Efficacy and Safety of a Once Daily Graded-Release Diltiazem Formulation in Essential Hypertension

Stephen P. Glasser, Joel M. Neutel, Theophilus J. Gana, and Kenneth S. Albert

Background: The efficacy and safety of a chronotherapeutic, graded-release diltiazem HCl extended-release (GRD) 120-, 240-, 360- and 540-mg dose administered once-daily at bedtime (10 PM) were evaluated in a 7-week randomized, double-blind comparison to placebo and to GRD 360 mg administered once-daily at 8 AM in 478 patients with moderate-to-severe essential hypertension.

Methods: We assessed the change from baseline to end point in trough diastolic blood pressure (DBP) at 6 PM to 10 PM and in mean DBP from 6 AM to 12 noon between GRD 360 mg PM and GRD 360 mg AM, measured by ambulatory BP monitoring (ABPM).

Results: Bedtime doses of GRD showed dose-related mean reductions in trough DBP that were significant for GRD doses of 240 mg and higher. Bedtime GRD 360 mg was associated with a significantly greater reduction in mean DBP between 6 AM and 12 noon compared to morning GRD 360 mg with a least squares mean for treatment difference of $-3.3 \text{ mm Hg (} P = .0004)$. Similar dose-related and significant reductions in systolic BP (SBP) and heart rate (HR) were obtained. Incidence of adverse events (AEs) for all GRD groups (44.5%) was less than that obtained for the placebo group (49.3%). The 540-mg group showed an incidence of AEs (43.5%) similar to that observed for the 240-mg group (42.6%).

Conclusions: The GRD dose-dependently significantly reduces BP and HR over the 24-h interval after once-daily bedtime dosing. Further greater reductions were obtained between 6 AM and 12 noon, when circadian BP is highest, compared to morning administration of the same dose. The 540-mg GRD was safe, well tolerated, and offers further therapeutic option for patients with severe hypertension who required additional BP control. Am J Hypertens 2003;16:51–58 © 2003 American Journal of Hypertension, Ltd.

Key Words: Diltiazem extended release, hypertension, chronotherapy, nighttime dosing.

Results of several large epidemiologic studies have shown that there is an increased incidence of nonembolic stroke, silent myocardial ischemia, myocardial infarction, and sudden cardiac death in the early morning period, between 6 AM and 12 noon. This peak incidence of cardiovascular events coincides with the period of the early morning surge in blood pressure (BP) and heart rate (HR) in normotensive and hypertensive individuals. Although several potential triggers for cardiovascular events have been identified during the early morning period, there is growing evidence of an important association between the early morning surge in BP and myocardial ischemia. Consequently, this has led to the need to develop chronotherapeutic antihypertensive medications, which synchronize their antihypertensive effect with the body’s circadian rhythm of BP, thereby optimizing control.

Recently, a new once-daily, graded-release formulation of diltiazem (GRD), designed to achieve maximum plasma levels between the critical morning hours of 6 AM and 12 noon has been developed. Pharmacokinetic studies comparing nighttime administration of GRD to morning administration of an identical dose showed peak plasma concentrations during the period 6 AM to 12 noon. Because plasma concentrations of diltiazem are known to correlate with its antihypertensive effects, the latter results suggest that GRD may be an ideal chronotherapeutic agent for the management of hypertension. To date, no chronotherapeutic diltiazem formulation has been approved for mar-

Received July 1, 2002. First decision July 25, 2002. Accepted September 5, 2002.

From the Division of Epidemiology (SPG), School of Public Health, University of Minnesota, Minneapolis, Minnesota; University of California (JMN), Irvine, California; and Biovail Technologies, Ltd. (TJG, KSA), Chantilly, Virginia.

Address correspondence and reprint requests to Dr. Stephen P. Glasser, Division of Epidemiology, School of Public Health, University of Minnesota, 1300 South Second Street, Suite 300, Minneapolis, MN 55454-1015; e-mail: glasser@epi.umn.edu

© 2003 by the American Journal of Hypertension, Ltd. Published by Elsevier Science Inc.
keting in the United States by the Food and Drug Administration.

In this study, we have assessed four doses of GRD, 120-mg PM, 240-mg PM, 360-mg PM and AM, and 540-mg PM compared to placebo in stages II and III hypertension. A unique feature of this study was a comparison of the safety and efficacy of 360-mg dosed PM and AM, and a 540-mg dose of diltiazem.

Methods

Study Design

A total of 39 centers in the United States participated in this randomized, double-blind, parallel-group, dose-response, placebo-controlled, multicenter study. The study protocol and amendments were approved by an appropriately constituted institutional review board. The study consisted of an initial screening period followed by a 3-to-4-week single-blind, placebo run-in period. Thereafter, patients were randomized to receive either placebo or active treatment (GRD—Biovail Laboratories, Steinbach, Manitoba, Canada), for a 7-week double-blind treatment period as follows: placebo, GRD 120-mg PM, GRD 240-mg PM, GRD 360-mg AM, GRD 360-mg PM, or GRD 540-mg PM in a ratio of 1:1:1:1:5:1:5:1 by telephone from an Interactive Voice Response System (IVRS). Patients randomized to 540 mg had an initial 1-week titration period on 360 mg, followed by forced titration to 540 mg from weeks 2 to 7. Patients randomized to the remaining groups received their respective doses throughout the 7-week treatment period.

Study medications were taken each morning at 8 AM ± 1 h (360-mg AM only) and evening at 10 PM ± 1 h. Patients were evaluated for safety and efficacy at weekly intervals during the run-in and titration periods, and at 2-week intervals during the double-blind treatment period.

Patients

Adult male and female patients, aged 18 to 70 years, with moderate-to-severe essential hypertension who gave written informed consent were included into the study if their average seated systolic blood pressure (SBP) was <200 mm Hg and mean seated diastolic blood pressure (DBP) was ≥100 mm Hg and ≤114 mm Hg at rest on 2 consecutive weeks during the run-in period. Furthermore, the average seated DBP readings at the two qualifying visits could not vary by more than 7 mm Hg. In addition, patients were eligible for randomization only if their mean daytime (8 AM to 4 PM) DBP by ambulatory BP monitoring (ABPM) was ≥90 mm Hg and ≤114 mm Hg at baseline.

Patients were excluded from the study if they had a recent history of serious cardiovascular or cerebrovascular events, secondary hypertension, or any serious chronic or uncontrolled medical conditions. In addition, nightshift workers and patients with a known sensitivity to diltiazem were excluded.

Measurements of BP and HR

A 36-h ABPM was performed on each patient at baseline and at the end of the double-blind treatment period using a Spacelabs 90207 monitor (Spacelabs, Inc., Redmond, WA). The ABPM monitor was applied to the patient’s nondominant arm at 6 PM ± 1 h, and the patients were instructed to dose this medication at 10 PM ± 1 h that night, and to return to the clinic the next morning at 8 AM ± 1 h to have the monitor checked. The next morning trough office cuff seated BP measurements were obtained at 8 AM ± 1 h. The ABPM was programmed to take one measurement every 20 min during the 24-h interval. The patient returned to the clinic again the following morning (after 36 h of ABPM application) at 8 AM ± 1 h to have the monitor removed and the recorded data downloaded.

In addition, seated office BP measurements were taken at all clinic visits. The average of three BP measurements taken 2 min apart after the patient had been sitting quietly for 5 min was used. Seated HR was measured after the second BP determination. Office cuff BP measurements were obtained at 6 PM ± 1 h (trough for PM dosing) and at 8 AM ± 1 h (trough for AM dosing) on the days ABPM was performed.

Efficacy Parameters

One primary measure of efficacy was the change from baseline to end point in trough DBP, recorded between 6 PM and 10 PM by ABPM, for the evening GRD treatment groups (GRD 120 mg, 240 mg, 360 mg PM and 540 mg) compared with placebo. The co-primary was the change from baseline to end point in mean DBP recorded by ABPM between 6 AM and 12 noon for GRD 360 mg AM compared to 360 mg PM.

Twelve secondary efficacy variables assessed the changes from baseline to end point in SBP, DBP, and HR by ABPM and clinic measurements, for the periods 4 AM to 8 AM, 6 AM to 12 noon, 6 PM to 10 PM, and the overall 24-h mean.

Responder rates were also determined for BP values assessed by office cuff sphygmomanometry. The DBP responder rate was defined as the proportion of patients achieving a mean DBP <90 mm Hg at end point or a decrease of at least 10 mm Hg from the baseline mean DBP; SBP responder rate was defined as the proportion of patients achieving a mean SBP <140 mm Hg at end point or a decrease of at least 10% from the baseline mean SBP.

Statistical Analysis

All statistical analyses were performed using SAS Version 6.12 or higher (Statistical Analysis System Institute, Inc., Cary, NC). Intent-to-treat analyses of efficacy data were performed. Separate analysis of covariance (ANCOVA) models were used to analyze each continuous primary and secondary efficacy variable, using the change from baseline to end point as the dependent variable, treatment and study site as the main effects, and baseline BP included as
a covariate. The treatment-by-baseline and treatment-by-site interactions were examined. Multiple comparisons between the placebo group and each active treatment group were made using Dunnett’s test. Responder rates were summarized by counts and percentages, and compared between treatment groups using Fisher’s exact test.

Sample size was determined based on the change from baseline to end point in the mean DBP between 6 AM and 12 noon as measured by ABPM between the GRD 360-mg PM and 360-mg AM treatment groups. Assuming a common standard deviation of 8 mm Hg, it was estimated that 99 patients in each 360-mg group (AM and PM) and 66 in each of the other groups will provide greater than 80% power to detect a mean difference of 4 mm Hg between the two 360-mg groups, and a mean difference of 5 mm Hg between the rest of the groups at the 0.05 level of significance. Hence, 462 patients were planned for randomization.

Results

Patient Disposition

A total of 478 patients were randomized and received at least one dose of study medication; overall, 429 (89.1%) of these patients completed the study. The patient demographics and baseline characteristics are summarized in Table 1. The most common reason for premature withdrawal from the double-blind period was an adverse event, in 3.2% of GRD-treated patients and 4.3% of placebo-treated patients. Other reasons for withdrawal included noncompliance, withdrawal of consent, and lack of efficacy.

Efficacy Results

Blood Pressure  The mean ± SD reductions in trough SBP, DBP, and HR measured by ABPM between 6 PM and 10 PM in all treatment groups are summarized in Table 2. The mean reductions in trough DBP were dose related and were statistically significant for the GRD 240-mg (P < .0001), 360-mg (P = .002), and 540-mg (P < .0001) groups. The largest mean reduction in trough DBP was observed in the 540-mg group. Similarly, there were dose-related, mean reductions in trough (6 PM to 10 PM) SBP from baseline to end point for all evening GRD groups (Table 2), which were only statistically significant for the GRD doses greater than 120 mg. The 540-mg group also showed the greatest reduction. The greater reductions in BP observed for the 240-mg dose (DBP: −5.3 mm Hg; SBP: −8.1 mm Hg) compared with the 360-mg PM dose (DBP: −3.3 mm Hg; SBP: −4.6 mm Hg), may be due to significant baseline BP differences between the two groups. There was a 5 mm Hg difference in DBP and a 7.5 mm Hg difference in SBP between the two groups (Table 1). This is especially likely because with diltiazem, the extent of the BP reduction is related to the severity of the baseline hypertension.12,16,17 The least squares mean results, adjusting for baseline differences, confirmed the dose-related reductions in trough DBP and eliminated the latter difference in the responses observed between the GRD 240-mg and 360-mg PM treatment groups. The least squares means for the change from baseline to end point in trough DBP were: −1.92 mm Hg, −4.26 mm Hg, −4.38 mm Hg, and −8.02 mm Hg, respectively, for GRD 120-, 240-, 360-mg PM and 540-mg treatment groups (Fig. 1A). Similar least squares mean results were obtained for the corresponding change from baseline to end point in trough SBP (Fig. 1A).

There was a significant difference between the GRD 360-mg PM and 360-mg AM groups in the mean change from baseline to end point in DBP measured by ABPM between 6 AM and 12 noon (Table 2). The least squares mean for treatment difference was −3.30 mm Hg (P = .0004) for DBP (Fig. 1B). For SBP, similar results were obtained (Table 2) with a least squares mean for treatment difference of −5.32 mm Hg (P = .0004) in favor of the PM treatment group (Fig. 1B). In addition, there was a significant (P < .0001), dose-related increase in the antihypertensive effect observed between 6 AM and 12 noon for all the GRD evening doses with the 540-mg group showing the greatest effect (Fig. 1B).

The 24-h DBP (Fig. 2A) and SBP (Fig. 2B) profiles for the GRD 360-mg PM, 360-mg AM, and placebo treatment groups obtained by ABPM after 7 weeks of treatment, using the mean hourly values, showed bedtime administration of GRD provided the greatest antihypertensive effect, for DBP and particularly SBP, during the critical morning period (about 6 AM to 12 noon) and the least effect during the hours of 2 to 4 AM, when BP is at its lowest. The lower reductions in the 24-h mean DBP and SBP for the GRD 360-mg AM group compared to the 360-mg PM group (Table 2) can similarly be attributed to the lower baseline BP values of the PM group, as shown previously in other reports.18,19

The DBP responder rates achieved for all GRD treatment groups above the 120-mg dose were significantly (P < .05) higher than those observed for placebo (Fig. 3). For SBP, only the GRD 240-mg and 540-mg treatment groups achieved significantly higher responder rates compared to placebo. The SBP responder rates for the 360-mg groups did not achieve statistical significance, probably because the significantly lower baseline BP values (Table 1) reduced the extent of the antihypertensive response.16,17,19 Overall, the largest responder rates were observed in the 540-mg treatment group and were 73.4% for DBP and 67.2% for SBP. Between the 360-mg PM and 360-mg AM groups, the responder rates were similar.

Heart Rate  There were dose-related mean reductions in HR from baseline to end point during the time periods assessed (Table 2), with the greatest reductions seen during the 6 AM to 12 noon period. The mean reductions in 24-h HR were only significant (P < .05) for the GRD doses above 240 mg. Compared to placebo, only the mean 24-h reductions for the GRD 360-mg doses and higher
Table 1. Patient demographics and baseline characteristics

| Characteristic | Placebo  
|               | \(n = 69\) | GRD 120 mg  
|               | \(n = 67\) | GRD 240 mg  
|               | \(n = 68\) | GRD 360 mg  
|               | AM \(n = 102\) | PM \(n = 103\) | GRD 540 mg  
|               | \(n = 69\) | \(P\) |
| Age (y) | 51.5 ± 9.6 | 51.6 ± 10.3 | 52.8 ± 9.2 | 53.6 ± 9.6 | 52.5 ± 8.4 | 51.4 ± 9.5 | .6103 |
| Height (cm) | 171.2 ± 10.8 | 170.5 ± 9.6 | 173.6 ± 9.5 | 171.9 ± 9.7 | 172.8 ± 10.2 | 172.0 ± 8.3 | .4792 |
| Weight (kg) | 92.5 ± 18.3 | 86.6 ± 17.4 | 90.5 ± 19.7 | 94.5 ± 22.9 | 91.8 ± 18.0 | 92.1 ± 18.0 | .3501 |
| Gender - n (%) | 45 (65.2) | 46 (68.7) | 42 (61.8) | 61 (59.8) | 69 (67.0) | 40 (58.0) | .7023 |
| Male | | | | | | | .7023 |
| Female | 24 (34.8) | 21 (31.3) | 26 (38.2) | 41 (40.2) | 34 (33.0) | 29 (42.0) | .2151 |
| Ethnicity - n (%) | 45 (65.2) | 35 (52.2) | 42 (61.8) | 66 (64.7) | 67 (65.0) | 47 (68.1) | .2151 |
| White | | | | | | | .2151 |
| African American | 16 (23.2) | 22 (32.8) | 24 (35.3) | 28 (27.5) | 28 (27.2) | 14 (20.3) | .2151 |
| Other | 8 (11.5) | 10 (15.0) | 2 (3.0) | 8 (7.8) | 8 (7.8) | 8 (11.5) | .2151 |
| Baseline ABPM parameters | | | | | | | .2151 |
| Trough (6 PM–10 PM)* | | | | | | | .2151 |
| SBP (mm Hg) | 155.7 ± 14.1 | 154.9 ± 14.4 | 160.7 ± 14.7 | 151.5 ± 19.9 | 153.2 ± 14.5 | 156.4 ± 15.8 | .0061 |
| DBP (mm Hg) | 98.6 ± 8.3 | 97.8 ± 9.6 | 100.3 ± 9.5 | 92.5 ± 10.6 | 95.3 ± 9.8 | 98.3 ± 10.1 | .0398 |
| HR (beats/min) | 85.0 ± 12.6 | 81.3 ± 13.2 | 84.7 ± 10.1 | 75.7 ± 10.1 | 83.8 ± 11.8 | 85.3 ± 13.1 | .4718 |
| 6 AM–12 noon | | | | | | | .2151 |
| SBP (mm Hg) | 156.6 ± 12.7 | 155.2 ± 12.5 | 159.3 ± 13.7 | 161.0 ± 17.1 | 156.0 ± 12.2 | 157.3 ± 12.7 | .0718 |
| DBP (mm Hg) | 101.7 ± 7.4 | 100.1 ± 7.1 | 101.7 ± 8.3 | 100.3 ± 8.1 | 100.1 ± 7.0 | 100.7 ± 6.7 | .6190 |
| HR (beats/min) | 80.6 ± 10.3 | 79.1 ± 10.8 | 80.4 ± 10.1 | 82.9 ± 9.6 | 82.0 ± 11.4 | 82.1 ± 10.0 | .2609 |
| 24-h mean | | | | | | | .2151 |
| SBP (mm Hg) | 151.2 ± 12.3 | 150.4 ± 11.8 | 154.5 ± 12.6 | 156.0 ± 16.6 | 150.5 ± 12.0 | 151.6 ± 12.7 | .0300 |
| DBP (mm Hg) | 96.0 ± 7.0 | 95.0 ± 6.5 | 96.5 ± 7.4 | 94.9 ± 7.4 | 94.3 ± 6.4 | 95.2 ± 6.9 | .4141 |
| HR (beats/min) | 80.2 ± 9.9 | 78.2 ± 10.8 | 80.1 ± 8.6 | 81.5 ± 8.9 | 80.7 ± 10.2 | 80.8 ± 9.8 | .4672 |

GRD = graded-release diltiazem HCI extended release; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

Values are mean ± SD.

* Trough values for GRD 360 mg AM are for the period 4 AM to 8 AM.
Table 2. Change from baseline to end point in mean DBP, SBP, and HR recorded by ABPM

<table>
<thead>
<tr>
<th>Period</th>
<th>Placebo (n = 57)</th>
<th>GRD 120 mg (n = 59)</th>
<th>GRD 240 mg (n = 63)</th>
<th>GRD 360 mg AM (n = 94)</th>
<th>GRD 360 mg PM (n = 95)</th>
<th>GRD 540 mg (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough (6 PM–10 PM)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.5 ± 12.2</td>
<td>-2.8 ± 13.0</td>
<td>-8.1 ± 12.7††</td>
<td>-8.4 ± 10.7††</td>
<td>-4.6 ± 12.9††</td>
<td>-9.9 ± 13.2††</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-0.2 ± 7.8</td>
<td>-2.1 ± 9.2††</td>
<td>-5.3 ± 9.6††</td>
<td>-6.4 ± 7.7††</td>
<td>-3.3 ± 10.0††</td>
<td>-8.2 ± 9.1††</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>-1.5 ± 10.5</td>
<td>-0.2 ± 10.1</td>
<td>-1.5 ± 8.8</td>
<td>-4.2 ± 6.8††</td>
<td>-4.6 ± 9.3††</td>
<td>-5.4 ± 9.1††</td>
</tr>
<tr>
<td>6 AM–12 noon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.5 ± 11.5</td>
<td>-5.9 ± 10.8††</td>
<td>-12.6 ± 11.3††</td>
<td>-8.4 ± 9.8††</td>
<td>-12.0 ± 9.5††</td>
<td>-18.5 ± 12.5††</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-0.3 ± 8.0</td>
<td>-4.5 ± 6.9††</td>
<td>-9.3 ± 7.7††</td>
<td>-6.8 ± 5.9††</td>
<td>-9.9 ± 7.0††</td>
<td>-14.8 ± 8.2††</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>0.5 ± 8.7</td>
<td>-0.7 ± 7.4</td>
<td>-3.2 ± 7.7††</td>
<td>-5.1 ± 7.9††</td>
<td>-5.8 ± 9.7††</td>
<td>-8.3 ± 8.7††</td>
</tr>
<tr>
<td>24-h mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>1.0 ± 7.7</td>
<td>-4.3 ± 9.0††</td>
<td>-9.2 ± 8.8††</td>
<td>-10.1 ± 8.3††</td>
<td>-8.2 ± 7.7††</td>
<td>-13.5 ± 9.7††</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-0.1 ± 5.0</td>
<td>-2.9 ± 5.3††</td>
<td>-5.9 ± 5.8††</td>
<td>-8.1 ± 5.1††</td>
<td>-6.6 ± 5.2††</td>
<td>-10.8 ± 6.1††</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>-0.3 ± 6.9</td>
<td>-0.4 ± 5.2</td>
<td>-2.4 ± 6.1††</td>
<td>-6.1 ± 6.4††</td>
<td>-4.6 ± 6.9††</td>
<td>-6.7 ± 6.2††</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Values are mean ± SD.
* Trough values for GRD 360 mg AM are for the period 4 AM to 8 AM; † P < .05 for change from baseline to end point; ‡ P < .05 v placebo.

Safety Results
Overall, 216 (45.2%) patients in the GRD treatment groups and 34 (49.3%) of the placebo-treated patients. Incidence of AEs was similar to that observed for the 240-mg dose was associated with the greatest reductions in SBP, DBP, and HR. The incidence of AEs was reported in 34 (49.3%) of the placebo-treated patients, and 32 (40.5%) of the GRD-treated patients. There were no episodes of upper respiratory tract infection (5.6%), and lower limb oedema (5.4%). There were no episodes of headache and lower limb oedema (5.4%). There were no episodes of headache.

FIG. 1. A) Least squares mean changes from baseline in trough ambulatory blood pressure (BP) monitoring between 6 AM and 10 PM. B) Least squares mean changes from baseline in diastolic BP and systolic BP obtained by ambulatory blood pressure monitoring between 6 AM and 10 PM.
block requiring discontinuation from the study in the GRD treatment groups. Clinical laboratory abnormalities observed in the GRD groups were consistent with those reported previously in the approved package insert for diltiazem.\(^{17}\)

**Discussion**

The results of this study clearly demonstrate that GRD, a novel graded-release diltiazem HCl extended-release formulation, designed for once-daily nighttime dosing, reduces BP over the 24-h dosing interval in a dose-dependent fashion. The antihypertensive effect for SBP and DBP were significant for doses above 120 mg/day. Nighttime administration of GRD 360 mg was associated with significantly greater reductions in DBP (−3.3 mm Hg) and SBP (−5.3 mm Hg), during the period 6 AM to 12 noon compared to the same dose administered in the morning. The 24-h BP profiles obtained at the end of the 7-week treatment period confirm that GRD synchronizes its antihypertensive effect with the circadian variation of BP. These results confirm GRD as a chronotherapeutic antihypertensive agent that maximizes its effect during the period of early morning BP surge, which coincides with the reported peak incidence of nonembolic stroke,\(^2\) silent myocardial ischemia,\(^3,4\) myocardial infarction,\(^1,5,6\) and sudden cardiac death.\(^1,7,8\) In addition, the smallest BP reduction occurred between 2 and 4 AM when BP is physiologically at its lowest level. The findings in this study confirm previous reports of a linear dose–response for the antihypertensive effects of different formulations of diltiazem over the dosage range 120 to 540 mg/day.\(^14,16,20\)

Furthermore, the high DBP response rate of 73% achieved in this study is similar to the 72% rate achieved for diltiazem in the VA Cooperative Study.\(^21,22\) In addition, the sustained 24-h antihypertensive effect after once-daily administration, and the timing of its maximum effect at the time of abrupt increase of BP after arising from overnight sleep are desirable features of an optimal antihypertensive formulation described in Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI).\(^15\)

Heart rate was similarly reduced in a dose-dependent fashion during the 24-h dosing interval in this study. The greatest reduction in HR occurred during the early morning post-awakening period. The combined reductions in SBP and HR may have beneficial clinical implications in reducing the SBP–HR product.\(^23,24\) The latter is a well-recognized index of myocardial oxygen demand and has been shown to parallel silent myocardial ischemia.\(^25\) In addition, the findings of the Framingham study reveal that the risk of developing cardiovascular disease in hypertensive patients and cardiovascular mortality increased in a continuous graded fashion with their accompanying increase in HR.\(^24,26\) These findings and the fact that increased HR is an underappreciated accompaniment of hypertension, suggest that antihypertensive agents that reduce the HR may be particularly beneficial in reducing hypertensive cardiovascular mortality.\(^24\)

The GRD was safe and very well tolerated across the dose range studied. Adverse events were qualitatively similar to those reported previously with other diltiazem formulations.\(^17\) A most significant finding in this trial was,
may be carried out. That review also revealed that in starting dose for diltiazem and titration up to 540 mg/day proved products) states that 180 to 240 mg/day is the usual reference (containing Food and Drug Administration-approved products) for complete control of hypertension compared to mg/day was the most commonly required dose (by 85% of ing the ef

1) physicians routinely use subtherapeutic doses of diltiazem, which revealed that: fi

240 mg/day for angina; and 3) the

patients) for complete control of hypertension compared to

mg/day was the most commonly required dose (by 85% of

ing the ef

history of its development; 2) previous studies investigat-

1) physicians routinely use subtherapeutic doses of dilti-

anomalies in the dosing of diltiazem, which revealed that:

and lower than that observed for the placebo group. These

greatest reductions in BP and HR, the incidence of AEs

fact, although the 540-mg dose was associated with the

despite a dose-dependent reduction in BP, no obvious
dose-related trends in the incidence of AEs observed. In

contrast, the prescribing patterns of physicians showed

that prescriptions of diltiazem for the treatment of hyper-

tension were most frequently for the 240-mg capsule

that further increasing the dose of diltiazem to 540 mg

le no greater

impressively reduces BP with a safety pro

that GRD is associated with signi

cant and clinically mean-

in January 2003–VOL. 16, NO. 1

Table 3. Number (%) of the most frequently reported AE/s from the GRD and placebo treatment groups

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n = 69)</th>
<th>GRD 120 mg (n = 67)</th>
<th>GRD 240 mg (n = 68)</th>
<th>GRD 360 mg AM (n = 102)</th>
<th>GRD 360 mg PM (n = 103)</th>
<th>GRD 540 mg (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache NOS</td>
<td>10 (14.5)</td>
<td>8 (11.9)</td>
<td>10 (14.7)</td>
<td>13 (12.7)</td>
<td>11 (10.7)</td>
<td>6 (8.7)</td>
</tr>
<tr>
<td>Edema lower limb</td>
<td>4 (5.8)</td>
<td>2 (3.0)</td>
<td>4 (5.9)</td>
<td>8 (7.8)</td>
<td>3 (2.9)</td>
<td>5 (7.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection NOS</td>
<td>2 (2.9)</td>
<td>3 (4.5)</td>
<td>3 (4.4)</td>
<td>7 (6.9)</td>
<td>6 (5.8)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1.4)</td>
<td>1 (1.5)</td>
<td>2 (2.9)</td>
<td>2 (2.0)</td>
<td>4 (3.9)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Sinusitis NOS</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
<td>2 (1.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (4.9)</td>
<td>1 (1.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Urinary tract infection NOS</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

NOS = not otherwise specified; other abbreviations as in Tables 1 and 2.

References


Appendix:
List of multicenter principal investigators: Neville Bittar, MD, Gemini Scientific, Madison, WI; Albert Carr, MD, Southern Clinical Research and Management, Augusta, GA; Hal Chadow, MD, Brookdale Cardiovascular Associates, Brooklyn, NY; Steven Chrysant, MD, Oklahoma Cardiovascular and Hypertension Center, Oklahoma City, OK; Deanna Cheung, MD, Memorial Research Medical Clinic, Long Beach, CA; Adnan Dahdul, MD, FutureCare Studies, Springfield, MA; George Dennish, MD, San Diego Cardiovascular Associates, La Jolla, CA; Walter Gaman, MD, North Texas Clinical Research, Irving, TX; Larry Gilderman, MD, University Clinical Research, Inc., Pembrook Pines, FL; Stephen Glasser, MD, USF CURE and Lipid Clinic, Tampa, FL; Daniel Gottlieb, MD, Seattle, WA; Robert Grossman, MD, Western Clinical Research, Torrance, CA; Robert Guthrie, MD, Ohio State University Research Clinic, Columbus, OH; Michael Korren, MD, Jacksonville Center for Clinical Research, Jacksonville, FL; David Kraus, MD, Memphis Heart Clinic, Memphis, TN; Mark Kutner, MD, Miami Research Associates, Miami, FL; Irving Loh, MD, Ventura Heart Institute, Thousand Oaks, CA; Puneet Narayan, MD, Clinical Research Institute of Northern Virginia, Inc., Springfield, VA; Joel Neutel, MD, Orange County Heart Institute, Orange, CA; Gilberto Neri, MD, Rush Presbyterian, Chicago, IL; Vasilios Papademetriou, MD, VA Medical Center, Washington DC; John Pappas, MD, Central Kentucky Research Associates, Inc., Lexington, KY; Henry Punzi, MD, Punzi Medical Center, Carrolton, TX; Bruce Rankin, DO, University Clinical Research DeLand, DeLand, FL; William Sokol, MD, Health Research Institute, Newport Beach, CA; William B. Smith, MD, New Orleans Center for Clinical Research, New Orleans, LA; Danny Sugimoto, MD, Cedar-Crose Research Center, Chicago, IL; Matthew Weir, MD, University of Maryland, Clinical Research Unit, Baltimore, MD; Robert Weiss, MD, Androscoggin Cardiology Research, Auburn, ME; John Zerbe, MD, The Lindner Center, Cincinnati, OH; Benjamin Lewis, MD, Piedmont Clinical Research Center, Ninety Six, SC; Eleuterio Delfin, MD, Advanced Center for Clinical Research, LLC, Norwalk, CA; Jon Ruckle, MD, Radiant Research, Honolulu, HI; Howard Offenberg, MD, Radiant Research, Daytona Beach, FL; Rodney Schmidt, MD, Radiant Research, Lakewood, WA; Douglas Schumacher, MD, Radiant Research, Columbus, OH; Daniel Crow, MD, Radiant Research; Duncan, SC; Harry Geisberg, MD, Radiant Research, Anderson, SC; Richard Heuser, MD, Discovery Alliance, Inc., Phoenix, AZ.