Effects of mirodenafil on the hemodynamics in hypertensive patients taking amlodipine

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While phosphodiesterase type 5 inhibitors have been used for erectile dysfunction with acceptable safety profile, they can induce orthostatic hypotension in patients taking antihypertensive drugs with blood pressure lowering effect. This study evaluated the hemodynamic effects of 100 mg mirodenafil in hypertensive patients taking amlodipine. Thirteen hypertensive patients who were taking 5 or 10 mg of amlodipine once daily participated in a randomized, double-blind, placebo-controlled, crossover study. A single oral dose of mirodenafil 100 mg or placebo was administered at 4.5 hour after administration of amlodipine. The maximal change in systolic and diastolic blood pressure (∆maxSBP and ∆maxDBP) and pulse rate (∆maxPR) were compared between mirodenafil and placebo periods. Twelve patients completed this study and were included analysis. The values of ∆maxPR in standing and supine position were significantly greater in the mirodenafil period (13.25±7.12 and 11.17±4.86 beats/minute) when compared to the placebo (8.50±4.72 and 6.58±3.90 beats/minute). The ∆maxSBP and ∆maxDBP in standing position appeared to be lower in the mirodenafil period, but they were not statistically different from those in the placebo period (∆maxSBP = -7.42±5.6 vs -4.42±5.37 mmHg and ∆maxDBP = -7.17±5.72 vs -3.50±3.37 mmHg). Both ∆maxSBP and ∆maxDBP in standing and supine position were not significantly different between mirodenafil and placebo. This study demonstrated that mirodenafil exerted minimal hemodynamic effects in the patients taking amlodipine, that is unlikely associated with a clinically significant hypotensive event.

Introduction

Phosphodiesterase type 5 (PDE5) inhibitors are widely used to treat erectile dysfunction (ED).[1-3] Hypertension is a frequent comorbidity of men with ED and 30% of men who had ED also reported a history of hypertension.[4,5] Considering that both PDE5 inhibitors and antihypertensive drugs have vasodilatory effects, there is a possibility that co-administration of the two classes of drugs would result in synergistic hemodynamic effects.[6-8] When PDE5 inhibitors were administered to hypertensive patients who are on any of the several antihypertensive agents (e.g. β-blockers, calcium channel blocker, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or diuretics), there was a synergistic decreasing effect in blood pressure.[6,9,10]

Mirodenafil is a novel PDE5 inhibitor that has been approved in Korea.[11,12] Preclinical studies have shown that mirodenafil has an equivalent pharmacologic effect for the treatment of ED as other PDE5 inhibitors do, and it has a high selectivity for PDE5.[13,14] A phase III study demonstrated that mirodenafil, in doses of 50 mg or 100 mg, significantly improved ED and was well tolerated in men with ED of various etiologies and severities.[11,12,15-17] Mirodenafil is most frequently prescribed with calcium channel blockers rather than other antihyperten-
**Methods**

**Subjects**

Patients aged between 19 and 65 years with essential hypertension were eligible for the study. The criteria for eligibility were systolic blood pressure (SBP) between 100 and 140 mmHg and diastolic blood pressure (DBP) between 65 and 90 mmHg, for more than 4 weeks, and current therapy with 5 or 10 mg amlodipine once daily. Subjects with any of the following conditions were excluded from the study: history of any acute disease within the 4 weeks prior to study drug administration, any gastrointestinal surgery that could impact drug absorption, hypercalcemia, resulting in reduced blood pressure.[19] In clinical situations, amlodipine is prescribed as 5 mg or 10 mg once daily to treat hypertension.[20]

Mirodenafil was effective and well tolerated in patients with both ED and hypertension. However, mirodenafil group exhibited a higher proportion of subjects experiencing adverse events, such as flushing, compared with the placebo group, an observation which can be attributed to the modest vasodilatory property of the drug. The effects of concomitant administration of mirodenafil and antihypertensive agents on blood pressure and pulse rate were somewhat limited in that they were measured only on the patients’ scheduled visits to the hospital and mirodenafil was administered on an “as needed basis”.[5] There is no reported study to explore the synergetic hemodynamic effects of mirodenafil and antihypertensive agents primarily, thus the effect should be evaluated in those patient population.

In present study, we evaluated the hemodynamic effects of 100 mg mirodenafil in hypertensive patients taking amlodipine as a first-line antihypertensive medication.

**Hemodynamic Analysis**

The primary endpoint of the study was a maximal change in SBP (ΔmaxSBP) from the baseline, caused by mirodenafil or placebo administration while in the standing position. The maximal drug-induced changes in DBP (ΔmaxDBP) and pulse rate (ΔmaxPR) were also measured in the standing and supine positions. ΔmaxSBP was measured in the supine position as well. To compare the overall hemodynamic effects, the total area under the effect curve (AUEC) from 0-8 h after the administration of mirodenafil or placebo was also calculated for each drug. Statistical analyses were conducted using data from patients who underwent all the procedures specified in the study. Descriptive statistics using mean differences and 95% confidence intervals were used to analyze the data. Estimated untransformed values were compared using the analysis of variance (ANOVA) statistical method. Baseline blood pressure was compared between the mirodenafil and placebo groups using Wilcoxon-signed rank sum test. The statistical significance was evaluated with criteria for p < 0.05. All statistical analyses were performed using the SAS software package (version 9.1.3; SAS Institute, Cary, NC, USA).

**Safety assessment**

Subjects were continuously monitored by investigators throughout the study period. Adverse events were identified through inquiries, self-report by the subjects, and repeated investigations. Clinical laboratory evaluation (hematology, chemistry, serology, and urinalysis), vital sign measurements in-
including blood pressure and heart rate, and physical examination were performed at predetermined times throughout the study. The frequency and severity of adverse events in the mirodenafil and placebo groups were compared using chi-square test or Fisher’s exact test.

Results

Subjects
A total of 24 patients with essential hypertension were screened and 13 patients (8 from Busan Paik Hospital and 5 from Asan Medical Center) were enrolled in the study. Of the 13 patients enrolled, 1 subject was lost to follow-up during the pretreatment period. Consequently, 12 patients completed the study. The mean age and body mass index of the patients were 49.3±8.3 years and 24.6±3.0, respectively. The baseline hemodynamic variables for the patients are shown in Table 1. There were no significant differences in the baseline hemodynamic variables between the two groups of patients.

Hemodynamics
Concomitant administration of mirodenafil and amlodipine tended to lower SBP and DBP and increase pulse rate, in both standing and supine positions (Figs. 1 and 2, respectively). All the maximal changes in SBP, DBP, and pulse rate from baseline were observed at 8 h after administration of mirodenafil or placebo. The mean ∆maxSBP, ∆maxDBP, and ∆maxPR at 8 h are shown in Table 1. The ∆maxPR after mirodenafil administration was significantly higher than that with placebo (p = 0.018 in the standing position, p = 0.014 in the supine position) without significant changes in blood pressure. The AUEC for pulse rate from zero to 8 hour also revealed statistically significant differences between the mirodenafil and placebo groups (p = 0.013 for the standing position and p = 0.002 for the supine position) (Table 2).

Safety
The safety of combining amlodipine with mirodenafil was evaluated using data from all the patients. Five adverse events occurred in 4 patients. After the administration of mirodenafil, nasal congestion with oropharyngeal pain, facial flushing, and headache were reported. After placebo administration, dizziness was reported in one patient. All the adverse events were mild and resolved without medication except for the painful nasal congestion, which was of moderate intensity and required treatment with a decongestant. No serious adverse events were observed. There were no significant differences in the frequency and severity of adverse events between the mirodenafil and placebo groups (p < 0.05).

Discussion
While concomitant administration of PDE5 inhibitors and different classes of antihypertensive drugs is considered relatively safe,[14,24] concomitant administration of PDE5 inhibitors with antihypertensive drugs cause an additive or synergistic hemodynamic interaction owing to blood pressure lowering effect. For safety information in prescribing to patients with ED taking antihypertensive medication, the hemodynamic effects of

Table 1. Baseline and effects of mirodenafil or placebo on hemodynamic variables in stable hypertensive patients taking amlodipine (n=12)

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine + mirodenafil*</th>
<th>Amlodipine + placebo*</th>
<th>Mean difference†</th>
<th>p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline SBP</td>
<td>121.1 (8.7)</td>
<td>122.2 (5.3)</td>
<td>0.594</td>
<td></td>
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<tr>
<td>Baseline DBP</td>
<td>81.4 (8.0)</td>
<td>81.5 (5.9)</td>
<td>0.664</td>
<td></td>
</tr>
<tr>
<td>Baseline PR</td>
<td>74.0 (11.5)</td>
<td>72.8 (10.0)</td>
<td>0.400</td>
<td></td>
</tr>
<tr>
<td>∆maxSBP</td>
<td>-7.42 (5.60)</td>
<td>-4.42 (5.37)</td>
<td>-2.51 (-6.24~1.22)</td>
<td>0.164</td>
</tr>
<tr>
<td>∆maxDBP</td>
<td>-7.17 (5.72)</td>
<td>-3.50 (3.37)</td>
<td>-3.31 (-7.17~0.54)</td>
<td>0.084</td>
</tr>
<tr>
<td>∆maxPR</td>
<td>13.25 (7.12)</td>
<td>8.50 (4.72)</td>
<td>5.16 (1.09~9.22)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Supine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline SBP</td>
<td>119.2 (9.9)</td>
<td>119.1 (9.2)</td>
<td>0.860</td>
<td></td>
</tr>
<tr>
<td>Baseline DBP</td>
<td>74.5 (7.0)</td>
<td>75.4 (7.2)</td>
<td>0.824</td>
<td></td>
</tr>
<tr>
<td>Baseline PR</td>
<td>64.4 (7.7)</td>
<td>63.7 (7.0)</td>
<td>0.365</td>
<td></td>
</tr>
<tr>
<td>∆maxSBP</td>
<td>-6.25 (5.05)</td>
<td>-4.33 (7.23)</td>
<td>-1.92 (-6.44~3.78)</td>
<td>0.575</td>
</tr>
<tr>
<td>∆maxDBP</td>
<td>-7.00 (4.67)</td>
<td>-5.25 (4.71)</td>
<td>-1.50 (-4.28~1.28)</td>
<td>0.257</td>
</tr>
<tr>
<td>∆maxPR</td>
<td>11.17 (4.86)</td>
<td>6.58 (3.90)</td>
<td>4.39 (1.11~7.66)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Δ, delta; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. *Values are presented as arithmetic means (standard deviation). †Values are presented as arithmetic means (95% confidence interval). ‡Calculated by analysis of variance.
PDE5 inhibitor should be characterized thoroughly. Currently available PDE5 inhibitors such as sildenafil and tadalafil provide the changes of hemodynamic profile when co-administered with calcium channel blockers and alpha blockers. This study evaluated the immediate hemodynamic effects of concomitant treatment with mirodenafil in hypertensive patients who were taking amlodipine daily.

The mean $\Delta_{\text{maxSBP}}$ and $\Delta_{\text{maxDBP}}$ observed after mirode-
Despite the known hemodynamic changes of PDE5 inhibitors, especially in special conditions such as the use of multiple drugs and intractable hypertension.

The transient pulse rate increase observed in patients taking amlodipine may not have any clinical relevance. Nevertheless, precautions and a dose adjustment in the hypertensive patients, especially in special conditions such as the use of multiple drugs and intractable hypertension.

Effects of mirodenafil in hypertensive patients taking amlodipine administration in standing position (-2.51 with range from -6.24 to 1.22 and -3.31 with range from -7.17 to 0.54 mmHg) were lesser than those reported in the interaction study of sildenafil (50 mg) with amlodipine (5 mg) in hypertensive patients (approximately -9.9 and -7.6 mmHg).[25] The mean ΔmaxSBP and ΔmaxDBP in supine position (-1.33 with range from -6.44 to 3.78 and -1.50 with range from -4.28 to 1.28 mmHg, respectively) also appeared to be smaller than those in the study between sildenafil and amlodipine. The mean reduction of SBP and DBP in supine position was comparable to that observed in the interaction study of tadalafil (10 mg) and amlodipine (5 mg) (-3 and -2 mmHg, respectively).[26] While the changes in the blood pressure observed after mirodenafil administration were not significant, pulse rate showed statically significant increases in supine as well as standing position. The calculated AUEC values of the hemodynamic variables after mirodenafil or placebo treatment in stable hypertensive patients (n=12)

AUEC, area under the effect curve; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate. *Values are presented as arithmetic means (standard deviation). †Values are presented as arithmetic means (95% confidence interval). ‡Calculated by analysis of variance.

**Table 2.** Calculated AUEC values of the hemodynamic variables after mirodenafil or placebo treatment in stable hypertensive patients (n=12)

<table>
<thead>
<tr>
<th></th>
<th>Amlodipine + Mirodenafil*</th>
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<th>Mean Difference†</th>
<th>p-value‡</th>
</tr>
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<tbody>
<tr>
<td>Standing</td>
<td></td>
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</tr>
<tr>
<td>AUEC0-8h, SBP</td>
<td>-19.65 (18.40)</td>
<td>-10.52 (14.45)</td>
<td>-7.64 (-18.81–3.54)</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>-19.54 (18.86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUEC0-8h, DBP</td>
<td>-19.54 (18.86)</td>
<td>-7.44 (7.62)</td>
<td>-10.55 (-21.47–0.37)</td>
<td>0.057</td>
</tr>
<tr>
<td>AUEC0-8h, PR</td>
<td>56.42 (36.25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUEC0-8h, SBP</td>
<td>-18.56 (18.42)</td>
<td>-13.19 (28.38)</td>
<td>-3.43 (-18.85–11.99)</td>
<td>0.631</td>
</tr>
<tr>
<td>AUEC0-8h, DBP</td>
<td>-22.25 (21.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUEC0-8h, PR</td>
<td>44.50 (21.40)</td>
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</table>

This study has a limitation of the sample size which was determined by the exploratory purpose, not a hypothesis testing. A limited number of subjects may be responsible for the failure to detect a statistical significance in the differences of blood pressure parameters between mirodenafil and placebo. In addition, the patients with a higher dose of 10 mg were not enrolled sufficiently. The relatively higher variability of hemodynamic parameters in patients treated with mirodenafil suggests that its cardiovascular effect need be evaluated in a larger number of patients taking amlopidine or other calcium channel blockers.

Mirodenafil showed an additive blood-lowering effect when concomitantly administered with amlopidine in hypertensive patients with a compensatory increase of pulse rate, but the changes in the blood pressure were minimal. Mirodenafil was tolerated without any reported adverse event related with hemodynamic change in the hypertensive patients. These results suggest that mirodenafil may not cause any clinically significant symptom due to hemodynamic changes in patients taking a calcium channel blocker. However, an additive change of mirodenafil in blood pressure when co-administered with anti-hypertensive drugs including calcium channel blocker may warrant a caution and a dose adjustment in the hypertensive patients, especially in special conditions such as the use of multiple drugs and intractable hypertension.
Conflict of interest

Jihong Shon is currently employed by the U.S. Food and Drug Administration. His contribution to the manuscript was based on his prior employment, and the current manuscript does not necessarily reflect any position of the U.S. Food and Drug Administration or the U.S. government. This study was funded by SK Chemicals Life Science Biz, Seoul, Korea. We would like to thank the patients who participated in the study.

Ji-Hwa Ryu is an employee of Life Science Biz., SK Chemicals Co. Ltd., Seoul, Korea. After careful review, all authors indicated that they have no other conflicts of interest regarding the contents of this article.

References


