Published by Elsevier Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.09.023

EXPRESS PUBLICATION

Time Course of the Interaction Between Tadalafil and Nitrates

Robert A. Kloner, MD, PHD,* Adolph M. Hutter, MD,† Jeffrey T. Emmick, MD, PHD,‡ Malcolm I. Mitchell, MBBS, MFPM,§ Jonathan Denne, PHD,‡ Graham Jackson, MD‖

Los Angeles, California; Boston, Massachusetts; Indianapolis, Indiana; and Windlesham and London, United Kingdom

OBJECTIVES This study was designed to determine the time course of nitrate interaction with tadalafil, a phosphodiesterase 5 (PDE5) inhibitor with a half-life ($t_{1/2}$) of 17.5 h.

BACKGROUND The PDE5 inhibitors augment the blood pressure (BP)-lowering effects of nitrates, yet the time course of this interaction is unclear. Recent guidelines from the American College of Cardiology/American Heart Association recommend that nitrates be withheld for 24 h after taking sildenafil ($t_{1/2}$ = 4 h).

METHODS Male subjects (n = 150) received seven consecutive daily doses of placebo or tadalafil (20 mg). On day 7 and beyond, subjects received repeated doses of sublingual nitroglycerin (0.4 mg) after the last dose of placebo or tadalafil. After a 10- to 21-day washout period, subjects crossed over to either placebo or tadalafil, and nitrate dosing was repeated.

RESULTS In response to nitroglycerin at 4, 8, and 24 h, standing systolic BP fell below 85 mm Hg in more subjects on tadalafil compared with placebo ($p < 0.05$), with no difference in the response to nitroglycerin at 48, 72, and 96 h ($p > 0.2$). Similar observations were made for standing diastolic BP <45 mm Hg, decrease in systolic BP >30 mm Hg, and decrease in diastolic BP >20 mm Hg. Nitroglycerin also evoked greater mean maximal decreases in standing systolic BP at 8 and 24 h after taking tadalafil versus placebo ($p < 0.02$), with no significant difference at 48, 72, or 96 h ($p > 0.49$).

CONCLUSIONS The hemodynamic interaction between tadalafil and sublingual nitroglycerin lasted 24 h, but was not seen at 48 h and beyond. Similar to other PDE5 inhibitors, tadalafil should not be administered in combination with organic nitrates. (J Am Coll Cardiol 2003;42:1855–60)

Phosphodiesterase 5 (PDE5) inhibitors such as sildenafil and tadalafil interact with organic nitrates to result in a synergistic drop in blood pressure (BP) (1–3). Organic nitrates donate nitric oxide, which stimulates guanylate cyclase to catalyze the formation of cyclic guanosine monophosphate (cGMP). Cyclic guanosine monophosphate decreases calcium flux into smooth muscle cells evoking relaxation of arteries, arterioles, and sinusoids of the corpus cavernosum and resulting in improved erectile function (4). The actions of cGMP are terminated by PDE5 (3,5,6). Administration of a nitric oxide donor with a PDE5 inhibitor can evoke a large build-up of cGMP, marked vasodilation, and in some patients frank hypotension (1). Thus, organic nitrate use remains an absolute contraindication to the use of PDE5 inhibitors. One concern is: when is it safe to administer nitrates to a patient who has taken a PDE5 inhibitor and then develops angina? Established guidelines recommend that nitrates not be given until 24 h (6 half-lives) after taking sildenafil (7).

Tadalafil is an effective treatment for erectile dysfunction and has a half-life ($t_{1/2}$) of 17.5 h (8). Previous studies showed there was little interaction with sublingual nitrate 26 h after an oral dose of 5 or 10 mg tadalafil when subjects remained supine or sitting (3). However, there are no data with 20 mg of tadalafil (a dose to be used clinically) nor are there data that follow changes in BP when nitrate is administered beyond 26 h after dosing. Our objective was to determine whether 20 mg of tadalafil augments the hypotensive response to sublingual nitroglycerin dosed 2 to 96 h after tadalafil administration.

METHODS

This was a randomized, placebo-controlled, double-blind, two-period, cross-over, multi-center study. The study was approved by institutional review committees, and each subject gave written, informed consent. A total of 166 men entered the study (mean age 57 ± 11 years, range 40 to 83 years). The subjects were evaluated as a group and were also split into four subpopulations that included men with diabetes (mean age 60 ± 9.5 years, range 41 to 81 years, n = 32), and three populations of otherwise healthy men

From *The Heart Institute, Good Samaritan Hospital, Cardiovascular Division, Keck School of Medicine, University of Southern California, Los Angeles, California; †Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‡Eli Lilly and Company, Indianapolis, Indiana; §Erl Wood Manor, Windlesham, Surrey, United Kingdom; and ‖Guys and St. Thomas Hospital, London, United Kingdom. This study was supported by Lilly ICOS LLC. Dr. Kloner is a consultant, speaker, and researcher for Bayer, Pfizer, and Lilly ICOS. Dr. Hutter is a consultant in the area of erectile dysfunction for Lilly ICOS, Bayer, and Pfizer. Drs. Emmick, Mitchell, and Denne are employees and stockholders of Eli Lilly and Company.

Manuscript received July 25, 2003; revised manuscript received September 11, 2003, accepted September 15, 2003.

JACC Vol. 42, No. 10, 2003
November 19, 2003:1855–60

Abbreviations and Acronyms

BP = blood pressure
cGMP = cyclic guanosine monophosphate
PDE5 = phosphodiesterase 5
$t_{1/2}$ = half-life

(men ≥40 to ≤55 years [mean age = 46 ±4.5 years, n = 63], men >55 to ≤60 years [mean age = 58 ± 1.7 years, n = 25], and men >60 years [mean age = 69 ± 5.7 years, n = 46]).

Subjects were Caucasian (n = 151), Afro-Caribbean (n = 11), and Asian (n = 4). Ten subjects were hypertensive, 43 smoked tobacco, and 133 reported at least occasional alcohol intake. A total of 150 out of 166 men completed the study, including 26 subjects ≥70 years.

During treatment period 1, subjects received seven consecutive daily doses of either tadalafil (20 mg) or placebo. The dosing of tadalafil 20 mg to steady state results in plasma concentrations that are ~1.6-fold higher than those observed with a single 20 mg dose. On day 7, after a final dose of either tadalafil or placebo, sublingual nitroglycerin (0.4 mg) was administered at 2 (supine only), 4, 8, 24, 48, 72, and 96 h post-tadalafil or placebo. After a washout period of 10 to 21 days, subjects were crossed over in treatment period 2 to either placebo or tadalafil.

A DINAMAP PRO (GE Medical Systems) noninvasive BP system was used to measure BP and heart rate. Supine BP was measured after 30 s in the supine position and standing BP was measured 2 min after standing. Heart rate and BP were measured on days 1 to 6 pre-dose, on day 7 pre-dose, 1 h post-tadalafil or placebo dosing, and before and for 2 h after each nitroglycerin dose. The first nitroglycerin dose was administered 2 h after the final dose of placebo or tadalafil to coincide with the maximum plasma concentration of tadalafil. Because previous studies showed that the hypotensive effect of nitroglycerin is augmented 2 h after tadalafil, only supine measurements were made following the 2-h nitroglycerin administration in the interest of safety.

End points. PRIMARY END POINT. The primary end point was to test the null hypothesis that, after taking sublingual nitroglycerin, the percentage of subjects having a minimum standing systolic BP <85 mm Hg after tadalafil (20 mg) does not differ from placebo. This hypothesis was tested separately following nitroglycerin at 4, 8, 24, 48, 72, and 96 h after either tadalafil or placebo.

SECONDARY END POINTS. The secondary end points were to test the hypotheses that tadalafil compared to placebo does not augment the hypotensive response to sublingual nitroglycerin based on frequency of subjects having: 1 and 2) a minimum standing and supine diastolic BP <45 mm Hg; 3 and 4) a decrease in standing and supine systolic BP >30 mm Hg; 5 and 6) a decrease in standing and supine diastolic BP >20 mm Hg; and 7) a minimum supine systolic BP <85 mm Hg. We also analyzed the mean maximal decrease in standing and supine systolic and diastolic BP and examined the tolerability of nitroglycerin given at the various times following tadalafil.

Statistics. Frequencies of subjects experiencing potentially clinically significant BP findings were analyzed by repeated-measures logistic regression (9), except for time-points at which no subjects on one of the two treatments experienced a particular clinically significant finding in which case a non-parametric method (Prescott test) was used (10). Odds ratios, p values, and 95% confidence limits were calculated for the comparisons between tadalafil and placebo. Mean maximal decreases in BP were analyzed using a linear mixed effects model (9). Differences in least-squares means, p values, and 95% confidence limits were calculated for the comparisons between tadalafil and placebo. All hypothesis tests were two-sided. No adjustment was made to p values for multiple comparisons.

RESULTS

Figure 1 shows that the decreases in mean systolic and diastolic BP in response to nitroglycerin were greater after tadalafil compared with placebo at 4, 8, and 24 h, but were similar at 48, 72, and 96 h.

Table 1 shows that the percentage of subjects experiencing episodes of standing systolic BP <85 mm Hg after nitroglycerin (the primary end point) was significantly greater in the presence of tadalafil compared with placebo from 4 to 24 h post-tadalafil or placebo, with no significant difference at 48, 72, or 96 h. Analysis of the other outlier criteria in Table 1 shows the same general pattern, with no significant treatment differences in the response to nitroglycerin at 48 to 96 h post-tadalafil or placebo.

Table 2 shows that the number of episodes of clinically significant BP effects was also greater for all parameters following nitroglycerin from 2 to 24 h post-tadalafil compared with placebo. After 24 h, the number of clinically significant hypotensive episodes was similar following nitroglycerin in the presence of tadalafil versus placebo, and in 15 of 24 comparisons it was higher after placebo.

We also analyzed maximal decreases in BP. The mean maximal decreases in standing systolic and diastolic BP were greater in the tadalafil versus placebo treatment period after the 8- and 24-h doses of nitroglycerin ($p < 0.02$), with no significant differences at 48, 72, and 96 h ($p > 0.33$) (data not shown). Similar responses were observed for nitroglycerin-induced mean maximal decreases in supine systolic and diastolic BP, with no differences at 48 to 96 h after tadalafil compared with placebo ($p > 0.06$).

The compensatory heart rate responses to nitroglycerin-induced decreases in BP were similar after tadalafil compared with placebo (Fig. 2). In both the standing and supine positions, the differences in mean maximal increases (tadalafil minus placebo) in heart rate ranged from −1.6 to

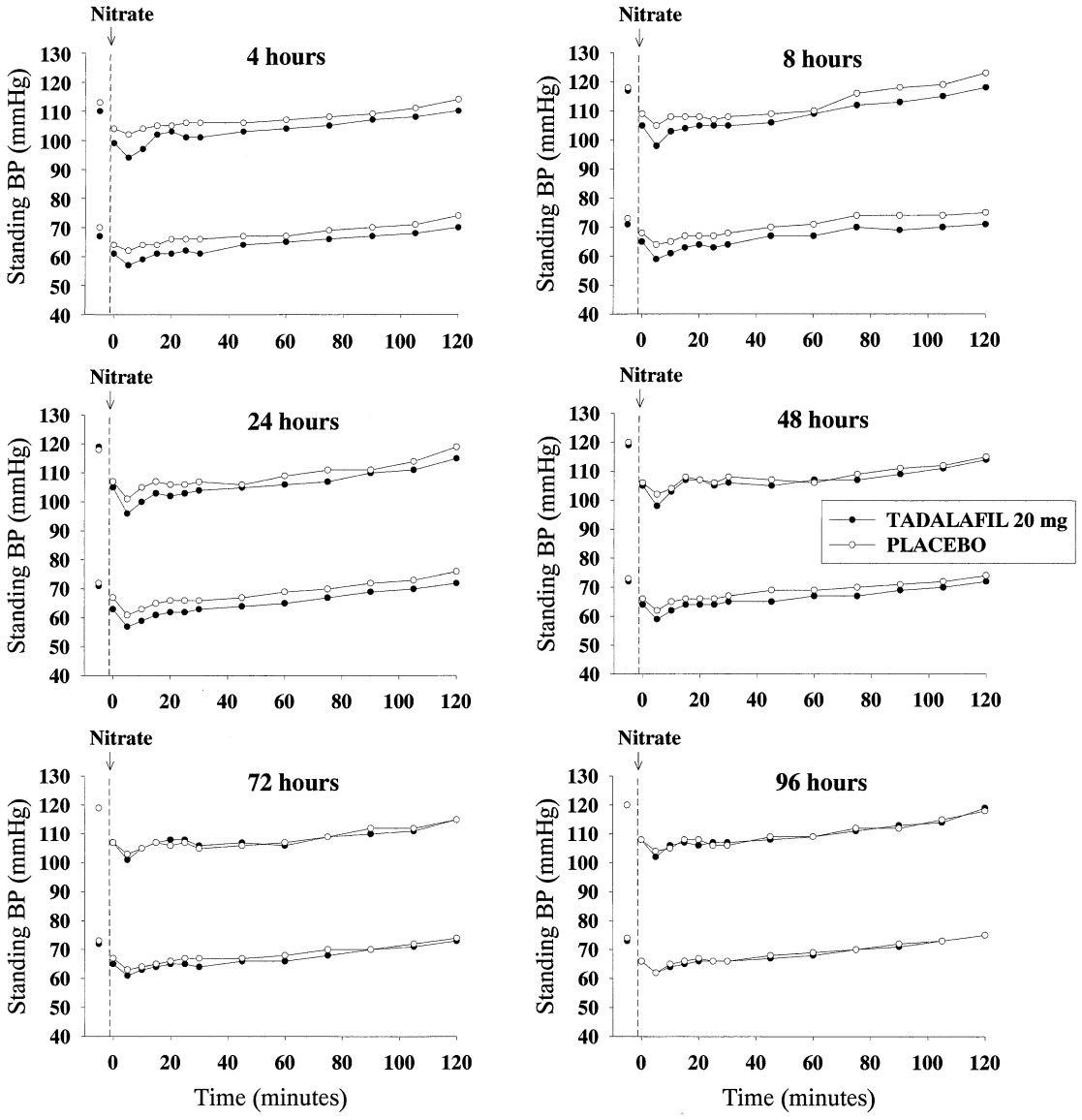

Figure 1. Mean standing systolic and diastolic blood pressure (BP) in tadalafil (20 mg)- and placebo-treated subjects. Sublingual nitroglycerin (0.4 mg) is indicated by the **dashed vertical line**. The 4- to 96-h time intervals represent time of nitroglycerin administration after the last dose of tadalafil or placebo. In each **graph**, **the upper set of curves** represent systolic BP and the **lower set of curves** represent diastolic BP. Standard deviation for systolic and diastolic BP ranged from 12 to 19 mm Hg and 9 to 13 mm Hg, respectively.

2.3 beats/min. Although some of the mean differences were statistically significant, they were not of sufficient magnitude to be considered clinically significant.

In the analysis of subpopulations, tadalafil did not interact with nitroglycerin to further lower BP at 48 h or beyond in subjects with diabetes or in subjects >60 years of age.

The data in Table 3 show that headache, myalgia, back pain, dizziness, dyspepsia, flushing, and postural dizziness were the most frequently observed adverse events. Most adverse events were mild in severity. It is noteworthy that the frequency of dizziness was similar after tadalafil or placebo, with most episodes of dizziness occurring during the period of nitroglycerin administration. One subject on placebo treatment experienced a serious adverse event of sinus arrest following nitroglycerin given 24 h after the final dose of placebo. The sinus arrest resolved spontaneously and this subject was withdrawn from the study. No serious adverse events occurred in subjects taking tadalafil.

DISCUSSION

The main finding of this study was that tadalafil augmented the hypotensive effect of sublingual nitroglycerin given from 2 to 24 h after the last dose of tadalafil. This interaction was no longer detectable when nitroglycerin was administered 48 to 96 h after tadalafil. Also, no clinically significant differences existed in the compensatory heart rate responses irrespective of the time nitroglycerin was given after tadalafil or placebo.

Table 1. Percentage of Subjects Experiencing Clinically Important Blood Pressure Findings (Tadalafil/Placebo)

Criteria	Nitroglycerin Dose (h)						
	2	4	8	24	48	72	96
Standing							
Systolic <85 mm Hg	NP	46/31 [<0.001]	31/21 [0.008]	41/32 [0.028]	28/27 [0.754]	23/28 [0.210]	27/25 [0.687]
Diastolic <45 mm Hg	NP	19/6 [<0.001]	12/5 [0.018]	16/8 [0.010]	11/13 [0.581]	8/10 [0.582]	6/7 [0.807]
Decrease in systolic >30 mm Hg	NP	25/22 [0.423]	30/17 [0.002]	48/33 [0.002]	35/29 [0.133]	36/32 [0.338]	33/30 [0.416]
Decrease in diastolic >20 mm Hg	NP	15/10 [0.126]	18/13 [0.158]	31/20 [0.010]	26/22 [0.263]	22/22 [0.891]	18/17 [0.766]
Supine							
Systolic <85 mm Hg	12/5 [0.020]	12/4 [0.005]	7/2 [0.016]	8/3 [0.012]	3/3 [0.700]	3/2 [0.560]	3/2 [0.651]
Diastolic <45 mm Hg	4/1 [0.117]	5/4 [0.503]	4/1 [0.054]	2/2 [0.837]	2/1 [0.177]	1/2 [0.184]	1/1 [0.996]
Decrease in systolic >30 mm Hg	8/4 [0.074]	3/2 [0.646]	4/2 [0.320]	10/3 [0.016]	6/8 [0.628]	3/7 [0.066]	8/4 [0.126]
Decrease in diastolic >20 mm Hg	8/3 [0.017]	3/1 [0.136]	5/1 [0.047]	6/1 [0.049]	3/2 [0.700]	3/6 [0.190]	1/3 [0.215]

Data are presented as tadalafil/placebo and [p value for odds ratio]; n = 154 to 157. The p value for the test of the null hypothesis of an odds ratio of 1 (corresponding to no treatment effect relative to placebo) was calculated separately for each time point (2, 4, 8, 24, 48, 72, and 96 h) for each of the criteria using a repeated measures logistic regression model accounting for the crossover design, with terms for treatment and period.
NP = not performed.

Tadalafil 20 mg was generally well tolerated. Compared with placebo, the incidence of myalgia and back pain during tadalafil treatment was markedly higher. Myalgia and back pain have been reported for the PDE5 inhibitors, especially with daily dosing (7). Most of the episodes were mild in severity, with a peak incidence occurring at two to three days of the seven consecutive daily dosing period. The incidence decreased with continued daily dosing of 20 mg tadalafil, and only 2 of 166 subjects discontinued the study as a result of myalgia or back pain. The myalgia that is sometimes observed with PDE5 inhibitors has not been associated with any significant underlying etiology such as elevations in creatine kinase (7).

Previous studies have reported an interaction between PDE5 inhibitors and organic nitrates (1–3). These studies have shown that both tadalafil and sildenafil increased the frequency of subjects having clinically significant decreases in BP in response to sublingual nitroglycerin compared with placebo (1–3). Webb et al. (2) also demonstrated that subjects were less tolerant of an intravenous infusion of nitroglycerin given 1 h after sildenafil 25 mg compared with placebo, and when subjects were given sublingual nitroglycerin 1 h after taking sildenafil 25 mg, they experienced a four-fold greater decrease in systolic BP compared with placebo (2). Although these studies described the interaction between nitrates and PDE5 inhibitors (1–3), none of them were designed to robustly evaluate the time course of the interaction. Our data extend these studies by measuring the time course of the nitrate-tadalafil interaction out to 96 h. Further studies to better evaluate the extent of the interaction at time points between 24 and 48 h post-tadalafil dosing would be of interest from both a basic science and clinical perspective.

Tadalafil administration with nitrates is contraindicated.

Table 2. Number of Clinically Important Blood Pressure Findings (Tadalafil/Placebo)

Criteria	Nitroglycerin Dose (h)						
	2	4	8	24	48	72	96
Standing							
Systolic <85 mm Hg	NP	229/149	119/89	157/115	104/116	74/101	75/91
Diastolic <45 mm Hg	NP	67/29	48/21	65/37	34/38	29/34	11/25
Decrease in systolic >30 mm Hg	NP	106/67	118/56	181/111	146/142	129/147	128/152
Decrease in diastolic >20 mm Hg	NP	55/32	67/36	103/54	80/56	64/70	48/53
Supine							
Systolic <85 mm Hg	46/22	55/29	41/10	25/10	10/10	14/7	10/8
Diastolic <45 mm Hg	10/3	15/10	25/6	14/9	10/6	5/8	3/8
Decrease in systolic >30 mm Hg	51/7	6/4	28/10	30/5	20/36	9/22	23/16
Decrease in diastolic >20 mm Hg	39/11	7/1	28/3	23/4	4/3	23/21	1/8

Data are presented as tadalafil/placebo. n = 154 to 157.
NP = not performed.

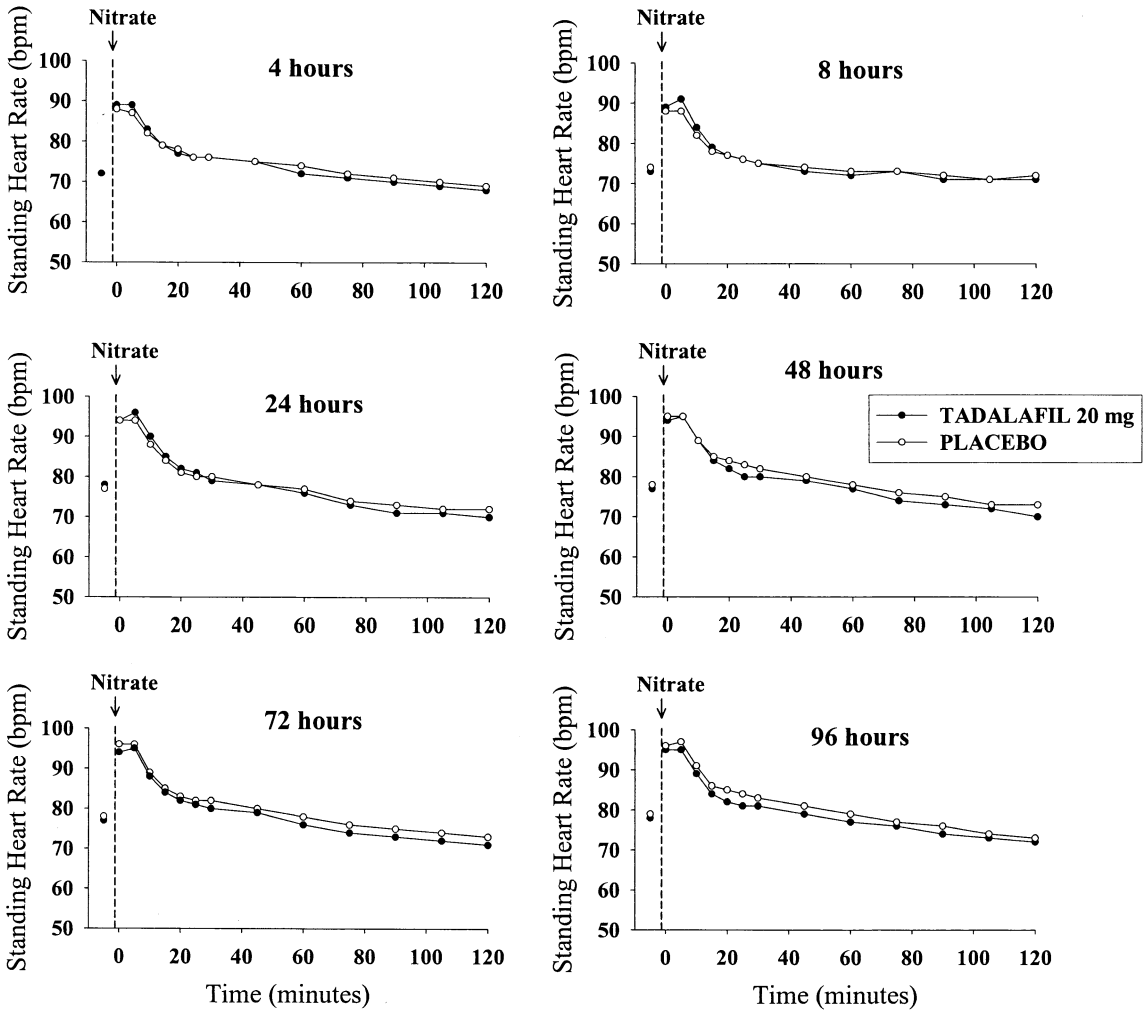

Figure 2. Mean standing heart rate in tadalafil (20 mg)- and placebo-treated subjects. Sublingual nitroglycerin (0.4 mg) is indicated by **dashed vertical line**. The 4- to 96-h time intervals represent time of nitroglycerin administration after last dose of tadalafil or placebo. Standard deviation for time points ranged from 10 to 16 beats/min (bpm).

As is the case with sildenafil (11), physicians and paramedics need to be aware of this potentially serious interaction. Thus, if a patient presents with chest pain, it will be imperative to question whether the patient has used a PDE5 inhibitor. If the patient has taken tadalafil within 48 h, then organic nitrates should not be given. Furthermore, if nitrates are deemed medically necessary 48 h or more after the use of tadalafil, they should be administered under close medical supervision with hemodynamic monitoring. It is noteworthy that in up to 33% of patients on placebo, nitroglycerin decreased standing BP >30 mm Hg. Thus, one should always be aware of the potentially marked hypotensive effects of nitrates.

Table 3. Adverse Events

	Placebo + Nitrate (n = 161)	Tadalafil + Nitrate (n = 160)
Headache	308 [81]	485 [110]
Myalgia	15 [10]	172 [71]
Back pain	13 [10]	143 [67]
Dizziness	103 [49]	110 [47]
Dyspepsia	3 [3]	74 [41]
Flushing	24 [11]	30 [17]
Postural dizziness	6 [5]	14 [8]

Data are presented as number of adverse events [number of subjects with adverse event].

If a patient takes tadalafil and reports chest pain within 48 h, it would be prudent to use non-nitrate anti-anginal agents (7). Beta-blockers, calcium channel blockers, morphine, oxygen, and aspirin could all be considered for treating ischemic chest pain, but nitrates should be avoided. Should a patient present within 48 h after taking tadalafil with an acute myocardial infarction, there is no contraindication to using usual therapy such as aspirin, heparin, percutaneous coronary intervention, or thrombolytics; but again, nitrates should not be given.

In conclusion, the hypotensive effect of sublingual nitroglycerin was augmented by tadalafil compared with placebo for 24 h following tadalafil administration, with no difference in the hypotensive responses at 48 to 96 h following

tadalafil. Similar to other PDE5 inhibitors, tadalafil should not be used in combination with organic nitrates.

Reprint requests and correspondence: Dr. Robert A. Kloner, Good Samaritan Hospital, Cardiovascular Division, 1225 Wilshire Boulevard, Los Angeles, California 90017. E-mail: rkloner@goodsam.org.

REFERENCES

1. Webb DJ, Muirhead GJ, Wulff M, et al. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. J Am Coll Cardiol 2000;36:25–31.
2. Webb DJ, Freestone S, Allen MJ, et al. Sildenafil citrate and blood pressure lowering drugs: results of drug interaction studies with an organic nitrate and calcium antagonist. Am J Cardiol 1999;83:21C–8C.
3. Emmick JT, Stuewe SR, Mitchell M. Overview of the cardiovascular effects of tadalafil. Eur Heart J 2002;4:H32–47.
4. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998;338:1397–404.
5. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. Physiol Rev 1995;75:725–48.
6. Kloner RA. Sex and the patient with cardiovascular risk factors: focus on sildenafil. Am J Med 2000;109:13S–21S.
7. Cheitlin MD, Hutter AM Jr., Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. J Am Coll Cardiol 1999;33:273–82.
8. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002;168:1332–6.
9. Brown H, Prescott R. Cross over trials. In: Applied Mixed Models in Medicine. Chichester, UK: Wiley, 1999:261–93.
10. Prescott R. The comparison of success rates in cross-over trials in the presence of an order effect. Appl Stat 1981;30:9–15.
11. Kloner RA, Jarow JP. Erectile dysfunction and sildenafil and cardiologists. Am J Cardiol 1999;83:576–82.