et al^22^ who obtained 24-hour Holter electrocardiographic
tracings found that the frequency of myocardial ischemic episodes was significantly decreased after treatment with carvedilol. According to them, the frequency of myocardial infarction not only during the day but also during the night was reduced after carvedilol therapy. Lahiri et al⁵) found that carvedilol used in a 25 mg b.i.d. regimen improved the ejection fraction and diastolic dysfunction at rest in coronary artery diseases and that more marked improvements were obtained by a 50 mg b.i.d. regimen. The mode of action of carvedilol seems to be based on an improvement of myocardial ischemia, no matter whether the ischemia is symptomatic or asymptomatic. According to Lahiri et al⁵) the magnitude of ST depression and exercise tolerance during exercise testing improved after treatment with carvedilol in a 25 mg b.i.d. regimen and according to Kaski et al⁴) similar results were obtained by a 35 mg s.i.d. regimen. In the present study, on the other hand, carvedilol benefited myocardial ischemic episodes, especially asymptomatic ischemia, in a 20 mg s.i.d. regimen. The dose level which proved effective in our study is lower than that reported by other investigators.

3. Clinical Pharmacologic Actions of Carvedilol

Carvedilol is a β-blocking agent with a vasodilator action. In this study the mean heart rate remained decreased by about 15 beats/min for about 10 hours after treatment with carvedilol, and some effect lasted for 24 hours. According to Rodrigues et al²²) carvedilol down-regulated the heart rate, as determined by Holter monitoring, for 24 hours when administered in a 25 mg or 50 mg b.i.d. regimen, and it also reduced the systolic blood pressure, heart rate and double product in both the resting and exercise conditions during exercise testing. Lahiri et al⁵) presume that the beneficial action of carvedilol on left ventricular function resides in its systemic vasodilator action which decreases the afterload and dilates the coronary arteries.

Since the main subjects of this study were the patients with angina pectoris of effort, information was not obtained which helps to elucidate the mechanism of vasodilator action of the drug. Given the finding, however, that carvedilol down-regulated the heart rate for 24 hours after administration and also diminished the frequency of ST depression, suppression of myocardial oxygen consumption resulting from a decrease in heart rate may provide a partial explanation of its antiischemic action. The mean minimum heart rate was above 50 beats/min at night in our series. This means that carvedilol does not reduce the heart rate excessively. Considering that myocardial ischemic episodes which occurred during the night and early in the morning were inhibited, the vasodilating action of carvedilol may account for part of its antiischemic action.
There is a report that some types of classic angina are associated with vasoconstriction resulting from an increase in coronary artery tone.\textsuperscript{23} It has been pointed out, on the other hand, that an increase in myocardial oxygen consumption and a decrease in myocardial oxygen supply resulting from an increase in coronary artery tone explain the higher frequency of transient myocardial ischemic episodes in the morning.\textsuperscript{24,25} Accordingly, β-blocking agents like carvedilol which have a vasodilator action will find wider clinical application than conventional β-blockers and will prove more useful as antianginal and antiischemic agents.

REFERENCES


