

Cardiovascular Parameter Changes in Patients With Erectile Dysfunction Using Pde-5 Inhibitors: A Study With Sildenafil and Vardenafil

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ABSTRACT: Sildenafil is the most prescribed oral agent for patients with erectile dysfunction (ED). Vardenafil is a new phosphodiesterase type 5 (Pde-5) inhibitor that was approved by the US Food and Drug Administration last year to treat patients with ED of various causes. Both of these Pde-5 inhibitors have vasodilating properties and effects on blood pressure (BP), and like nitrates, they work through the nitric oxide cyclic guanosine monophosphate pathway. The aim of this study was to investigate the influence of these Pde-5 inhibitors on BP and heart rate (HR) in normotensive men with ED by a crossover comparison. Thirty-five patients with ED were enrolled to evaluate and compare the effect of sildenafil (50 mg) and vardenafil (10 mg) on BP and HR. At the screening (baseline [B]) visit, sitting systolic blood pressure (B-SBP), diastolic blood pressure (B-DBP), and HR were measured. We performed a multiple administration for both drugs and, therefore, multiple measurements of BP and HR changes, 3 doses a week, on alternate days, late in the afternoon, and on an empty stomach. B-SBP, B-DBP, and HR were recorded before each 50-mg sildenafil dosing and after 30, 60, 120, and 240 minutes. Data were averaged over the 4 time points and compared with the baseline values obtained before each dosing. After a 3-week wash-out period, patients were crossed over to vardenafil (10 mg) with the same study design. After administration of both drugs, we observed a statistically significant decrease of BP and an increase of HR. On average, sildenafil caused a decrease

of SBP ranging from 5.1 ± 3.9 mm Hg during the first dosing to 4.7 ± 4.2 mm Hg during the third dosing, DBP ranged from 4.4 ± 4.9 to 4 ± 4.1 mm Hg, and HR increased 1.8 ± 2.0 bpm (first dose) and 1.2 ± 0.9 bpm (third dose). With vardenafil, we recorded a greater variation for SBP and DBP. SBP decreased from 8.02 ± 8.0 mm Hg during the first dosing to 5.4 ± 5.5 mm Hg during the third dosing, whereas DBP decreased from 6.6 ± 7.2 to 5.0 ± 5.3 mm Hg, respectively. Recorded HR showed an increase of 3.1 ± 3.2 bpm (first dose) and 2.4 ± 2.3 bpm (third dose). After the first vardenafil administration, we recorded fainting episodes in 3 patients because of a decrease in BP greater than 20 mm Hg. Two of the patients were in therapy with doxazosin for benign prostatic hyperplasia (BPH). Cardiovascular response was not significantly different after the first dose between the 2 treatments. Vardenafil demonstrated clinically significant differences (fainting) with respect to sildenafil only during the first doses. We suggest that before starting therapies with Pde-5 inhibitors, particularly with the newer ones, that baseline cardiovascular parameters are measured and monitored, especially during the first dose, because of the presence of a "first dose effect." Moreover, it is necessary to pay particular attention to those patients in treatment with other drugs that could have a synergistic hypotensive effect as a result of vasodilation potentiation.

Key words: hypotensive effect, side effect, crossover study.

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Erectile dysfunction (ED) is the inability to achieve and maintain an erection adequate for sexual intercourse. Epidemiologic estimates of ED incidence in the United States range from 10 million to 30 million (NIH Consensus Panel, 1993). A panel of experts at the first International Consultation on Erectile Dysfunction (World Health Organization [WHO], International Consultation on Urological Disease [ICUD], and Societe Internationale d'Urologie [SIU]; Paris 1999) recommended oral agents

as the first-line treatment of this condition regardless of etiology.

Sildenafil, an inhibitor of the enzyme phosphodiesterase type 5 (Pde-5), is the most prescribed oral agent. A considerable number of clinical trials have been conducted worldwide in numerous patient categories establishing its efficacy and safety in the treatment of ED. Vardenafil is a new Pde-5 inhibitor approved last year by the U.S. Food and Drug Administration to treat patients with ED of various causes.

These Pde-5 inhibitors have vasodilating properties and effects on blood pressure (BP; Cheitlin et al, 1999; Thadani et al, 2002), and like nitrates, they work through the nitric oxide cyclic guanosine monophosphate (cGMP)

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pathway. Until now, there were no controlled clinical data comparing the safety and efficacy of sildenafil or vardenafil in patients with resting hypotension; therefore, caution is suggested when prescribing either of these agents in this category of men. Hypertensive men have an increased risk of ED, and they can be treated with Pde-5 inhibitors. Therefore the possibility of interaction between Pde-5 inhibitors and antihypertensive medications to produce a significant decrease in BP was investigated. In the studies published to date, however, clinically insignificant BP decreases in normotensive and hypertensive men are reported with sildenafil (Morales et al, 1998; Vardi et al, 2002). More data are required for new Pde-5 inhibitors. The aim of this study was to investigate the influence of these Pde-5 inhibitors on BP and heart rate (HR) in normotensive men with ED by a crossover comparison.

Materials and Methods

Thirty-five normotensive patients with ED were enrolled to evaluate and compare the effect of sildenafil and vardenafil on BP and HR by a crossover study. Age varied between 50 and 73 years (mean 60, SD = 5.5).

Vardenafil exhibits an inhibitory potential on Pde-5 approximately 5 times greater than that of sildenafil; therefore, to assess efficacy (not evaluated in this study) or tolerance, it is important to use equipotent dosages (ie, 5, 10, and 20 mg of vardenafil vs 25, 50, and 100 mg of sildenafil). We selected the dosage of sildenafil and vardenafil according to the characteristics of the study population. Because all patients enrolled in the study did not have a prior history of oral treatment for ED with Pde-5 inhibitors, we decided to use the starting dose of 50 and 10 mg for sildenafil and vardenafil, respectively, instead of using the maximum dosage recommended. Normotension was defined as BP values below 140/90 mm Hg according to guidelines for the management of hypertension (World Health Organization, 1999). Exclusion criteria were: major illnesses (hypertension, unbalanced diabetes mellitus or associated untreated proliferative diabetic retinopathy, previous history of stroke or myocardial infarction, life-threatening arrhythmia), treatment with nitrates or anticoagulants, a known history of retinitis pigmentosa, genital anatomical deformities that would impair erection, elevated plasma prolactin level, and low plasma level of free testosterone. Free testosterone was measured in early morning by an enzyme immunoassay. Four patients taking α_1 -blocker therapy (3 doxazosin, 1 tamsulosin) for a mean period of 4 months (range 5–3 months) for BPH were also enrolled because they were normotensive before and after starting therapy with α -blockers. The study started after Ethical Committee approval. BP was measured with an automatic digital oscillometric device (Omron model HEM-705 CP, Hoofddorp, The Netherlands) to avoid observer bias.

At the screening (baseline [B]) visit, sitting systolic blood pressure (B-SBP), diastolic blood pressure (B-DBP), and HR were measured. Although each patient completed the International Index of Erectile Function (Rosen et al, 1997) during the screening visit, data were not analyzed in this study.

We performed a multiple administration for both drugs and, therefore, multiple measurements of BP and HR changes, 3 administrations a week on an empty stomach on alternate days (days I, III, and V) for sildenafil, and the same for vardenafil after the wash-out period. At each drug administration, BP and HR were measured before dosing and after 30, 60, 120, and 240 minutes. During every administration, data were averaged over the 4 time points and then compared with the baseline values obtained before each dosing. We chose a 3-week wash-out period to be sure to avoid carryover effects.

The 4 patients in treatment for BPH were informed to take α_1 -blockers at least 4 hours after taking sildenafil or vardenafil. All reported side effects were recorded.

The observed results are expressed as mean \pm SD. Differences were compared by paired or unpaired Student's *t* test, as appropriate. BP and HR behaviors over time were analyzed by analysis of variance for repeated measures, and Scheffe's test was applied for multiple comparison testing. Differences were considered statistically significant at $P < .05$.

Results

The mean baseline BP, measured during the first screening visit, was $128.0 \pm 9.9/78.1 \pm 5.9$ mm Hg (range 108–138/60–88 mm Hg). After the wash-out period, remeasured mean BP was $126.4 \pm 8.5/77.9 \pm 4.6$ mm Hg (range 110–136/65–87 mm Hg). These baseline BPs did not show a statistically significant difference (1° B-SBP vs 2° B-SBP: mean difference = 1.5 mm Hg, $P = .08$; 1° B-DBP vs 2° B-DBP: mean difference = 0.14 mm Hg, $P = .88$). Median baseline HR was 75.6 ± 4.2 bpm (range 67–84 bpm) and 75.3 ± 3.8 bpm (range 67–82 bpm) before and after the wash-out period, respectively.

After administration of either sildenafil or vardenafil, we observed a statistically significant decrease of BP and an increasing HR (Tables 1 and 2). Peak effect was at 60 minutes for sildenafil and at 30 minutes for vardenafil (Figure 1). On average, sildenafil caused a decrease of SBP ranging from 5.1 ± 3.9 mm Hg during the first dosing to 4.7 ± 4.2 mm Hg during the third dosing and of DBP ranging from 4.4 ± 4.9 mm Hg to 4 ± 4.1 mm Hg, respectively; HR increased 1.8 ± 2.0 bpm (first dose) and 1.2 ± 0.9 bpm (third dose; Figure 2).

With vardenafil, we recorded a greater variation of SBP and DBP. SBP ranged from 8.02 ± 8.0 mm Hg during the first dosing to 5.4 ± 5.5 mm Hg during the third dosing, whereas DBP ranged from 6.6 ± 7.2 to 5.0 ± 5.3 mm Hg, respectively. Recorded HR showed an increase of 3.1 ± 3.2 bpm (first dose) and 2.4 ± 2.3 bpm (third dose; Figure 2).

Comparing SBP and DBP modifications and decrements to pressures obtained before each dosing after all 3 sildenafil or vardenafil administrations, we observed that the cardiovascular parameters were always greater

Table 1. Change in cardiovascular parameters with sildenafil: total population*

Parameter	SBP, mm Hg	DBP, mm Hg	Heart Rate, bpm
Day I			
Baseline	128.0 ± 9.9	78.1 ± 5.8	75.6 ± 4.2
Sildenafil	122.9 ± 9.1	73.6 ± 5.1	77.4 ± 4.0
P	.03	.0007	.07
Day III			
Baseline	127.9 ± 8.5	79.2 ± 5.1	75.4 ± 4.3
Sildenafil	123.9 ± 9.2	76.4 ± 5.7	77.1 ± 4.0
P	.06	.02	.11
Day V			
Baseline	127.7 ± 9.0	78.6 ± 4.8	75.3 ± 4.2
Sildenafil	122.9 ± 10.0	74.6 ± 5.4	76.6 ± 3.9
P	.06	.02	.04

* Data are provided as the mean ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Change in cardiovascular parameters with vardenafil: total population*

Parameter	SBP, mm Hg	DBP, mm Hg	Heart Rate, bpm
Day I			
Baseline	126.4 ± 8.5	77.9 ± 4.6	75.3 ± 3.8
Vardenafil	118.4 ± 8.8	71.3 ± 6.6	78.4 ± 4.0
P	<.0001	<.0001	.001
Day III			
Baseline	126.1 ± 8.0	78 ± 3.7	74.9 ± 3.5
Vardenafil	120.1 ± 7.8	72.4 ± 5.6	77.5 ± 4.0
P	.001	<.0001	.001
Day V			
Baseline	126 ± 8.5	77.9 ± 4.1	74.5 ± 4.1
Vardenafil	120.5 ± 7.9	72.8 ± 6.0	76.9 ± 3.7
P	.001	<.0001	.001

* Data are provided as the mean ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

after vardenafil intake (Figure 2). For all analyzed parameters, the greatest changes were recorded during the first administration with both Pde-5 inhibitors. Moreover, during first intake, differences between sildenafil and vardenafil were statistically significant for SBP and HR but not for DBP ($P = .06$), whereas they were not significant at the second and third dosing. These findings suggest the existence of a “first dose effect.”

Of the patients on α_1 -blockers, 3 were on doxazosin and 1 was on tamsulosin. After first administration in patients on doxazosin, mean BP fall was greater with vardenafil (from 129.0/79.3 to 106.7/62.2 mm Hg) than with sildenafil (from 127.7/81.0 to 119.7/72.7 mm/Hg). However, BP decrease was lower after the second (from 126.0/80.0 to 114.0/69.0 mm Hg) and third (from 128.0/78.3 to 117.7/68.7 mm Hg) vardenafil dosing.

The most frequent side effects reported for both drugs were facial flushing, 8 points (sildenafil) vs 7 points (vardenafil), and mild headache, 5 points (sildenafil) vs 6 points (vardenafil). In 3 patients (8.5%) after first vardenafil administration, we recorded fainting episodes from a decrease in BP of more than 20 mm Hg. One patient was not on an α_1 -blocker, and his BP decreased from 135/86 to 115/69 mm Hg, whereas the other 2 patients were on doxazosin, with a mean BP fall from 130.5/79.5 to 105.0/60.5 mm Hg. In the patient on doxazosin who did not faint after the first vardenafil administration, BP fell from 126/69 to 110/65 mm Hg, and in the patient on tamsulosin who did not faint, BP decreased from 127/84 to 120/78 mm Hg.

Discussion

The association between ED and changes in BP is not surprising. There are in fact many histological and phar-

macological similarities between human cavernosal and other vascular tissues (Thadani et al, 2002). The nitric oxide–cGMP system, for example, plays a vital role in both the hemodynamic mechanisms of penile erection and vasodilation. The Pde-5 inhibitors sustain nitric oxide–mediated smooth muscle relaxation in the corpus cavernosum of the penis, but they also act systemically with vasodilator properties, similar to the effect of a moderately effective nitrate (Vickers et al, 1990). In fact, the most common adverse events associated with Pde-5 inhibitors treatment are headache and flushing, which reflect the vasodilator properties of these drugs (Jackson et al,

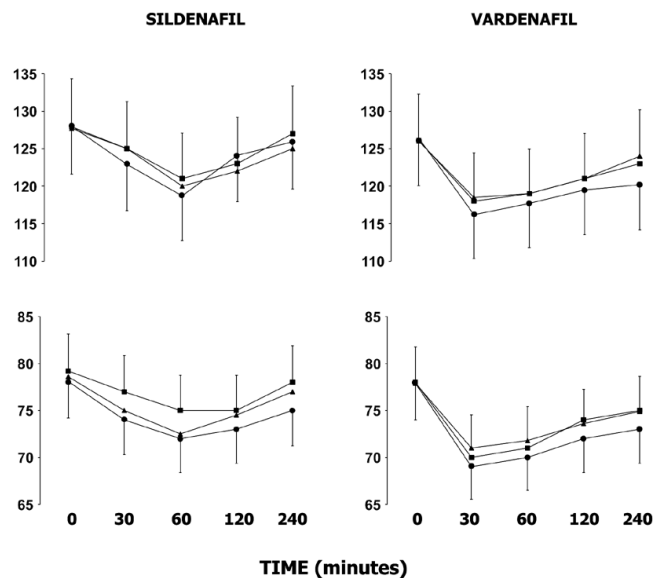


Figure 1. Line graph shows changes (mean ± SD) in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after sildenafil or vardenafil administration at different time points on days I (circles), III (triangles), and V (squares).

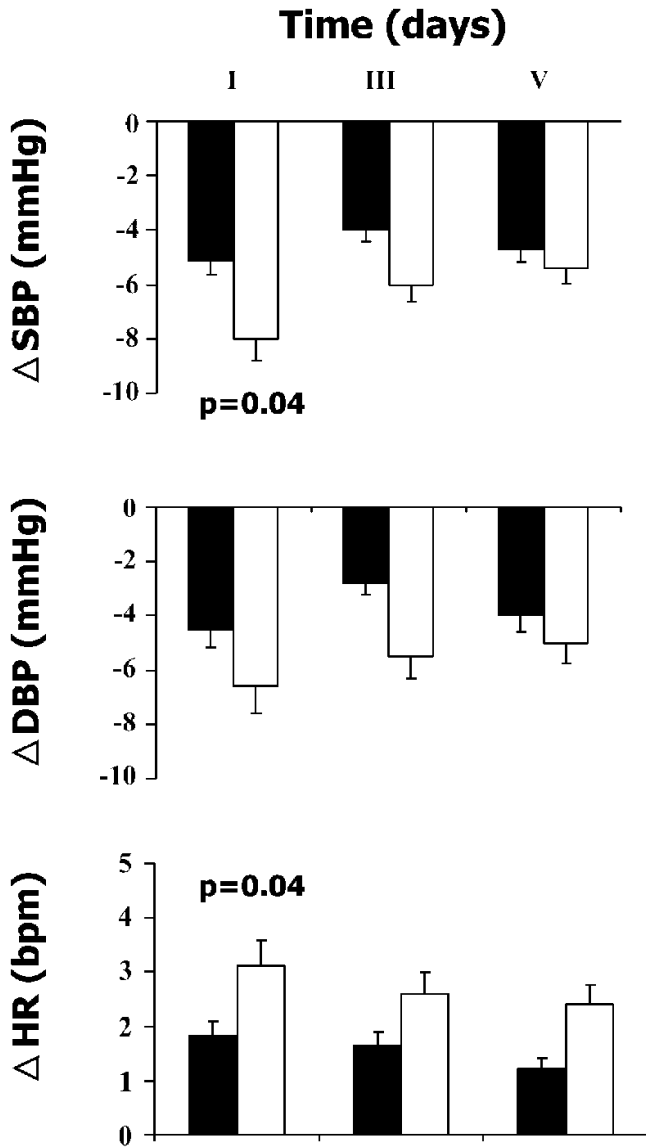


Figure 2. Line bars show maximal decrement (Δ) compared with baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) after sildenafil (black bars) or vardenafil (white bars) administration on days I, III, and V.

1999). Moreover, it is already known that Pde-5 inhibitors produce transient decreases in SBP and DBP (Morales et al, 1998; Thadani et al, 2002) associated with a mild increase of HR (Morales et al, 1998; Thadani et al, 2002; Vardi et al, 2002).

This study was undertaken to assess and compare the effects of sildenafil and vardenafil on SBP, DBP, and HR in men with ED. To the best of our knowledge, this is the first crossover comparison in the literature.

This study is not randomized or blind, but our results show that the Pde-5 inhibitor effects on cardiovascular parameters are homogeneous and reproducible, indicating that office monitoring with 3 administrations probably had the potential to eliminate artifacts.

Vardenafil elicited a greater change in cardiovascular parameters compared with sildenafil, which also produced different clinical effects. These differences were statistically significant only during first administration. Peak effect was at 60 minutes for sildenafil and at 30 minutes for vardenafil (Figure 1), in accordance with the velocity of action reported for both drugs.

Recently, Pryor (2002) published an update on clinical experience with vardenafil, and Porst et al (2001) reported the first at-home clinical trial of its safety in a large group of patients. Moreover, other studies on vardenafil reported its higher potency and selectivity for Pde-5 compared with sildenafil (Bischoff, 2000), even though more data probably are required to better understand whether this issue will translate into major clinical benefits. It is important, however, to observe that Pde-5 is present on vessel smooth muscle and platelets apart from the corpus cavernosum (Wallis et al, 1999), and it could be reasonable to expect greater adverse effects with vardenafil because of its higher potency and cross-reactivity. Our study results seem to confirm this issue. In fact, very significant clinical side effects (fainting episodes) were recorded only after the first vardenafil intake in 3 men in whom we recorded a decreased BP of more than 20 mm Hg. Two of these men were taking doxazosin, and certainly this association could produce a synergistic BP reduction (De Rose et al, 2002). Nevertheless, this was the first time we observed this side effect with Pde-5 inhibitors, even if it was associated with α_1 -adrenoreceptor antagonists.

Another unexpected finding was the first dose effect observed with both drugs, which explains the early appearance of major side effects and their subsequent disappearance.

Nevertheless, one of the major findings of this study was no significant difference in the cardiovascular response (after the first dose effect) between the 2 treatments. Moreover, although our data further support the harmful interaction (fainting) of vardenafil at first administration, especially in patients taking α_1 -receptor antagonists, this interaction becomes less clinically significant in subsequent administrations. We believe this finding of some interest. In fact, as standard deviation values show, some patients are more subject than others to this influence on cardiovascular parameters. Our results point out that even if important side effects appear after ingestion of newer Pde-5 inhibitors, these effects disappear during following intakes. Safety does not change, but more attention is required.

This study confirms that both sildenafil and vardenafil are mild vasodilators having a significant hypotensive effect in healthy patients. The effect on the average HR indicates that these BP reductions are sufficient to stimulate moderate reflex tachycardia. These findings are more significant with vardenafil. Fortunately, in normo-

tensive patients, these statistically significant changes in BP rarely cause important clinical consequences. Adverse effects are generally mild to moderate in nature and transient, which is consistent with rapid elimination of the molecule. In effect, experiences with sildenafil showed that BP generally returns to pretreatment values by 4 to 8 h after dosing in healthy men (Jackson et al, 1999).

We suggest that before starting therapy with new Pde-5 inhibitors, baseline cardiovascular parameters be measured and monitored, especially during the first doses because of an apparent first dose effect. Moreover, it is necessary to pay particular attention to those patients in treatment taking other drugs, such as α_1 -blockers for BPH, that could have a synergistic hypotensive effect as a result of vasodilation potentiation.

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