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Novel Phosphodiesterase Type 5 Inhibitors: Assessing Hemodynamic Effects and Safety Parameters

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Summary: The relaxing effect of the phosphodiesterase type 5 (PDE5) inhibitors on vascular smooth muscle has attracted much attention, especially in persons with cardiovascular disease. The results of early studies showed that sildenafil slightly reduces systolic and diastolic blood pressures and has no effect on heart rate, while being safe and well tolerated. Studies also indicate that sildenafil does not contribute to the development of myocardial infarction or ischemia. Similar benign effects on hemodynamics and cardiac events have also been demonstrated for tadalafil and vardenafil. None of the PDE5 inhibitors adversely affects total exercise time or time to ischemia during exercise testing in men with stable angina. It is key to avoid concomitant administration of nitrates with any of the PDE5 inhibitors, because this combination can cause increased vasodilation and a subsequent drop in blood pressure. Sildenafil has an alpha-blocker precaution; tadalafil is contraindicated with alpha blockers except for 0.4 mg tamsulosin; vardenafil is contraindicated with alpha blockers.

Key words: phosphodiesterase type 5 inhibitors, sildenafil, tadalafil, vardenafil, nitrates, hemodynamic effects, myocardial infarction, ischemia

Introduction

The phosphodiesterase type 5 (PDE5) inhibitors (i.e., sildenafil, tadalafil, and vardenafil) have had a major impact on the treatment of erectile dysfunction (ED), and these drugs are taken by men all over the world. Given this widespread usage, the efficacy and safety of the PDE5 inhibitors in men with various comorbidities have been and continue to be the focus of clinical research.

The effect of the PDE5 inhibitors on hemodynamic parameters has also attracted much attention, particularly in men with cardiovascular disease. Phosphodiesterase type 5 is located not only in the vasculature of the corpus cavernosum of the penis, but also in the smooth muscle cells of the vasculature in the systemic arteries and veins. Thus, PDE5 inhibitors act as mild vasodilators. During sexual stimulation, release of nitric oxide (NO) induces cyclic guanosine monophosphate (cGMP) formation, which promotes vascular smooth muscle relaxation in the penis. The PDE5 inhibitors facilitate the erectile process by blocking the breakdown of cGMP. Mediation of NO-induced vasodilation by cGMP also plays a role in maintenance of resting arterial blood pressure.

The focus of this article is on the impact of the PDE5 inhibitors on hemodynamic parameters, particularly their effects on blood pressure, and on the interactions between PDE5 inhibitors and nitrates, as well as interactions with alpha blockers and other antihypertensive medications. Finally, this paper will address cardiovascular safety in men taking PDE5 inhibitors.

Effects of Phosphodiesterase Type 5 Inhibitors on Hemodynamic Parameters

Effects on Blood Pressure

Zusman *et al.*[1] reviewed the overall cardiovascular profile of sildenafil, the first PDE5 inhibitor to be approved by the Food and Drug Administration (FDA). The cardiovascular effects of sildenafil, given alone and at therapeutic dosage levels, were relatively modest (Fig. 1A). Following administration of sildenafil 100 mg, the mean decrease in supine diastolic blood pressure (DBP) was 6.8 mmHg, and the mean maximal decrease in supine systolic blood pressure (SBP) was 10.2 mmHg. This effect on blood pressure was independent of oral sildenafil dose.

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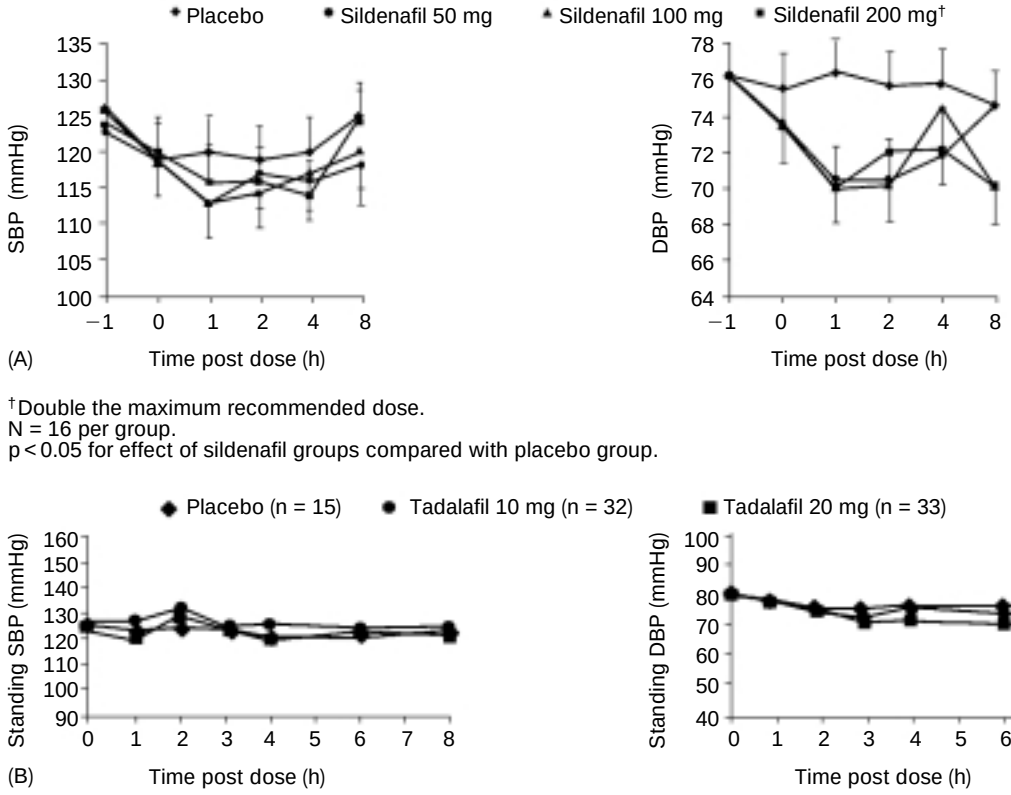


FIG. 1 (A) The effects of single oral doses of sildenafil (50, 100, 200 mg [double the maximum recommended dose]) versus placebo on mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) over time. The effect was not significantly influenced by sildenafil dosage. Adapted from Ref. No. 1 with permission. (B) Mean decreases over time in standing SBP and DBP following a single oral dose of tadalafil (10 mg, 20 mg) or placebo in healthy men. At the 10 and 20 mg doses, tadalafil caused only a modest decrease in standing SBP and DBP. Tadalafil 20 mg caused only a minimal decrease of 4.6 mmHg in standing DBP. Adapted from Ref. No. 3 with permission.

Effects of tadalafil on blood pressure are mild. In healthy volunteers receiving tadalafil 10 or 20 mg/day, standing DBP dropped slightly, by approximately 3 to 5 mmHg (Fig. 1B). Heart rate did not change in men taking tadalafil (20 mg/day), nor did SBP change appreciably over time compared with placebo. Similarly, tadalafil (20 mg/day) produced minimal effects on heart rate, SBP, and DBP while the patient was supine (20 mg/day).[2–4]

In patients with coronary artery disease (CAD), tadalafil at a dosage of 10 mg/day was associated with a mean decrease in standing SBP of 7 mmHg; the decrease in standing DBP averaged 4 mmHg.[4] This study also compared the numbers and proportion of outliers among subjects taking placebo, tadalafil 5 mg, or tadalafil 10 mg. Outliers were defined as subjects with clinically significant changes in blood pressure measured as SBP < 85 mmHg or SBP showing a decrease of > 30 mmHg from baseline, or DBP < 45 mmHg or DBP showing a decrease > 20 mmHg from baseline. Significant differences were found in the number of patients who had a decrease in standing DBP > 20 mmHg during tadalafil 10 mg treatment compared with placebo ($p \leq 0.01$), and in the number of patients who had a decrease in sitting SBP > 30 mmHg during tadalafil 5 mg treatment compared with placebo ($p \leq 0.05$). However, none of the measured decreases in blood pressure was associated with significant hypotensive symptoms.

In general, patients with CAD may have relatively higher baseline values for SBP and DBP than young, healthy volunteers. They, therefore, are expected to experience a more marked decline in blood pressure in response to vasodilators.

Single-dose studies involving vardenafil at dosages of 20 and 40 mg similarly show negligible hemodynamic effects.[5] Vardenafil produced a slight decrease in supine SBP and DBP and a minor compensatory increase in heart rate. The magnitude of these effects was clinically insignificant.[5]

Interaction of PDE5 Inhibitors with Nitrates

All PDE5 inhibitors can potentiate the hypotensive effects of organic nitrates by facilitating cGMP-induced vasodilation.[6] In studies examining the combined effects of sildenafil and nitrates as well as those of tadalafil and nitrates on blood pressure of healthy patients,[7] almost twice as many patients receiving a PDE5 inhibitor had a standing SBP of < 85 mmHg compared with those taking placebo. In another study examining the effects of tadalafil and nitrates in patients with stable angina,[8] 10 times as many patients taking tadalafil had a standing SBP < 85 mmHg compared with placebo.

The drop in blood pressure resulting from this combination of nitrates and PDE5 inhibitors has the potential to be clinically significant.[6] For this reason, all PDE5 inhibitors are contraindicated in patients receiving any form of nitrate therapy.[2, 6] In an emergency situation, the administration of nitrates may be considered at least 24 h after taking sildenafil.[6] This precaution also presumably applies to vardenafil, because its pharmacokinetic profile is similar to that of sildenafil. Although the safe time to administer nitrates following vardenafil in an emergency situation has not been definitely determined, additional blood pressure and heart rate changes were not detected when vardenafil 20 mg was dosed 24 h before nitroglycerin (NTG) in healthy subjects.[9] Tadalafil, on the other hand, is present in the bloodstream longer than sildenafil and vardenafil. The results of a recent placebo-controlled study to assess the timing of interaction between NTG and tadalafil showed that tadalafil 20 mg enhanced the hypotensive effects of sublingual NTG at 24 h following tadalafil dosing.[10] However, this interaction was not observed when NTG was used at 48, 72, and 96 h following tadalafil administration. For the management of patients presenting with chest pain within 48 h of receiving tadalafil, organic nitrates should be avoided and non nitrate antianginal agents are recommended. If a patient experiences chest pain at or > 48 h after taking tadalafil, nitrates may be used under close medical supervision (Fig. 2).[2, 10] Nonetheless, regular or intermittent use of nitrates remains a contraindication to treatment with all the PDE5 inhibitors.[2, 9, 11, 12]

Effects of Phosphodiesterase 5 Inhibitors in Patients with Coronary Artery Disease

Exercise Tolerance

Various studies have involved administration of a PDE5 inhibitor to patients with CAD who performed exercise testing at a level of intensity comparable to that achieved during sexual intercourse. These studies closely examined whether treatment with PDE5 inhibitors would exacerbate ischemia in patients with known CAD.

In one such study, the investigators used echocardiograms to evaluate ischemia during exercise in men who received either sildenafil (50 or 100 mg) or placebo.[13] The two groups did not differ with respect to the incidence of ischemia (i.e., 24% in the sildenafil group vs. 26% in the placebo group). Normal echocardiograms were reported in approximately 15% of the sildenafil group and 13% of the placebo group. Thus, in men with known or probable CAD, sildenafil did not significantly alter the cardiovascular response to exercise.

Thadani *et al.*[14] measured total exercise time and time to ischemia in patients with CAD and ED who were taking vardenafil. Total treadmill exercise time and time to angina did not differ between the vardenafil and placebo groups. Exercise time was 7 min, 7 s for the placebo group, and 7 min, 13 s for the vardenafil 10 mg group. Time to angina was 4 min, 52 s with placebo, and 4 min, 51 s with vardenafil. Patients taking vardenafil showed some improvement in the total time to ST-segment depression: 6 min, 21 s, versus 5 min, 34 s for the placebo group ($p = 0.0004$). Thus, in symptomatic patients with stable CAD, vardenafil 10 mg/day did not reduce total exercise time or time to angina compared with placebo. It did, however, significantly delay the onset of ST-segment changes relative to placebo.

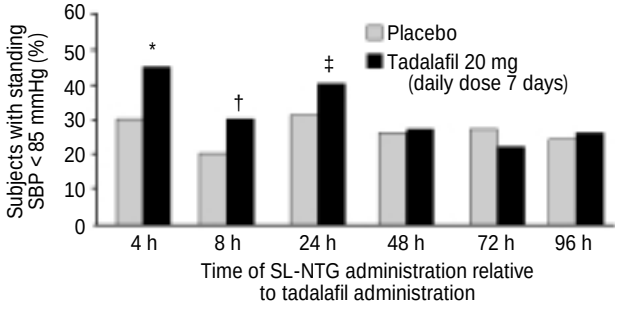
In a preliminary report of tadalafil in men with stable CAD[15] who had documented ischemia during exercise, no significant difference in mean total exercise time or time to ischemia during exercise stress testing was found between patients who received 10 mg of tadalafil (13:36 min:s) and those who received placebo (13:31 min:s).

All of these studies show that the PDE5 inhibitors do not exacerbate ischemia during exercise performed at a level equivalent to—or even greater than—that achieved during sexual intercourse.

Long-Term Cardiac Safety

Several studies have examined the issue of cardiac safety and cardiovascular events in men taking PDE5 inhibitors. During the Prescription Event Monitoring study from England, the investigators compared mortality rates in men taking sildenafil with those of an age-matched control population.[16] There was no evidence to indicate that sildenafil increases the mortality rate. Mortality rates appeared to be lower in older men (> 75 years of age) taking sildenafil than in their population-based peers, but that was probably related to selection of patients taking the drug. The overall results of this study suggest that sildenafil does not increase the rate of cardiovascular mortality.

Likewise, studies with tadalafil have found no evidence of increased cardiovascular mortality. Analyses of the overall safety database for tadalafil indicated that morbidity and mortality rates from serious cardiovascular events in tadalafil trials were no higher than those reported for the general population of men with ED.[4] However, current recommendations call for



*p < 0.001 vs. placebo, †p < 0.01 vs. placebo, ‡p < 0.05 vs. placebo.

FIG. 2 Percentage of subjects with standing systolic blood pressure < 85 mmHg in tadalafil 20 mg- and placebo-treated subjects. The hypotensive effect of sublingual nitroglycerin (SL-NTG) was apparent at 24 h but was no longer detectable when nitroglycerin was administered 48 to 96 h after tadalafil. Adapted from Ref. No. 10 with permission.

avoiding the PDE5 inhibitors in patients with a cardiac condition that precludes participation in sexual activity.[2, 9, 12, 17]

Rates of myocardial infarction (MI) with PDE5 inhibitors are generally low.[2–4, 9, 12, 17] Data from studies examining MI show very low incidences per 100 patient-years in age-standardized males (0.60), placebo-treated patients (0.60), and tadalafil-treated patients in open-label (0.50) or double-blind studies (0.25). The overall incidence in all tadalafil-treated patients was 0.43 (Table I).[4] The incidence of MI in double-blind sildenafil studies was 1.4 per 100 patient-years with placebo and 1.7 per 100 patient-years for patients receiving sildenafil.[1] The overall incidence rate of MI with sildenafil was 0.57 per 100 patient-years.[17] Thus, there appears to be no evidence that the PDE5 inhibitors are associated with an increase in the incidence of MI.

Effects of Phosphodiesterase 5 Inhibitors on Cardiac Electrophysiology

The PDE5 inhibitors have not been found to have a clinically significant effect on cardiac electrophysiology. Examination of the effects of a 50 mg dose of sildenafil on QT intervals in 36 patients with ED found average increases of 3 and 7 ms in maximum QT_c (Bazzet's formula) and minimum QT_c, respectively. These increases were not statistically significant ($p > 0.05$).[18] Similarly, QT_c dispersion did not change significantly ($p > 0.05$). A study of 11 healthy men who received sildenafil 50 mg or placebo in a double-blind, randomized, crossover study found no significant changes in QT_c (Bazzet's formula) after sildenafil administration (change in $QT_c = -0.5 \pm 10$ ms; $p = 0.33$).[19] However, there was a significant decrease after administration of placebo (change in $QT_c = -15 \pm 6$ ms; $p = 0.04$).

The effect of a single 100 mg dose of tadalafil on QT interval was evaluated at the time of peak tadalafil concentration in a randomized double-blind, placebo, and active (intravenous ibutilide)-controlled crossover study in 90 healthy males, 18 to 53 years of age.[2] The mean change in QT_c (Fridericia QT correction) for tadalafil, relative to placebo, was 3.5 ms (two-sided 90% confidence interval [CI] = 1.9, 5.1). The mean change in QT_c (individual QT correction) for tadalafil, relative to placebo, was 2.8 ms (two-sided 90% CI = 1.2, 4.4). A 100 mg dose of tadalafil (5 times the recommended dose) was chosen because this dose yields exposures covering those observed upon coadministration of tadalafil with potent CYP3A4 inhibitors or those observed in renal impairment. The mean increase in heart rate associated with a 100 mg dose of tadalafil compared with placebo was 3.1 beats/min. These changes are not likely to be clinically relevant.[2]

The effects of vardenafil on cardiac electrophysiology were also examined. Therapeutic (10 mg) and supratherapeutic (80 mg) doses produced similar, small increases of 7 and 9 ms, respectively, in QT_c (Fridericia QT correction) intervals at T_{max} (time to maximum serum concentration) compared with placebo. Moxifloxacin, as a positive control, also caused a similar, small increase in QT_c intervals (8 ms).[20] While the impact of these changes is not entirely clear, it was recommended that concomitant use of Class IA or Class III antiarrhythmic medications should be avoided, and that patients with congenital QT prolongation should not receive vardenafil.[9]

Adverse Cardiovascular Events

It is not surprising that adverse events of the PDE5 inhibitors are primarily related to their vasodilating properties.[21] With sildenafil, headache was reported by 16%, flushing by 10%, and dizziness by 2% of patients receiving the drug.[12] Tadalafil studies have shown the most common treatment-emergent adverse events to be headaches (15%), flushing (3.7%), and dizziness (2.4%).[3] For vardenafil, headaches were reported by 15% of patients, flushing by 11% of patients, and dizziness by 2%.[9] The incidence of hypertension, syncope, and hypotension was < 2% for all of the PDE5 inhibitors.[2, 9, 12]

Interactions of Phosphodiesterase 5 Inhibitors and Alpha Blockers

Examination of the interactions between PDE5 inhibitors and alpha blockers found a general augmentation of the hypotensive effects of these medications. It is currently recommended that sildenafil doses > 25 mg be avoided in patients within 4 h of receiving an alpha blocker, which is a precaution shown in the labeling.[12] Vardenafil is contraindicated with any administration of alpha blockers. Studies examining the interactions of 10 and 20 mg doses of vardenafil with either terazosin 10 mg or tamsulosin 0.4 mg administered simultaneously or 6 h apart found that some patients experienced a

TABLE I Tadalafil: Incidence of myocardial infarction (MI) across all studies

			Tadalafil-treated patients		
	Age-standardized male population	Placebo-treated patients	Double-blind studies	Open-label safety studies	All studies
Total no. of patients	—	1,437	3,666	1,707	4,196
Total patient exposure as patient-years	—	334.5	791.7	1,786.2	2,578.0
No. of patients with MI	—	2	2	9	11
Rate of MI/100 patient-years	0.60[17]	0.60	0.25	0.50	0.43

No increase in rate of MI. Adapted from Ref. No. 4 with permission.

standing SBP < 85 mmHg in all trials.[9] In a clinical pharmacology study, in which a single dose of tadalafil 20 mg was administered to healthy subjects taking 0.4 mg once-daily tamsulosin, no significant decreases in blood pressure were observed.[2] However, augmentation of the blood pressure-lowering effects of alpha blockers was found when tadalafil was administered with doxazosin 8 mg.[2] Therefore, administration of tadalafil to patients taking alpha blockers other than 0.4 mg once-daily tamsulosin is contraindicated.[2]

Effects in Patients Taking Other Antihypertensive Medications

Current evidence indicates that the PDE5 inhibitors are generally safe to take with other antihypertensive drugs.[21–25] The results of a randomized, crossover trial examining patients who were taking the calcium-antagonist amlodipine and who received sildenafil or placebo found no synergistic interactions between sildenafil and amlodipine.[22] A post hoc subanalysis examined the efficacy and safety of sildenafil in men with ED who were receiving concomitant antihypertensive medication.[23] These agents were classified as a diuretic, beta blocker, $alpha_1$ blocker, angiotensin-converting enzyme (ACE) inhibitor, or a calcium-channel blocker. For patients taking sildenafil and antihypertensive medication, the incidence of treatment-related adverse events (34%) was similar to that for sildenafil-treated patients not taking any antihypertensive agent (38%). It was concluded that sildenafil was an effective and well-tolerated treatment for ED in patients taking concomitant antihypertensive medication, including those on multidrug regimens.

Randomized, placebo-controlled, two-period crossover studies examined tadalafil interactions with an ACE inhibitor, calcium antagonist, thiazide diuretic, a beta blocker, and angiotensin II-receptor blockers in patients taking only one antihypertensive agent.[21] In all cases, the observed additional blood pressure reduction was mild, with no increase in clinically relevant hypotensive symptoms.

Several phase 3 studies compared patients who were taking tadalafil concomitantly with multiple antihypertensives or with placebo.[21] The most commonly used classes of antihypertensive agents included all classes examined in the single antihypertensive studies, as well as loop diuretics. There were no statistically significant differences between tadalafil and placebo in the mean changes in blood pressure from baseline in patients taking ≥ 2 antihypertensive agents. Hypotension was not reported in tadalafil-treated patients; however, it was reported in placebo-treated patients. Therefore, the data show that tadalafil is safe in patients receiving ≥ 1 concomitant antihypertensive agent.

Studies have also examined vardenafil in combination with antihypertensive medicines. In a double-blind, two-way crossover study of 22 hypertensive men who were taking nifedipine 30 or 60 mg/day, patients were randomly assigned to placebo or a single dose of vardenafil 20 mg repeated after more than 7 days. There were no clinically significant changes in hemodynamic effects with vardenafil, and no serious adverse events were reported.[24]

Two randomized, double-blind studies evaluated 545 men with ED receiving at least one antihypertensive agent during treatment with vardenafil 5, 10, or 20 mg or placebo for 12 or 26 weeks. Vardenafil treatment was associated with a minimally significant decrease in standing blood pressure, but no clinically significant elevation in standing heart rate.[25]

Conclusions

The PDE5 inhibitors generally produce mild vasodilation and minimal hemodynamic effects. They do not adversely affect total exercise time or time to ischemia during exercise stress testing.

The PDE5 inhibitors have only a modest additive effect on nitrate-induced decreases in mean blood pressure in many patients. However, the potential for significant blood pressure effects in some patients indicates that they should not be used at all in combination with nitrates. Likewise, PDE5 inhibitors may potentiate the hypotensive effects of alpha blockers. However, the PDE5 inhibitors only minimally augment the hypotensive effects of other antihypertensive agents in patients receiving one or more of these drugs. In controlled clinical trials, PDE5 inhibitors are not associated with an increase in MI or death rates. In general, PDE5 inhibitors are safe and effective for the treatment of ED in healthy men and in those with cardiovascular disease.

References

1. Zusman RM, Morales A, Glasser DB, Osterloh IH: Overall cardiovascular profile of sildenafil citrate. *Am J Cardiol* 1999;83: 35C–44C
2. Cialis® (tadalafil) (package insert). Indianapolis, Ind. and Bothell, Wash.: Lilly ICOS LLC; 2003
3. Emmick JT, Stuewe SR, Mitchell M: Overview of the cardiovascular effects of tadalafil. *Eur Heart J Suppl* 2002;4(suppl H): H32–H47
4. Kloner RA, Mitchell M, Emmick JT: Cardiovascular effects of tadalafil. *Am J Cardiol* 2003;92(suppl):37M–46M
5. Stark S, Sachse R, Liedl T, Hensen J, Rohde G, Wensing G, Horstmann R, Schrott KM: Vardenafil increases penile rigidity and tumescence in men with erectile dysfunction after a single oral dose. *Eur Urol* 2001;40:181–190
6. Jackson G, Betteridge J, Dean J, Hall R, Holdright D, Holmes S, Kirby M, Riley A, Sever P: A systematic approach to erectile dysfunction in the cardiovascular patient: A consensus statement. *Int J Clin Pract* 1999;53:445–451
7. Kloner RA, Mitchell MI, Bedding A, Emmick J: Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil (abstr 708). *J Urol* 2002;167(suppl):176–177
8. Kloner RA, Emmick J, Bedding A, Humen D: Pharmacodynamic interactions between tadalafil and nitrates (abstr 291A). *J Am Coll Cardiol* 2002;39(suppl A)
9. Levitra® (vardenafil) (package insert). West Haven, Conn: Bayer Pharmaceuticals Corp., 2003
10. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G: Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003;42:1855–1860
11. Padma-Nathan H, Eardley I, Kloner RA, Laties AM, Montorsi F: A 4-year update on the safety of sildenafil citrate (Viagra®). *Urology* 2002;60(suppl 2B):67–90
12. Viagra® (sildenafil) (package insert). New York, NY: Pfizer Inc., 2003

13. Arruda-Olson A, Mahoney DW, Nehra A, Leckel M, Pellikka PA: Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease. A randomized crossover trial. *J Am Med Assoc* 2002;287:719–725
14. Thadani U, Smith W, Nash S, Bittar N, Glasser S, Narayan P, Stein RA, Larkin S, Mazzu A, Tota R, Pomerantz K, Sundaresan P: The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002;40:2006–2012
15. Patterson D, MacDonald TM, Effron MB, Emmick JT, Mitchell MI, Kloner RA: Tadalafil does not affect time to ischemia during exercise stress testing in patients with coronary artery disease (abstr 1650). *Circulation* 2002;106(suppl):330
16. Boshier A, Wilton LV, Shakir SAW: Cardiovascular events in a cohort study of sildenafil users in England. Poster presented at 5th Congress of the European Society for Sexual and Impotence Research, Hamburg, Germany, December 1–4, 2002
17. Sadovsky R, Miller T, Moskowitz M: Three-year update of sildenafil citrate (Viagra®) efficacy and safety. *Int J Clin Pract* 2001; 55:115–128
18. Alpaslan M, Onrat E, Samli M, Dincel C: Sildenafil citrate does not affect QT intervals and QT dispersion: An important observation for drug safety. *Ann Noninvas Electrocardiol* 2003;8:14–17
19. Sofowora G, Dishy V, Roden D, Wood AJJ, Stein CM: The effect of sildenafil on QT interval in healthy men (abstr PIII-11). *Clin Pharmacol Ther* 2001;69:P67
20. Data on file. Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee: Levitra® tablets. Available at: http://www.fda.gov/ohrms/dockets/ac/03/slides/3956S1_03_Bayer.ppt. Accessed September 5, 2003
21. Kloner RA, Mitchell M, Emmick JT: Cardiovascular effects of tadalafil in patients on common antihypertensive therapies. *Am J Cardiol* 2003; 92(suppl):47M–57M
22. Webb DJ, Freestone S, Allen MJ, Muirhead GJ: Sildenafil citrate and blood pressure-lowering drugs: Results of drug interaction studies with an organic nitrate and a calcium antagonist. *Am J Cardiol* 1999;83:21C–28C
23. Kloner RA, Brown M, Prisant LM, Collins M: Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* 2001;14:70–73
24. Rohde G, Jordaan PJ: Influence of vardenafil on blood pressure and pharmacokinetics in hypertensive patients on nifedipine therapy (abstr). *Pharmacotherapy* 2002;22:418
25. Padma-Nathan H, Porst H, Eardley T, Thibonnier M: Efficacy and safety of vardenafil, a selective phosphodiesterase 5 inhibitor, in men with erectile dysfunction on antihypertensive therapy (abstr). *Am J Hypertens* 2002;15(suppl):48A