Sildenafil Citrate Potentiates the Hypotensive Effects of Nitric Oxide Donor Drugs in Male Patients With Stable Angina

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OBJECTIVE

We sought to study the effects of a single oral dose of sildenafil citrate (50 mg) on blood pressure (BP) in men taking the nitric oxide (NO) donor drugs isosorbide mononitrate (ISMN) or glyceryl trinitrate (GTN) for stable angina.

BACKGROUND

Sildenafil, a selective phosphodiesterase type 5 inhibitor, is an orally effective treatment for erectile dysfunction. The presence of phosphodiesterases in the vasculature suggests the possibility of an interaction between sildenafil and NO donor drugs.

METHODS

Two double-blind, placebo-controlled, randomized, two-way crossover trials were undertaken. Sixteen male patients received oral ISMN (20 mg twice a day) for five to seven days before their dose of sildenafil or placebo and continued receiving ISMN daily until administration of the alternate drug seven days later. For the second study, 15 male patients received sublingual GTN (500 μg) 1 h after sildenafil or placebo on each of two study days, which were seven days apart. Sitting or standing BP was measured before and for 6 h after the administration of the study drug.

RESULTS

The effects of sildenafil plus ISMN on BP (standing mean maximum reductions from baseline in systolic/diastolic BP, −52/−29 mm Hg) were greater than the effects of placebo plus ISMN on BP (−25/−15 mm Hg; p < 0.001). Sildenafil plus GTN also resulted in greater sitting mean maximum reductions from baseline in systolic/diastolic BP (−36/−21 mm Hg) compared with placebo plus GTN (−26/−12 mm Hg; p < 0.01).

CONCLUSIONS

Coadministration of sildenafil with ISMN or GTN produced significantly greater reductions in BP than ISMN or GTN alone. Based on these data, sildenafil should not be administered to patients taking nitrates. (J Am Coll Cardiol 2000;36:25–31) © 2000 by the American College of Cardiology

Sildenafil citrate is the first effective oral treatment for erectile dysfunction (ED) of various etiologies (1). Under conditions of normal sexual stimulation, the penile erectile process is regulated by release of the neurotransmitter nitric oxide (NO), which in turn induces the production of cyclic guanosine monophosphate (cGMP) (2,3). Increased levels of cGMP lead to relaxation of smooth muscle in the corpus cavernosum, reduces the metabolism of cGMP and thereby facilitates achieving and maintaining an erection satisfactory for sexual performance (4–7).

Nitric oxide is also an important regulator of cardiovascular function because it mediates tonic relaxation of vascular smooth muscle (8–11). Endothelium-bound NO synthase tightly controls the formation of NO from the amino acid L-arginine (8–10,12). Release of NO activates guanylate cyclase and the generation of cGMP (13). Once stimulated, the NO-cGMP pathway causes vasodilation of arteries and veins resulting in decreased preload and afterload. Over stimulation of the NO-cGMP pathway by administration of exogenous NO or through other mechanisms could result in significant decreases in systemic blood pressure (BP) and symptoms of hypotension.

Patients with ED of vascular etiology often suffer from some form of atherosclerotic cardiovascular disease such as angina. Therefore, a sizable patient population may possess risk factors that are shared by both ED and angina. Two commonly used therapeutics for angina are isosorbide mononitrate (ISMN), which functions as an NO donor and must be metabolized to release NO, and glyceryl trinitrate (GTN), which acts within tissues to generate the production of NO (14,15).

Administration of sildenafil alone causes modest reductions in BP (16,17), but these are not as pronounced as the reductions in BP observed after administration of therapeutic doses of nitrates used alone for control of angina (14). Because sildenafil and NO donors act at different points in

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the same NO-cGMP pathway and PDE5 may participate in the termination of NO-induced actions generated in blood vessels, there is likely to be a significant interaction when these two types of drugs are coadministered. Indeed, an early clinical trial in normal, healthy volunteers suggested this (18), and, as a result, the coadministration of nitrates (or NO donors) and sildenafil is strictly contraindicated. The two phase II clinical studies reported here further address the interaction of nitrates and sildenafil in patients with stable angina using a pragmatic crossover design. In these studies, hemodynamic responses were measured for 6 h after the administration of therapeutic doses of sildenafil to patients already using ISMN and also for 6 h after the administration of sublingual GTN in patients who recently had taken sildenafil.

**METHODS**

**Patient group.** Two separate studies were performed to evaluate the cardiovascular effects of sildenafil and NO-donor drugs administered concomitantly. The volunteer patients recruited for these studies had a history of stable angina and were currently being treated with oral nitrate drugs. Table 1 presents patient demographics and baseline measurements of the study participants. Permissible concurrent medications included antihypertensive agents, calcium channel antagonists and beta-adrenergic blocking agents for treatment of angina. Patients were excluded from the study if there was any evidence of clinically significant diseases other than stable angina, including a history of recent (<6 months) myocardial infarction or unstable angina. Patients were also excluded if they had hypertension (systolic/diastolic BP > 170/100 mm Hg) or hypotension (systolic/diastolic BP < 100/60 mm Hg), any evidence of drug abuse or any condition that was likely to affect the absorption of sildenafil. Written informed consent was obtained from each patient before study entry. The protocols were reviewed and approved by the local ethics committee.

**ISMN study.** Sixteen male patients ages 45 to 78 years were entered into this double-blind, placebo-controlled, randomized, two-way crossover study. All patients had stable angina and were being treated with ISMN. All patients received oral ISMN tablets (20 mg twice a day after meals) beginning five to seven days before receiving a single 50-mg dose of sildenafil or placebo. Patients received sildenafil and ISMN simultaneously on the morning of the first study visit. Patients continued receiving ISMN treatment for a minimum of seven days after the first dose of study drug before receiving a single dose of the alternate study drug (sildenafil or placebo) simultaneously with ISMN at the second study visit. Sitting and standing BP and heart rate (HR) were measured at screening, immediately before receiving sildenafil or placebo (baseline) and at fixed intervals up to 6 h after receiving the study drug during each study visit. The maximum change in BP and HR from baseline was recorded. The systemic effects of the study drug plus ISMN on BP and HR were assessed by determining the area under the effect curve (AUEC) for BP and HR using the trapezoidal rule. Adverse events were recorded at each study visit, and laboratory safety tests were performed at screening, at each end of each treatment period and at a follow-up visit.

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics and Baseline Measurements</th>
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<tbody>
<tr>
<td><strong>ISMN Study Mean (Range)</strong></td>
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<tr>
<td>Sildenafil→Placebo (n = 9)</td>
</tr>
<tr>
<td>Age (yr)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Time since first diagnosis (yr)</td>
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<tr>
<td><strong>Sildenafil + ISMN (n = 16)</strong></td>
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<tr>
<td>Sitting systolic pressure (mm Hg)</td>
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<tr>
<td>Sitting diastolic pressure (mm Hg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>Concurrent medications:</td>
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<tr>
<td>ACE inhibitor or CCB</td>
</tr>
<tr>
<td>Beta-blocker</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>Vasodilator (e.g., GTN)</td>
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ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; GTN = glyceryl trinitrate; ISMN = isosorbide mononitrate.
GTN study. Fifteen male patients ages 46 to 77 years were enrolled into this double-blind, placebo-controlled, randomized, two-way crossover study. All patients had stable angina and were receiving sublingual GTN as needed at the time of entry into the study. During the study, patients were permitted to take GTN as needed except on the two days when the study drug was to be administered. On these days, patients were instructed not to take GTN within 4 h of their scheduled clinic visit. At the clinic visit, patients were given a single 50-mg dose of sildenafil or placebo followed 1 h later by a 500-μg dose of GTN administered sublingually. The two clinic visits were separated by a minimum of seven days; at the second visit, patients received the alternate study drug (sildenafil or placebo) and GTN as described above. Sitting BP and HR were measured at screening, immediately before receiving sildenafil or placebo (baseline) and at fixed intervals up to 6 h after receiving study drug. The maximum change in BP and HR from baseline was again recorded. The AUECs for BP and HR were calculated for each dosing regimen as in the first study. Adverse events were recorded at each study visit, and laboratory safety tests were performed at screening, at the end of each treatment period and at a follow-up visit.

Statistics. Maximum changes from baseline in BP and HR were determined for each individual patient. Mean maximum changes from baseline and 95% confidence intervals were calculated for BP and HR in the sildenafil and placebo groups. Analysis of covariance was used to determine the significance of the differences between patients receiving placebo or sildenafil. The between-subject and within-subject baseline values were included in the analysis of variance model as covariates.

RESULTS

ISMN study. All patients in this study received ISMN. In those patients also receiving placebo, the sitting mean maximum decrease from baseline (±SEM) in systolic/diastolic BP was 22 ± 2.5/13 ± 1.9 mm Hg (Table 2). In patients receiving ISMN plus sildenafil, the mean maximum decrease from baseline in sitting systolic/diastolic BP was 41 ± 3.8/26 ± 1.9 mm Hg (p < 0.01 compared with placebo). The BP results obtained with standing measurements were even more pronounced than those obtained while patients were sitting. In patients receiving placebo, the standing mean maximum decrease from baseline in systolic/diastolic BP was 25 ± 2.8/15 ± 1.3 mm Hg (Table 3). In patients receiving sildenafil, the mean maximum decrease from baseline in standing systolic/diastolic BP was 52 ± 6.2/29 ± 3.0 mm Hg (p < 0.001 compared with placebo). When viewed over time, it is clear that administration of ISMN plus sildenafil resulted in substantially greater decreases in BP from baseline over the 6-h recording period compared with the decreases in BP from baseline in patients receiving ISMN plus placebo (Fig. 1 and 2). The decreases in BP were greatest from approximately 1 to 3 h after dosing and were still apparent at the 6-h time point. The cumulative systemic effect of these changes over time are reflected in the AUEC values for both treatment groups (Tables 2 and 3). The decreases in the AUECs for systolic and diastolic BP were significantly greater (p < 0.001) for the sildenafil-treated patients compared with the AUECs for placebo-treated patients. The mean maximum increases from baseline in HR were not significantly different between treatment groups (Tables 2 and 3). However, the increase in the AUEC for standing HR was significantly greater in patients receiving sildenafil compared with those receiving placebo (p < 0.01, Table 3). These differences are reflected in the mean sitting and standing changes in HR over the 6-h period (Fig. 3). The most common adverse events associated with the administration of ISMN were dizziness (five patients—sildenafil, two patients—placebo), sweating (three patients—sildenafil, zero patients—placebo), postural hypotension (two patients—sildenafil, one patient—placebo) and headache (two patients—sildenafil, one patient—placebo). All treatment-emergent adverse events during the sildenafil and placebo study periods were mild to moderate in severity and were considered treatment-related. No serious adverse

Table 2. Sitting Mean Maximum Changes From Baseline and AUEC After Receiving Sildenafil or Placebo in Patients Concomitantly Receiving Oral ISMN (20 mg) Treatment*  
<table>
<thead>
<tr>
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<th>Sildenafil, 50 mg Mean (Range)</th>
<th>Placebo Mean (Range)</th>
<th>p Value</th>
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<tbody>
<tr>
<td><strong>Systolic Blood Pressure</strong></td>
<td></td>
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<tr>
<td>Maximum decrease (mm Hg)</td>
<td>−41.0 (−6 to −70)</td>
<td>−22.1 (−2 to −34)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AUEC (mm Hg/h)</td>
<td>−127.6 (−7 to −235)</td>
<td>−45.9 (56 to −158)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure</strong></td>
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<tr>
<td>Maximum decrease (mm Hg)</td>
<td>−25.8 (−15 to −42)</td>
<td>−12.7 (−1 to −25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUEC (mm Hg/h)</td>
<td>−98.2 (−40 to −188)</td>
<td>−25.2 (76 to −123)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Heart Rate</strong></td>
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<tr>
<td>Maximum increase (beats/min)</td>
<td>15.8 (−1 to 36)</td>
<td>14.0 (1 to 39)</td>
<td>0.35</td>
</tr>
<tr>
<td>AUEC (beats/min/h)</td>
<td>33.0 (−40 to 181)</td>
<td>23.3 (−36 to 165)</td>
<td>0.12</td>
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*n = 16 (adjusted arithmetic means).
AUEC = area under effect curve.
events were reported, and there were no reports of clinically significant tachycardia in either treatment group. There were no treatment-related abnormalities in laboratory test results.

GTN study. All patients in this study received GTN 1 h after receiving placebo or sildenafil (arrow, Fig. 4). In patients who also received placebo, the mean maximum

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<tr>
<th>Sildenafil, 50 mg Mean (Range)</th>
<th>Placebo Mean (Range)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
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<tr>
<td>Maximum decrease (mm Hg)</td>
<td>−51.6 (−17 to −90)</td>
<td>−24.5 (−1 to −49)</td>
</tr>
<tr>
<td>AUEC (mm Hg/h)</td>
<td>−166.2 (−5 to −363)</td>
<td>−57.9 (70 to −150)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum decrease (mm Hg)</td>
<td>−29.3 (−11 to −49)</td>
<td>−14.8 (−5 to −22)</td>
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<tr>
<td>AUEC (mm Hg/h)</td>
<td>−109.9 (−40 to −215)</td>
<td>−39.4 (46 to −91)</td>
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<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum increase (beats/min)</td>
<td>18.5 (−5 to 41)</td>
<td>17.1 (4 to 40)</td>
</tr>
<tr>
<td>AUEC (beats/min/h)</td>
<td>57.1 (−53 to 168)</td>
<td>35.8 (−52 to 151)</td>
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* n = 16 (adjusted arithmetic means). AUEC = area under effect curve.

Figure 1. Mean changes from baseline in sitting systolic (A) and diastolic (B) BP after ISMN administration. Sildenafil plus ISMN caused significant decreases in systolic and diastolic BP compared with placebo plus ISMN. Oral ISMN (20 mg) and oral sildenafil (50 mg) or placebo were administered at time 0, as indicated by the arrows. Baseline (time 0) is the average of the measurements taken immediately before sildenafil or placebo administration. Values represent mean ± SEM; n = 16; BP = blood pressure; ISMN = isosorbide mononitrate.

Figure 2. Mean changes from baseline in standing systolic (A) and diastolic (B) BP after ISMN administration. Sildenafil plus ISMN caused significant decreases in systolic and diastolic BP compared with placebo plus ISMN. Oral ISMN (20 mg) and oral sildenafil (50 mg) or placebo were administered at time 0, as indicated by the arrows. Baseline (time 0) is the average of the measurements taken immediately before sildenafil or placebo administration. Values represent mean ± SEM; n = 16; BP = blood pressure; ISMN = isosorbide mononitrate.
decrease from baseline (±SEM) in sitting systolic/diastolic BP was 26 ± 3.6/11 ± 1.9 mm Hg (Table 4). In patients receiving sildenafil, the mean maximum decrease from baseline in systolic/diastolic BP was 36 ± 4.8/21 ± 2.1 mm Hg (p < 0.01 compared with placebo). These decreases are apparent when viewed over the 6-h recording period (Fig. 4), during which it can be seen that the greatest differences in BP measurements between the sildenafil and placebo treatment groups occurred within 1 h after GTN administration. The differences between the two groups were still apparent at the 6-h time point. As with the ISMN study, the cumulative systemic effects of these changes are reflected in the AUEC values (Table 4). The decreases in the AUECs were significantly greater for systolic BP (p < 0.01) and diastolic BP (p < 0.001) in the sildenafil-treated patients compared with the AUECs in the placebo-treated patients.

Minimal mean changes in HR occurred until the administration of GTN at 1 h (arrow, Fig. 5). From that point, there were significantly greater (p < 0.01) mean maximum increases from baseline in sitting HR in patients receiving sildenafil compared with the HR in patients receiving placebo (Table 4). The increases in the AUECs for HR were not significantly different between patients receiving sildenafil and GTN and those receiving placebo and GTN (Table 4), suggesting that the effects on HR were transient in nature.

Eight patients reported an adverse event after sildenafil treatment compared with four patients reporting an adverse event after placebo treatment. The most common adverse events associated with the administration of sildenafil were headache (five patients) and dizziness (three patients). Of these, headache in one patient and dizziness in two patients were considered treatment-related. No treatment-related adverse events occurred after administration of placebo. No serious adverse events or laboratory test abnormalities related to treatment were reported.

One patient was withdrawn from the sildenafil/GTN group with lowered BP. Six minutes after GTN administration (1 h, 6 min after sildenafil) he reported feeling unwell and had a mild headache. At baseline his BP reading was 167/88, and 56 min after taking sildenafil, his reading was 155/80. Ten minutes later (6 min after taking GTN), his BP reading was 86/47 and dropped further to 70/39 during the next 6 min. His systolic pressure remained below
minute; HR
5
sildenafil (50 mg), as indicated by the
arrow. Sublingual GTN (500
m
administration. Values represent mean
average of the measurements taken immediately before sildenafil or placebo
5
AUEC (mm Hg)
6
Sildenafil, 50 mg
Mean (Range) Placebo Mean
p Value
Systolic Blood Pressure
Maximum decrease (mm Hg)
35.9 (−15 to −84) −26.0 (−3 to −52) <0.01
AUEC (mm Hg/h)
−65.6 (6 to −252) −28.8 (57 to −119) <0.01
Diastolic Blood Pressure
Maximum decrease (mm Hg)
−21.1 (−11 to −34) −11.4 (4 to −25) <0.01
AUEC (mm Hg/h)
−46.6 (−2 to −121) −15.1 (44 to −54) <0.001
Heart Rate
Maximum increase (beats/min)
15.8 (3 to 31) 10.2 (1 to 15) <0.01
AUEC (beats/min/h)
27.2 (−18 to 87) 15.0 (−13 to 46) 0.15

*p = 15 (adjusted arithmetic means).
AUEC = area under effect curve.

100 mm Hg for an additional 9 min and did not rise above 130 mm Hg until 43 min after receiving GTN.

DISCUSSION

Treatment of stable angina with nitrates or NO donors is based on their rapid onset of action and vasodilator capacity (14). Evidence from other clinical trials suggested that sildenafil in combination with acute doses of GTN could result in synergistic decreases of BP (18). This study has expanded on these findings, demonstrating that nitrate-sildenafil hemodynamic interactions affecting BP persisted during the entire 6-h observation period. Furthermore, the present studies were conducted in patients using a trial design that more closely reflects the interactions likely to be observed with an unintentional coadministration of these two classes of drugs.

Study drugs alone. The magnitude of the BP-lowering effects observed after administration of ISMN alone (sitting and standing mean maximum decreases of 22/13 and 25/15 mm Hg) and of GTN alone (sitting mean maximum decrease of 26/11 mm Hg) were substantially greater than the BP-lowering effect previously observed after administration of sildenafil alone. In early clinical trials, the effect of high doses of sildenafil on BP in healthy men was modest, producing mean maximum decreases of systolic/diastolic BP of 10/7 mm Hg that were not dose-related (16,17).

Sildenafil-nitrate interaction. Because vasodilation is known to be mediated by changes in cGMP levels, and treatment with nitrates and sildenafil both result in increasing intracellular levels of cGMP, an interaction during concomitant administration was anticipated (6,13,19). In the studies reported here, sitting mean maximum decreases of 41/26 mm Hg were observed in patients receiving ISMN and sildenafil, and sitting mean maximum decreases of 36/21 mm Hg were observed in patients receiving GTN and sildenafil. However, the combination of ISMN and sildenafil produced an even larger interaction when BP was measured standing, with mean maximum decreases of 52/29 mm Hg observed. At a minimum, the effects on BP after coadministration of either ISMN or GTN with sildenafil appeared to be additive, with the possibility that a synergistic interaction was occurring, as reflected in the standing ISMN plus sildenafil BP recordings. By inhibiting the breakdown of cGMP, sildenafil was able to amplify the NO-related activity of exogenously administered ISMN and GTN on the vascular system, resulting in clinically significant reductions in BP.

The biochemical mechanism whereby sildenafil exerts an effect on BP is probably a result of the presence of PDE5 in the vasculature (20). Sildenafil has considerably lower affinity for other PDE isoforms involved in cardiovascular regulation. Phosphodiesterase type 1, PDE2 and PDE3 are located in myocardium, and PDE1 and PDE3 are located in vascular smooth muscle; but their IC50 values for sildenafil range from 20- to 8,000-fold higher compared with the IC50 value of sildenafil for PDE5 (6,7,20). The low level of vascular side effects after sildenafil treatment in placebo-controlled and open-label clinical trials is, therefore, not surprising (21). There are no known effects of sildenafil on myocardial tissue or the functioning of the heart, consistent with its PDE5 selectivity.
with the fact that there is no measurable level of PDE5 in the myocardium (22).

**Toleration.** Mild-to-moderate adverse events were reported in each study, including those related to vasodilation, such as headache and dizziness. Treatment-related adverse events were reported by 8 of 16 patients after ISMN and sildenafil coadministration, and 3 of 15 patients after GTN and sildenafil coadministration. In large-scale, double-blind, placebo-controlled clinical trials and in open-label extension studies, sildenafil was shown to be well-tolerated, with a low incidence of cardiovascular-related adverse events reported (21). These patients were not permitted to take nitrates or NO-donor drugs, because of the potential interaction with sildenafil. In these same trials, patients receiving concomitant treatment with antihypertensive medications, including vasodilators, reported no increase in adverse events or cardiovascular-related adverse events (20). As the antihypertensive medications were not NO donors, they were not expected to produce a similar interaction with sildenafil to that observed with nitrates.

**Conclusions.** The studies reported here have demonstrated that marked and clinically significant reductions in BP occur when sildenafil is administered concurrently with NO donors that are commonly used to treat angina. Based on these data, sildenafil should not be coadministered to patients taking nitrates.

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**REFERENCES**