Verapamil Administered Twice Daily in Stable Angina Pectoris*

Arthur T.H. Tan, M.B., B.S.; and Susan Quek, M.B., B.S.

To assess whether verapamil taken orally twice daily (bd) was as effective as four times daily (qd) in patients with angina a placebo controlled double blind crossover trial was conducted in 12 patients. Each patient was randomized to verapamil, 160 mg bd, 80 mg qd, or corresponding placebo, each for three weeks. Patients were assessed subjectively and by treadmill exercise test. On both verapamil regimens, patients had less angina with delayed onset of ST segment depression during exercise compared to placebo, without any differences between the two regimens. On bd verapamil, patients could increase their exercise capacity as much as on qd without any increase in adverse effects. Angina threshold during exercise was increased by both regimens with a slightly higher threshold on qd verapamil compared to bd. Therefore, administration of verapamil twice daily is effective in patients with stable angina pectoris, with a similar efficacy to taking verapamil four times daily without any increase in adverse effects.

Verapamil has been shown to be effective in stable effort angina. In these studies, verapamil was given three to four times daily, as short-term single dose pharmacokinetic studies have shown a half life of three to seven hours. Recent studies have suggested that less frequent administration may be adequate during long-term oral therapy. This study was designed to assess the antianginal efficacy of twice daily verapamil compared with four times daily in patients with stable effort angina.

METHODS

Twelve men (mean age 53 years, range 30 to 68 years) with a history of stable exertional angina for at least three months and having at least two anginal attacks a week participated in the study. Six patients had New York Association class 2 angina and six, class 3. Five patients had previous transmural myocardial infarction. All patients had a positive stress test defined as greater than 1 mm horizontal or downsloping ST segment depression of at least 0.08 second in duration in three consecutive beats at the time of angina. Patients with hypertension, valvular heart disease, unstable angina pectoris, cardiac failure, A-V nodal disease, diabetes mellitus, thyroid disorders, and resting ST segment abnormalities were not considered for the trial. All patients gave informed consent. The trial was placebo-controlled and double-blind. All previous anginal therapy was curtailed. Short acting nitrates were taken for symptomatic relief of angina with none taken at least six hours before each exercise test. Patients were randomized to verapamil, 160 mg twice daily (bd) or 80 mg four times daily (qd) or their corresponding placebo for three weeks. Thus, each patient went through four phases of therapy with subjective and objective assessment at the end of each phase. The protocol ensured that one half the patients started with verapamil 80 mg or placebo qd and one half with verapamil 160 mg or placebo bd. This helps to exclude any training effect from repeated exercise tests.

Assessment

At the end of each three-week treatment phase, each patient underwent a symptom-limited maximal exercise test on a treadmill (Avionics Model E-161-1) using the Bruce protocol. For each patient, the exercise test was done at the same time of the day just before the next dose was due. The ECG was monitored using the modified Mason lead system. During exercise 12-lead ECGs, heart rate, blood pressure (measured by sphygmomanometer) and symptoms were recorded every minute. The end points of exercise were symptom limiting chest pain and/or breathlessness and/or fatigue. A tablet count was done at the end of each phase to verify compliance.

Patients recorded anginal attacks during each three-week phase in a diary. Side effects were obtained by completion of a questionnaire and by inquiry. They were also asked to rank the order of preference for the four phases of therapy on completion of the trial.

Statistical Methods

Results were analyzed by two-way analysis of variance. When a statistical significance was obtained between the four treatment phases (p < 0.05), the treatment sum of squares was partitioned to identify the source of the statistical significance. Results are expressed as a mean ± SD unless otherwise indicated.

Results

Symptoms, Side Effects, and Preference

Patients receiving verapamil had fewer anginal attacks than those receiving placebo. On verapamil, 160 mg bd, there were 12 ± 22 anginal episodes in three weeks compared to placebo 17 ± 25 episodes (p < 0.05); on verapamil, 80 mg qd, 5 ± 5 episodes in three weeks compared to placebo 17 ± 22 episodes (p < 0.01). Patients taking verapamil four times daily had fewer anginal attacks than twice daily verapamil, but the difference was not significant.

The incidence of side effects was low during each regimen of verapamil. Three patients complained of constipation on each dosage regimen. All patients preferred verapamil to placebo. Eight patients preferred taking verapamil, 80 mg qd and two 160 mg bd.

*From the University Department of Medicine, (Division of Cardiology); National University of Singapore.
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Reprint requests: Dr. Tan, Department of Medicine II, Singapore General Hospital, Singapore 0316

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Two patients had no preference.

**Symptom Limited Exercise**

Heart Rate, Blood Pressure, and Rate Pressure Product:

On bd and qd regimens, exercise tests were performed 13 ± 3 and 5.8 ± 0.6 hours after the last dose of verapamil.

Heart rate at rest was lower with verapamil than with placebo (Fig 1) being lower on qd compared to bd regimens (p < 0.05). During exercise, the heart rate at each stage was lower on verapamil compared to placebo, with no significant difference between the two regimens. On both regimens of verapamil, blood pressure at rest and during exercise was not significantly different from placebo. The rate pressure product at each stage of exercise was lower with verapamil compared to placebo. While taking verapamil, patients were able to exercise longer than with placebo (Table 1) with similar increases in exercise capacity in both regimens. The heart rate, blood pressure, and rate pressure product was, however, unchanged at peak exercise.

**Anginal Threshold and ST-Segment Depression**

Receiving placebo, all patients developed angina at peak exercise with ST-segment depression. In contrast, during each regimen of verapamil therapy, seven patients developed angina with the other five limited by breathlessness at peak exercise.

The time to onset of angina was longer with verapamil than with placebo (Table 2). Patients taking

**Table 1—Effects of Verapamil on Maximum ST-Segment Depression and Exercise Capacity**

<table>
<thead>
<tr>
<th></th>
<th>QD</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verapamil</td>
<td>Placebo</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>6.5 ± 2.5*</td>
<td>5.1 ± 2.0</td>
</tr>
<tr>
<td>HR at peak exercise</td>
<td>132 ± 23</td>
<td>136 ± 25</td>
</tr>
<tr>
<td>Mean BP at peak exercise</td>
<td>96 ± 13</td>
<td>95 ± 13</td>
</tr>
<tr>
<td>Maximum ST-depression</td>
<td>2 ± 1.3*</td>
<td>3.5 ± 1</td>
</tr>
</tbody>
</table>

*Verapamil vs placebo p < 0.05.

**Table 2—Effects of Verapamil on Onset of Angina and 1 mm ST-Segment Depression During Exercise**

<table>
<thead>
<tr>
<th></th>
<th>QD</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verapamil</td>
<td>Placebo</td>
</tr>
<tr>
<td>Onset of angina (min)</td>
<td>4.7 ± 1.0*</td>
<td>3.5 ± 2.5</td>
</tr>
<tr>
<td>HR at onset of angina</td>
<td>123 ± 21</td>
<td>129 ± 20</td>
</tr>
<tr>
<td>BP (mean) at onset of angina</td>
<td>96 ± 13</td>
<td>96 ± 13</td>
</tr>
<tr>
<td>Onset of 1 mm ST-depression (min)</td>
<td>4.2 ± 2.4*</td>
<td>2.8 ± 1.8</td>
</tr>
<tr>
<td>HR at 1 mm ST-depression</td>
<td>120 ± 21</td>
<td>121 ± 16</td>
</tr>
<tr>
<td>BP (mean) at 1 mm ST-depression</td>
<td>94 ± 14</td>
<td>94 ± 16</td>
</tr>
</tbody>
</table>

*Verapamil vs placebo p < 0.05.

Twice Daily Verapamil in Stable Angina (Tan, Quek)
Verapamil four times daily could exercise longer before onset of angina than those taking verapamil twice daily (p<0.025) (Fig 2). The rate pressure product at onset of angina was not different on verapamil compared to placebo.

Receiving twice daily verapamil, all patients had ST-segment depression at peak exercise in contrast to ten patients on qd regimen. The time to onset of 1 mm ST depression was longer with verapamil compared to placebo (Fig 3) with no difference between the two regimens. Rate pressure product at onset of one ST-segment depression was not different with verapamil compared to placebo. Maximum ST-segment depression was equally reduced by both regimens of verapamil.

**Discussion**

Initial single dose pharmacokinetics have shown that verapamil has a half life of three to seven hours and should be given three to four times daily. More recent studies have shown that elimination kinetics of verapamil and its main metabolite norverapamil are prolonged after long-term oral administration, suggesting that less frequent dose schedules may be possible. This study was designed to establish the antianginal efficacy of verapamil given twice daily and to compare it with a more conventional regimen.

In patients with stable effort angina, this study has shown that verapamil taken twice daily is effective in the prevention of angina. Patients taking verapamil twice daily had fewer attacks of angina than on placebo. They could exercise longer before the onset of angina and ST-segment depression resulting in an increased exercise capacity.

We compared the antianginal efficacy of verapamil given orally either twice daily (160 mg bd) or four times daily (80 mg qd). Though patients felt that the latter regimen was more effective in improving angina, we could not detect any differences in heart rate and blood pressure response to exercise, onset of 1 mm ST-segment depression, and exercise capacity between the two regimens. These exercise tests were performed during the period when the expected plasma levels of verapamil from either regimen would have been at their trough. Furthermore, patients did not have any increase in adverse side effects from the
higher dosage. This study has shown that patients with stable effort angina can be effectively and safely managed on a twice daily regimen. In some patients, however, a qd regimen may lead to slightly greater improvement and may be necessary.

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