A New Chronotherapeutic Oral Drug Absorption System for Verapamil Optimizes Blood Pressure Control in the Morning

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A novel verapamil chronotherapeutic oral drug absorption system (CODAS–Verapamil) designed for bedtime dosing and with controlled onset and extended-release properties was evaluated in 257 patients with mild-to-moderate essential hypertension in an 8-week, double-blind, placebo-controlled trial.

After bedtime dosing (9 PM to 11 PM), this delivery system delays drug release for 4 to 5 h, and provides the highest concentrations of verapamil between 6 AM and noon. The study results showed that CODAS–verapamil produced its greatest antihypertensive effect during this morning period (6 AM to 12 noon) and also provided effective trough diastolic blood pressure reductions at 200, 300, and 400 mg. Significant trough systolic blood pressure reductions were achieved only with the 300- and 400-mg doses. The nighttime dosing regimen was not associated with excessive blood pressure (BP) reductions during the sleeping hours, when the antihypertensive effect was generally slightly less than that of the 24-h mean reduction.

The CODAS–verapamil provides enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period. Am J Hypertens 2001;14:14–19 © 2001 American Journal of Hypertension, Ltd.

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The tendency of adverse cardiovascular events to cluster in the morning hours between 6 AM and noon, when blood pressure (BP) tends to increase rapidly, suggests that enhanced BP control during this period may be valuable.1 Four extended-release verapamil products have approval from the Food and Drug Administration for use as once-daily drugs in the treatment of hypertension.2–4 One of these, verapamil COER, was designed to enhance morning control of hypertension.4 More recently, Verelan PM using a chronotherapeutic oral drug absorption system (CODAS–verapamil) was also granted Food and Drug Administration approval as a controlled onset, extended-release delivery system for verapamil intended for once-daily, bedtime dosing. After bedtime dosing, the release of verapamil is delayed for the initial 4 to 5 h, whereas maximal verapamil concentrations occur approximately 11 h later (Verelan PM product package insert. Schwarz Pharma, Milwaukee, WI. PC 3876, November 1998). Because drug concentrations are highest between 6 AM and noon, it was anticipated that this system would provide enhanced BP control in the morning period, when risk of adverse cardiovascular outcome is greatest.

We evaluated this hypothesis in a large multicenter, placebo-controlled clinical trial in which patients were randomized to bedtime dosing of either placebo or 100, 200, 300, or 400 mg of controlled onset, extended-release verapamil. We found that doses of 200 mg or greater produced sustained BP control for the 24-h dose interval. We also found that BP control was optimal during the morning period between 6 AM and noon, and that this was achieved without excessive BP lowering during the sleeping hours after dosing.

Methods

Study Design

This multicenter, parallel-group, randomized, double-blind, placebo-controlled study was conducted in patients with mild-to-moderate essential hypertension. Patients with secondary hypertension, recent serious cardiovascular events, or any chronic serious or uncontrolled medical conditions were excluded from the study. Night or variable shift workers were also excluded.

All participating patients provided written informed consent and discontinued their antihypertensive therapy...
from 6PM to 10 PM at the end of the 24-h dosing period. Subsets of this period were also of interest: the 4-h interval (morning period). Was applied and ending at 10 PM the next evening. Two periods commencing at 10 PM on the night that the monitor midnight and 6 AM. Of primary interest was the 24-h period between 6AM and midnight, and at 30-min intervals between midnight and 6 AM. Periods were programmed to measure BP at 20-min intervals before and at completion of the randomized phase.

**Study Medication and Dosing**

All patients took matching placebo during the single-blind lead-in period. During the double-blind randomized phase, patients were dosed with identical capsules containing 100, 200, 300, or 400 mg of CODAS–verapamil or placebo. Throughout the study, dosing took place at 10 PM ± 1 h (ie, between 9 PM and 11 PM).

**Office Visits**

Patients returned to the clinic for weekly visits during the lead-in period and for the first 2 weeks of the 8-week randomized period. Patients returned to the clinic every 2 weeks for the remaining 6 weeks of the randomized period. Blood pressure was measured at each office visit, and any adverse events or side effects were evaluated. Office BP was measured in accordance with American Heart Association guidelines. This involved the averaging of three seated BP measured 1 min apart after the patient had been sitting quietly for 5 min. On the two occasions (after completion of the lead-in and randomized phases) when ambulatory BP monitors were applied, additional office visits were made between 6 PM and 8 PM to establish trough office BP. Patients were also evaluated for compliance with the dosing schedule at each office visit. Blood samples for hematology and blood chemistries were drawn before and at completion of the randomized phase.

**Ambulatory Blood Pressure Monitoring**

On completion of each phase of the study, patients were subjected to 36-h ambulatory BP monitoring (ABPM) with a Spacelabs 90207 monitor (Spacelabs, Inc., Redmond, WA). Monitors were fitted between 6 PM and 8 PM after office trough BP had been obtained. The monitors were programmed to measure BP at 20-min intervals between 6 AM and midnight, and at 30-min intervals between midnight and 6 AM. Of primary interest was the 24-h period commencing at 10 PM on the night that the monitor was applied and ending at 10 PM the next evening. Two subsets of this period were also of interest: the 4-h interval from 6 PM to 10 PM at the end of the 24-h dosing period (trough BP period), and the 6-h interval from 6 AM to noon (morning period).

**Statistical Analysis**

Statistical analyses were performed using SAS (Statistical Analysis System, Inc., Cary, NC) software. The primary efficacy variable was the mean reduction in trough (6 PM to 10 PM) BP recorded by ABPM from the lead-in period to the end of the randomization period. Secondary efficacy variables included similarly measured BP reductions for the morning period from 6 AM to noon and for the 24-h period from 10 PM to 10 PM. The magnitude of ambulatory BP reductions immediately after dosing and during the period of sleep, from approximately 10 PM to 6 AM, were also assessed. For easier comparison with the trough period, this period was viewed as two 4-h periods, from 10 PM to 2 AM and from 2 AM to 6 AM. Additional secondary end points involved the reduction in office BP measured at trough (between 6 PM and 8 PM on the days that the ABPM was applied) and at peak (between 7 AM and 9 AM at each office visit during treatment).

All efficacy variables were analyzed by a one-way analysis of covariance, with baseline BP as the covariate and treatment group as the factor in the models. Placebo-subtracted values and associated means and standard deviations were calculated for each of the treatment groups. Dunnett’s test was used to make multiple comparisons. Categoric variables (such as adverse events and BP response rates) were presented with the frequency and percentage in each category and analyzed with Fisher’s exact test. All tests of hypotheses were two-sided and at least at the 5% level of significance.

**Results**

A total of 517 patients from 20 study sites in the United States entered the placebo run-in phase of the study. Of these, 278 met eligibility criteria and progressed to the 8-week randomized phase. This phase randomized 51 patients to placebo and the remaining 227 patients to one of the four CODAS–verapamil groups (53 to the 100-mg dose group and 58 to each of the 200-, 300-, and 400-mg dose groups). A total of 239 patients did not progress to randomization because of the failure to meet study entry criteria. Most of these (81%) were because of the failure to fulfill BP entry requirements.

Of the 278 patients who were randomized, all but 1 (lost to follow-up after the initial randomization visit) are included in the office BP and safety analysis data. The ABPM data reflect 257 patients (92.4%) who also completed adequate ABPM monitoring at baseline as well as final visits.

**Demographics**

The demographic and baseline characteristics of the various treatment groups are summarized in Table 1. All groups were comparable with regard to age, weight, baseline BP, sex, and race.
Ambulatory Blood Pressures

The results of the ambulatory BP reductions are summarized in Table 2. The 200-, 300-, and 400-mg doses were all effective in lowering DBP compared with placebo at all points of interest during the dosing interval. These doses also significantly reduced SBP, except for the 200-mg dose at the trough measurement. Increasing doses produced greater reductions in BP and heart rate during each of the periods of interest.

Blood pressure and heart rate reductions were greatest during the morning period (6 AM to noon). In this period, the lowest effective dose for reducing DBP was 100 mg, which reduced DBP by 3.1 mm Hg. The 200-, 300-, and 400-mg doses further reduced DBP by 7.1, 11.0, and 13.8 mm Hg, respectively. Systolic blood pressure reductions followed a similar pattern: the 200-mg dose reduced SBP by 9.5 mm Hg, and the 300- and 400-mg doses provided further reductions of 14.5 and 19.2 mm Hg, respectively. When compared with the 24-h mean BP reductions, the morning period SBP reductions were 56%, 54%, and 42% greater for the 200-, 300-, and 400-mg doses, respectively. Similarly, for DBP, the morning period reductions exceeded those of the 24-h mean reductions by 58%, 47%, and 35%, respectively. Thus, CODAS–verapamil produced its greatest antihypertensive effect during the morning period, from 6 AM to noon.

Table 1. Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Demographic Parameter</th>
<th>Placebo (n = 50)</th>
<th>CODAS–Verapamil Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg (n = 53)</td>
<td>200 mg (n = 58)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.9 ± 9.9</td>
<td>52.8 ± 10.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.8 ± 16</td>
<td>90.3 ± 12.8</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>71.7</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>28.3</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>80</td>
<td>84.9</td>
</tr>
<tr>
<td>African American</td>
<td>12</td>
<td>11.3</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>3.8</td>
</tr>
<tr>
<td>Base ABPM (SBP/DBP)</td>
<td>150.0/92.9</td>
<td>148.0/93.3</td>
</tr>
<tr>
<td>(HR)</td>
<td>78.4</td>
<td>76.7</td>
</tr>
</tbody>
</table>

Base ABPM = baseline 24-hour ambulatory blood pressure monitoring; SBP and DBP = systolic and diastolic blood pressures respectively (mm Hg); HR = heart rate in beats per minute.

*Mean ± standard deviation.

Table 2. Ambulatory blood pressure and heart rate reductions during various intervals of the 24-hour dosing cycle

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Placebo (n = 42)</th>
<th>100 mg (n = 49)</th>
<th>200 mg (n = 58)</th>
<th>300 mg (n = 53)</th>
<th>400 mg (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough (6 PM–10 PM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.5 ± 10.2</td>
<td>−0.5 ± 12.5</td>
<td>−3.6 ± 12.1</td>
<td>−6.1 ± 14.1*</td>
<td>−10.9 ± 13.7*</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.3 ± 6.8</td>
<td>1.2 ± 9.8</td>
<td>−2.6 ± 9.5*</td>
<td>−5.2 ± 11.3*</td>
<td>−8.8 ± 8.8*</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>3.2 ± 8.7</td>
<td>0.9 ± 9.2</td>
<td>−0.7 ± 7.7</td>
<td>−4.5 ± 9.7*</td>
<td>−7.4 ± 11.5*</td>
</tr>
<tr>
<td>Morning (6 AM–12 PM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>−1.0 ± 9.7</td>
<td>−4.5 ± 9.1</td>
<td>−9.5 ± 12.5*</td>
<td>−14.5 ± 10.9*</td>
<td>−19.2 ± 12.4*</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.5 ± 7.3</td>
<td>−3.1 ± 6.0*</td>
<td>−7.1 ± 8.3*</td>
<td>−11.0 ± 7.2*</td>
<td>−13.8 ± 8.1*</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0.0 ± 8.1</td>
<td>2.5 ± 7.6</td>
<td>3.5 ± 8.4*</td>
<td>−6.5 ± 8.3*</td>
<td>−7.2 ± 7.5*</td>
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<tr>
<td>24-hour mean (10 PM–10 PM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>0.6 ± 7.6</td>
<td>−2.1 ± 7.0</td>
<td>−6.1 ± 9.8*</td>
<td>−9.4 ± 7.8*</td>
<td>−13.5 ± 9.9*</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.0 ± 4.5</td>
<td>−1.2 ± 4.7*</td>
<td>−4.5 ± 6.1*</td>
<td>−7.5 ± 5.6*</td>
<td>−10.2 ± 6.4*</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0.9 ± 6.4</td>
<td>−1.3 ± 6.3</td>
<td>−2.7 ± 6.5</td>
<td>−4.6 ± 6.8*</td>
<td>−6.4 ± 6.0*</td>
</tr>
</tbody>
</table>

BP = blood pressure (mm Hg); heart rate (beats per minute).

*Mean ± standard deviation.

*P < .05 versus placebo.
Ambulatory BP profiles of placebo and the 100-, 200-, 300- and 400-mg doses are illustrated in Fig. 1. For both SBP and DBP, the differences between the placebo and treatment profiles are greatest during the morning period (6AM to noon). Also, for doses in excess of 100 mg an antihypertensive effect is sustained for the entire dosing interval, which supports 24-h efficacy.

Furthermore, excessive BP lowering does not occur as a result of the bedtime dosing at 10 PM, as differences between the baseline and final profiles appear to be lowest between 10 PM and 6 AM (Fig. 1). This was confirmed by an evaluation of SBP and DBP reductions during various periods of the 24-h dosing interval after bedtime dosing at 10 PM (Fig. 2). For all doses, BP reductions were significantly greater during the morning period compared with the two 4-h periods after bedtime dosing (10 PM to 2 AM and 2 AM to 6 AM) and with the 24-h mean BP reductions. Fig. 2 also shows that BP reductions for the first 8 h after bedtime dosing (10 PM to 6 AM) were less than reductions achieved for the 24-h mean, and were comparable to those achieved at the trough measurement (illustrated by the dashed lines). Thus, the 200-, 300-, and 400-mg dosages effectively lowered BP for 24 h, and did so most optimally during the morning period. This was achieved without an excessive lowering of BP in the hours after bedtime dosing.

Table 3 tabulates the trough-to-peak ratios of SBP and DBP reductions as well as response rates attained with each of the dosing strengths. Trough-to-peak ratios indicate that for each dose, more than 50% of the peak antihypertensive effect is attained in the final hour of the 24-h dosing interval.

Heart rates were slowed by the 200-mg dose only during the morning period, and by the 300- and 400-mg doses throughout the dosing interval (Table 2).

Office Blood Pressures
Seated trough office BP were measured between 6 PM and 8 PM. Reductions in BP were calculated by subtracting the baseline pressures from those measured at the final randomized visit. For SBP these reductions were $-2.4 \pm 14.5$...
mm Hg for placebo and −3.6 ± 11.8 mm Hg, −8.4 ± 13.8 mm Hg, −11.1 ± 11.3 mm Hg, and −11.2 ± 14.8 mm Hg for the 100-, 200-, 300-, and 400-mg doses, respectively. Corresponding DBP reductions were −0.6 ± 7.2 mm Hg for placebo and −4.0 ± 7.5 mm Hg, −6.8 ± 7.8 mm Hg, −10.0 ± 7.0 mm Hg, and −9.3 ± 8 mm Hg, respectively. All reductions achieved with active medication (except for SBP reductions with 100 mg) were statistically significant. Heart rate was statistically unchanged for the placebo, 100-mg, and 200-mg doses, and was reduced by 5.6 and 5.7 beats/min for the 300-mg and 400-mg doses, respectively.

Peak office BP was measured between 7 AM and 9 AM. As was observed for ambulatory BP, office BP also were reduced by CODAS–verapamil, to a greater degree at this time. Systolic and diastolic blood pressure were reduced by 3.9/4.6 mm Hg, 9.3/8.2 mm Hg, 14.3/11.0 mm Hg, and 19.1/14.2 mm Hg for the 100-, 200-, 300-, and 400-mg doses, respectively. Heart rates were reduced significantly for only the 300-mg (−4.8 beats/min) and 400-mg (−6.1 beats/min) doses.

### Adverse Events

Adverse events reported during the randomized phase of the trial were defined as new adverse events that did not occur before randomization, or previous adverse events that worsened during the randomized period. At least one such adverse event was reported during the randomization period by 165 patients (60%): 30 (60%) in the placebo group and 34 (64%), 30 (52%), 31 (53%), and 40 (69%) in the 100-, 200-, 300-, and 400-mg dosage groups, respectively.

The body systems most commonly affected were the body as a whole (range, 31% of patients in the 400-mg dose group to 40% of patients in the placebo group); the digestive tract (range, 9% in the 200-mg group to 36% in the 400-mg group); and the respiratory system (range, 7% in the 300-mg group to 16% in the placebo group). The incidence of adverse events was generally comparable among the treatment groups, except for the digestive system, for which the incidence of adverse events in the 400-mg group was higher than that observed in the other groups. This was primarily attributable to a higher incidence of constipation (22% for the 400-mg group compared with a range of between 2% and 10% for the other groups).

Among the actively treated groups, the most common adverse effects were headache (9% to 16%), infection (7% to 19%), and constipation (4% to 22%). Infections were mainly upper respiratory tract. Few of these adverse events were considered by investigators to be probably or definitely related to study drug. The only dose-related trend of adverse events considered probably or definitely related to the drug was constipation, which was reported more frequently as dosage increased. There were no instances of excessive bradycardia or first-degree atrioventricular block that required any patients to be discontinued from the study and no dose-related trends in laboratory abnormalities occurred. Adverse events were comparable to those reported for other verapamil preparations.4,6,7

### Discussion

Once-daily medication is increasingly viewed as the standard therapy for hypertension. The Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure states that long-acting formulations that provide 24-h efficacy are to be preferred over short-acting agents.8 This is because with long-acting formulations, the control of hypertension is persistent and smooth rather than intermittent; and protection is provided against any increased risk of sudden death, heart attack, and stroke attributable to the abrupt increase in BP after arising from an overnight sleep. However, some studies with ABPM have indicated that the antihypertensive effects of some once-daily antihypertensive agents may decline toward the end of the dosing interval.7,9 Different strategies have been used in attempts to minimize this problem. One involves the use of higher doses of medication so that the duration of antihypertensive effect would be more sustained toward the end of the dosing interval. But, this raises concerns regarding excessive BP reductions coinciding with the peak effect of the drug.
Another strategy was to use the nighttime dosing of conventional once-daily antihypertensive medication. This strategy aimed to provide higher antihypertensive drug levels in the morning hours, and thereby provide greater BP reductions during this period. However, nighttime hypotension remains a concern with this strategy, especially in view that the BP reductions achieved during sleep by conventional once-daily medications are enhanced when the medication is dosed at bedtime and raises concerns about possible hypoperfusion effects on the myocardium, the eye, and the brain—especially in the elderly. Although these findings need further validation, it might be prudent to avoid the dosing of conventional once-daily antihypertensive medication at bedtime.

The verapamil preparations of COER–verapamil and CODAS–verapamil are the only antihypertensive agents with a delivery system specifically designed for nighttime dosing. With CODAS–verapamil, this is achieved by delaying drug release for the initial 4 to 5 h after dosing, which avoids an excessive initial antihypertensive effect. Peak drug concentrations and antihypertensive effects are thus delayed to coincide with the morning hours. For doses of 200 mg or more, this study has demonstrated that the CODAS delivery system for verapamil has been successful in providing greater BP control during the morning period, without producing excessive BP reductions during the sleeping hours. This delivery system also provided effective 24-h BP control, as evidenced by trough BP reductions and the trough-to-peak ratios.

References