

Effects of mirodenafil on the hemodynamics in hypertensive patients taking amlodipine

Hyang-Ki Choi¹, Eon-Jeong Shim^{1,2}, Jihong Shon^{1,2}, Jin Ah Jung^{1,2}, Jong-Lyul Ghim³, Ji-Hwa Ryu⁴,
Kyun-Seop Bae⁵ and Jae-Gook Shin^{1,2*}

¹Department of Pharmacology and PharmacoGenomics Research Center, Inje University College of Medicine, Busan 47392, Korea,

²Department of Clinical Pharmacology, Inje University Busan Paik Hospital, Busan 47392, Korea, ³Department of Clinical Pharmacology and Toxicology, Anam Hospital, Korea University College of Medicine, Seoul 02841, Republic of Korea, ⁴Life Science Business, SK Chemicals Co. Ltd., Gyeonggi-do 13494, Korea, ⁵Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, Univ. of Ulsan, Seoul 05505, Korea

*Correspondence: J. G. Shin; Tel: +82-51-890-6709, Fax: +82-51-893-1232, E-mail: phshinjc@gmail.com

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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 an 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 (Δ maxSBP and Δ maxDBP) and pulse rate (Δ maxPR) were compared between mirodenafil and placebo periods. Twelve patients completed this study and were included analysis. The values of Δ 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 Δ maxSBP and Δ maxDBP in standing position appeared to be lower in the mirodenafil period, but they were not statistically different from those in the placebo period (Δ maxSBP = -7.42 ± 5.6 vs -4.42 ± 5.37 mmHg and Δ maxDBP = -7.17 ± 5.72 vs -3.50 ± 3.37 mmHg). Both Δ maxSBP and Δ 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 hyper-

tensive 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-

sive agents.[5]

Amlodipine is a one of the third-generation dihydropyridine calcium channel blocker used for the management of ischemic heart disease and hypertension.[18] It inhibits the influx of calcium ions into vascular smooth muscle cells and cardiac muscle cells, resulting in reduced blood pressure.[19] In clinical situation, 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.

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, hypersensitivity to the investigational drugs, orthostatic hypotension, a QTcF >440 ms in a 12-lead electrocardiogram (ECG), color sensation disorders, abnormal findings from physical examinations or laboratory tests (including vital signs, 12-lead ECG, complete blood count, blood chemistry screen, viral markers, and urine analysis), any chronic disease other than primary hypertension, and testing positive for a drug of abuse in a urine screening test.

Study Design

A multicenter, randomized, double-blind, placebo-controlled, two-way crossover study with a 7-day washout period was conducted to assess the hemodynamic effects of a single oral dose of mirodenafil in hypertensive patients taking amlodipine (5 or 10 mg) once daily. The study protocol was approved by the Institutional Review Board of Inje University Busan Paik Hospital,

and the Asan Medical Center. The study was registered on the ClinicalTrials.gov site (ID; NCT00626743).

On the study day (D1), patients were served a morning meal 30 min before the administration of amlodipine. At 4.5 h after the amlodipine dose, a single dose of 100 mg mirodenafil or the placebo was administered orally and set to zero time (0 h). The dosing schedule was designed to reveal any maximal hemodynamic changes caused by the drugs, based on the times of their maximum serum concentrations (6.5-8.5 h for amlodipine[21, 22] and 2-4 h for mirodenafil). Blood pressure and pulse rate were measured while patients were in a supine position and in a standing position, by using a Philips Intellivue MP40 patient monitor (Philips Healthcare, Foster City, CA, USA). The measurements were taken 4.5, 2.5, and 1 h before, and at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4.5, 6, 8 and 19.5 h after the administration of mirodenafil or placebo. Patients were maintained in a supine position for at least 5 min before each measurement in that position, after which they sat for 1 min, then stood for 2 min before measurements in the standing position. Hemodynamic measurements were performed twice in each position, or thrice if the SBP or DBP differed by more than 5 mmHg. The mean values at each time point and position were analyzed.[23] The mean values obtained before the administration of mirodenafil or the placebo, were used as the baseline values.

Hemodynamic Analysis

The primary endpoint of the study was a maximal change in SBP (Δ maxSBP) from the baseline, caused by mirodenafil or placebo administration while in the standing position. The maximal drug-induced changes in DBP (Δ maxDBP) and pulse rate (Δ maxPR) were also measured in the standing and supine positions. Δ maxSBP 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-

cluding 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 Δ maxSBP, Δ maxDBP, and Δ maxPR at 8 h are shown in Table 1. The Δ 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)

		Amlodipine + mirodenafil*	Amlodipine + placebo*	Mean difference [†]	p-value [‡]
Standing	Baseline SBP	121.1 (8.7)	122.2 (5.3)		0.594
	Baseline DBP	81.4 (8.0)	81.5 (5.9)		0.664
	Baseline PR	74.0 (11.5)	72.8 (10.0)		0.400
	Δ maxSBP	-7.42 (5.60)	-4.42 (5.37)	-2.51 (-6.24~1.22)	0.164
	Δ maxDBP	-7.17 (5.72)	-3.50 (3.37)	-3.31 (-7.17~0.54)	0.084
	Δ maxPR	13.25 (7.12)	8.50 (4.72)	5.16 (1.09~9.22)	0.018
Supine	Baseline SBP	119.2 (9.9)	119.1 (9.2)		0.860
	Baseline DBP	74.5 (7.0)	75.4 (7.2)		0.824
	Baseline PR	64.4 (7.7)	63.7 (7.0)		0.365
	Δ maxSBP	-6.25 (5.05)	-4.33 (7.23)	-1.33 (-6.44~3.78)	0.575
	Δ maxDBP	-7.00 (4.67)	-5.25 (4.71)	-1.50 (-4.28~1.28)	0.257
	Δ maxPR	11.17 (4.86)	6.58 (3.90)	4.39 (1.11~7.66)	0.014

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.

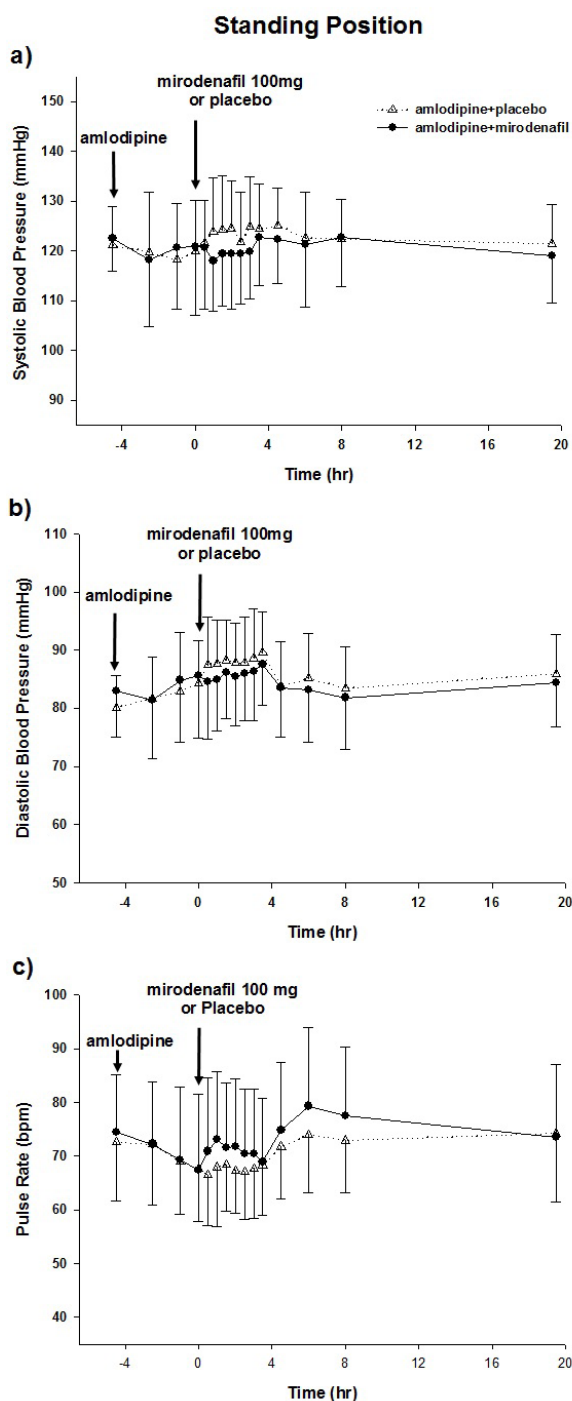


Figure 1. Effects of mirodenafil on hemodynamic variables while standing. Mean systolic (a) and diastolic (b) blood pressure, and pulse rate (c) following administration of amlodipine. Mirodenafil or placebo was administered at 4.5 h. All data are reported \pm standard deviations.

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

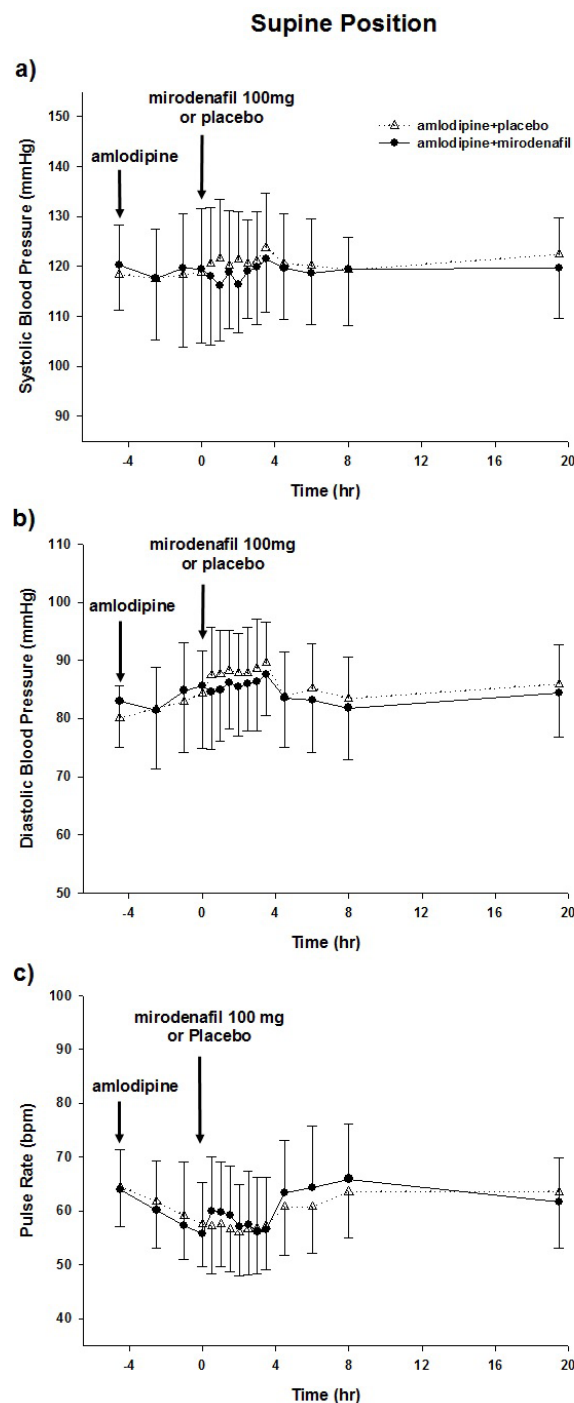


Figure 2. Effects of mirodenafil on hemodynamic variables while supine. Mean systolic (a) and diastolic (b) blood pressure, and pulse rate (c) following administration of amlodipine. Mirodenafil or placebo was administered at 4.5 h. All data are reported \pm standard deviations.

evaluated the immediate hemodynamic effects of concomitant treatment with mirodenafil in hypertensive patients who were taking amlodipine daily.

The mean Δ maxSBP and Δ maxDBP observed after mirode-

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

		Amlodipine + Mirodenafil*	Amlodipine + Placebo*	Mean Difference [†]	p-value [‡]
Standing	AUEC _{0-8h} , SBP	-19.65 (18.40)	-10.52 (14.45)	-7.64 (-18.81~3.54)	0.159
	AUEC _{0-8h} , DBP	-19.54 (18.86)	-7.44 (7.62)	-10.55 (-21.47~0.37)	0.057
	AUEC _{0-8h} , PR	56.42 (36.25)	26.67 (19.07)	32.28 (8.28~54.28)	0.013
Supine	AUEC _{0-8h} , SBP	-18.56 (18.42)	-13.19 (28.38)	-3.43 (-18.85~11.99)	0.631
	AUEC _{0-8h} , DBP	-22.25 (21.64)	-15.02 (18.31)	-6.11 (-14.77~2.55)	0.147
	AUEC _{0-8h} , PR	44.50 (21.40)	18.73 (13.70)	25.23 (11.75~38.70)	0.002

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.

nafil 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 Δ maxSBP and Δ maxDBP 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 were consistent with the actual results of blood pressure and pulse rate. In the interaction studies of other PDE5 inhibitors with the drugs which have a blood pressure lowering effect, a decrease in blood pressure was accompanied by an increase in pulse rate as a compensatory mechanism to minimize the hypotensive effects.[25,27] Accelerated heart rate is associated with a higher risk of all-cause mortality and cardiovascular events. It has been proposed that 10 per minute increase in heart rate is comparable to a 10 mmHg increase in SBP in relation to an increase in the risk of cardiac death.[28] The transient pulse rate increase observed in patients following mirodenafil administration (5.16 with range from 1.09 to 9.22 in standing position and 4.39 with range from 1.11 to 7.66 in supine position) appeared to be lower significantly than the reported clinically significant value (10 per minute). In addition, symptoms related with hemodynamic changes such as headache and dizziness were not reported in the mirodenafil period. Thus, the acute and slight increase in pulse rate caused by mirodenafil in patients taking amlodipine may not have any clinical relevance.

Despite of the known hemodynamic changes of PDE5 inhibitors, sildenafil, tadalafil and vardenafil have been reported to

be well-tolerated in ED patients on the concomitant medication of antihypertensive agents.[29,30] It implies that PDE5 inhibitors may cause minor hemodynamic changes within acceptable ranges in hypertensive patients receiving antihypertensive drugs. Given that the hemodynamic changes following co-administration of mirodenafil with amlodipine are lesser or comparable to those observed in the interaction studies of other PDE5 inhibitors, the reduction of blood pressure and increase of heart rate caused by mirodenafil in the hypertensive patients who are treated with calcium channel blockers is unlikely to cause clinically significant hypotensive events such as orthostatic hypotension.

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 amlodipine or other calcium channel blockers.

Mirodenafil showed an additive blood-lowering effect when concomitantly administered with amlodipine 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.

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References

- Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002;168:1332-1336.
- Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998;338:1397-1404.
- Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. *J Androl* 2002;23:763-771.
- Burchardt M, Burchardt T, Baer L, Kiss AJ, Pawar RV, Shabsigh A, et al. Hypertension is associated with severe erectile dysfunction. *J Urol* 2000;164:1188-1191.
- Paick JS, Kim JJ, Kim SC, Moon KH, Min KS, Park K, et al. Efficacy and safety of mirodenafil in men taking antihypertensive medications. *J Sex Med* 2010;7:3143-3152. doi: 10.1111/j.1743-6109.2010.01926.x.
- Reffellmann T, Kloner RA. Kloner, Cardiovascular effects of phosphodiesterase 5 inhibitors. *Curr Pharm Des* 2006;12:3485-3494.
- Xin Z. [Cardiovascular safety of vardenafil]. *Zhonghua Nan Ke Xue = Natl J Androl* 2004;10:790-793.
- Pomara G, Morelli G, Pomara S, Taddei S, Ghiadoni L, Dinelli N, et al. Cardiovascular parameter changes in patients with erectile dysfunction using pde-5 inhibitors: a study with sildenafil and vardenafil. *J Androl* 2004;25:625-629.
- Kloner RA, Brown M, Prisant LM, Collins M. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. Sildenafil Study Group. *Am J Hypertens* 2001;14:70-73.
- Kloner RA. Pharmacology and drug interaction effects of the phosphodiesterase 5 inhibitors: focus on alpha-blocker interactions. *Am J Cardiol* 2005;96:42M-46M.
- Chung JH, Kang DH, Oh CY, Chung JM, Lee KS, Kim TH, et al. Safety and efficacy of once daily administration of 50 mg mirodenafil in patients with erectile dysfunction: a multicenter, double-blind, placebo controlled trial. *J Urol* 2013;189:1006-1013. doi: 10.1016/j.juro.2012.08.243.
- Park HJ, Choi HK, Ahn TY, Park JK, Chung WS, Lee SW, et al. Efficacy and safety of oral mirodenafil in the treatment of erectile dysfunction in diabetic men in Korea: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *J Sex Med* 2010;7:2842-2850. doi: 10.1111/j.1743-6109.2010.01888.x.
- Rubio-Aurioles E, Porst H, Eardley I, Goldstein I; Vardenafil-Sildenafil Comparator Study Group. Comparing vardenafil and sildenafil in the treatment of men with erectile dysfunction and risk factors for cardiovascular disease: a randomized, double-blind, pooled crossover study. *J Sex Med* 2006;3:1037-1049.
- Jackson G, Montorsi P, Cheitlin MD. Cardiovascular safety of sildenafil citrate (Viagra): an updated perspective. *Urology* 2006;68:S47-S60.
- Bell AS, Palmer MJ. Novel phosphodiesterase type 5 modulators: a patent survey (2008 - 2010). *Expert Opin Ther Pat* 2011;21:1631-1641. doi: 10.1517/13543776.2011.614435.
- Lee SK, Kim Y, Kim TK, Im GJ, Lee BY, Kim DH, et al. Determination of mirodenafil and sildenafil in the plasma and corpus cavernous of SD male rats. *J Pharm Biomed Anal* 2009;49:513-518. doi: 10.1016/j.jpba.2008.11.004.
- Paick JS, Ahn TY, Choi HK, Chung WS, Kim JJ, Kim SC, et al. Efficacy and safety of mirodenafil, a new oral phosphodiesterase type 5 inhibitor, for treatment of erectile dysfunction. *J Sex Med* 2008;5:2672-2680. doi: 10.1111/j.1743-6109.2008.00945.x.
- Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992;22:22-31.
- Scholz H. Pharmacological aspects of calcium channel blockers. *Cardiovasc Drugs Ther* 1997;10:S869-S872.
- Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)* 2014;16:14-26. doi: 10.1111/jch.12237.
- Kim BH, Yi S, Kim J, Lim KS, Kim KP, Lee B, et al. Influence of alcohol on the hemodynamic effects and pharmacokinetic properties of mirodenafil: a single-dose, randomized-sequence, open-label, crossover study in healthy male volunteers in Korea. *Clin Ther* 2009;31:1234-1243. doi: 10.1016/j.clinthera.2009.06.008.
- Elliott HL, Green ST, Vincent J, Meredith PA. An assessment of the pharmacokinetics and pharmacodynamics of single doses of amlodipine in elderly normotensives. *Pharmacol Res* 1992;26:33-39.
- Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;45:142-161.
- Gu N, Kim J, Lim KS, Shin KH, Kim TE, Lee B, et al. Assessment of the effect of mirodenafil on the hemodynamics of healthy male Korean volunteers administered tamsulosin: a randomized, double-blind, placebo-controlled, 2-period crossover study. *Clin Ther* 2012;34:1929-1939. doi: 10.1016/j.clinthera.2012.08.002.
- Kloner RA, Mitchell M, Emmick JT. Cardiovascular effects of tadalafil. *Am J Cardiol* 2003;92:37M-46M.
- Eli Lilly. Tadalafil prescribing information. <http://pi.lilly.com/us/cialis-pi.pdf> Accessed Apr 20 2016
- Kloner RA, Mitchell M, Emmick JT. Cardiovascular effects of tadalafil in patients on common antihypertensive therapies. *Am J Cardiol* 2003;92:47M-57M.
- Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. *Prog Cardiovasc Dis* 2009;52:6-10. doi: 10.1016/j.pcad.2009.05.003.
- van Ahlen H, Wahle K, Kupper W, Yassin A, Reblin T, Neureither M. Safety and efficacy of vardenafil, a selective phosphodiesterase 5 inhibitor, in patients with erectile dysfunction and arterial hypertension treated with multiple antihypertensives. *J Sex Med* 2005;2:856-864.
- Pickering TG, Shepherd AM, Puddey I, Glasser DB, Orazem J, Sherman N, et al. Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents: a randomized controlled trial. *Am J Hypertens* 2004;17:1135-1142.