Drug Interactions With Phosphodiesterase-5 Inhibitors Used for the Treatment of Erectile Dysfunction or Pulmonary Hypertension

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Sildenafil and tadalafil were the 32nd and 74th, respectively, most popular prescription drugs dispensed in the United States in 2006. Erectile dysfunction (ED) currently affects >30 million men in the United States and >150 million men worldwide and will become more prevalent as the population ages.1 Phosphodiesterase-5 (PDE5) inhibitors (PDE5Is) (sildenafil [Viagra],2 vardenafil [Levitra],3 and tadalafil [Cialis]4) are first-line therapy for ED. Use of PDE5Is will increase because sildenafil (Revatio)5 and tadalafil (Adcirca)6 are now prescribed as first-line therapy for many patients with pulmonary hypertension (PHT).5–8

Several pooled analyses comprising dozens of trials and thousands of patients, including patients with coronary artery disease and on antihypertensive medications, reported that PDE5Is did not significantly affect the incidence of adverse cardiovascular events.9–12 However, PDE5 is distributed in many tissues, including platelets, veins, and arterial smooth muscle (pulmonary, coronary, and systemic arteries).13 Thus, PDE5Is affect the cardiovascular system, mostly via vasodilation, and often cause small decreases in blood pressure (BP). When PDE5Is are coadministered with nitrates or α-blockers, pronounced systemic vasodilation and severe hypotension are possible. Many patients with ED are elderly and have the same risk factors as patients with coronary artery disease, so these drug combinations are commonly considered or encountered in clinical practice.1 This article covers the important PDE5I drug interactions, including antihypertensive agents, nitrates, α-blockers, PHT agents, cytochrome P450 inhibitors, and other miscellaneous drugs.

Metabolic Clearance

Sildenafil is metabolized mainly by the cytochrome P450 3A4 pathway (79%) and to a lesser extent by 2C9 (20%).14,15 Vardenafil is metabolized in a similar manner, mainly by 3A4 with a smaller contribution by 2C9.15 Tadalafil is metabolized almost solely by 3A4.15 Therefore, drugs that inhibit the 3A4 pathway decrease the metabolism and increase the plasma concentrations of PDE5Is (Table 1). Area under the concentration-time curve (exposure) values for sildenafil ranged from 0.8- to 2.6-fold (mean, 1.2-fold increase) when coadministered with 250 mL grapefruit juice (a 3A4 inhibitor), and results would vary even more in an uncontrolled setting (Table 1).20 Data on changes in half-life and elimination time are less frequently reported, but 3A4 inhibitors reportedly have small effects or no effect on the half-lives of PDE5Is.15 An exception is ritonavir, a potent inhibitor of several P450 cytochromes, including 3A4 and 2C9. By simultaneously blocking both pathways, ritonavir prevents a compensatory shift to the 2C9 pathway. Ritonavir increases exposure to sildenafil by 11-fold and increases the half-life of vardenafil from 4 to 26 hours.3,18 Ritonavir initially inhibits 3A4 but later induces 3A4 after ~1 week of steady-state levels.6 The timing of observation likely accounts for the large difference in effects reported with ritonavir coadministration (Table 1). Cimetidine, a less potent, nonspecific cytochrome P450 inhibitor, increases exposure to sildenafil by 1.6-fold.21 Ketoconazole inhibits sildenafil metabolism to a degree similar to ritonavir.14 Although each drug combination has not been studied, the following 3A4 inhibitors would likely increase exposure to each of the PDE5Is: erythromycin, ketoconazole, itraconazole, clarithromycin, HIV protease inhibitors, and grapefruit juice.2–4 The 2C9 inhibitors do not significantly affect the metabolism of PDE5Is.15 It is unlikely and there is no evidence to date that other drugs metabolized by the 3A4 pathway competitively inhibit PDE5I metabolism because the 3A4 system has a high capacity.2–4,15,23

High doses of sildenafil (up to 800 mg) increased the incidence rates and severities of adverse events, although the types of adverse events were similar to those observed with lower doses, including visual disturbances, hypotension, syncope, and prolonged erection.2 It is likely that higher plasma concentrations resulting from coadministration of 3A4 inhibitors would similarly influence the side-effect profile. For instance, the combination of itraconazole and tadalafil caused priapism in a healthy 56-year-old man.24 In addition, higher PDE5I plasma concentrations resulting from 3A4 inhibitors can influence the severity and timing of other PDE5I drug interactions, including with nitrates and α-blockers. PDE5I dose adjustments are usually indicated when coadministered with 3A4 inhibitors (Table 2).
Table 1. PDE5I Drug Interactions Involving Cytochrome P450 Isoenzyme CYP3A4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (mg/L)</td>
<td>Cmax (mg/L)</td>
<td>AUC (mg/L)</td>
</tr>
<tr>
<td>3A4 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2.8</td>
<td>2.6</td>
<td>4</td>
</tr>
<tr>
<td>Clarithromycin&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2.3</td>
<td>2.4</td>
<td>...</td>
</tr>
<tr>
<td>Ketoconazole&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>...</td>
<td>...</td>
<td>10</td>
</tr>
<tr>
<td>Saquinavir&lt;sup&gt;18&lt;/sup&gt;</td>
<td>3.1</td>
<td>2.4</td>
<td>...</td>
</tr>
<tr>
<td>Indinavir&lt;sup&gt;2&lt;/sup&gt;</td>
<td>...</td>
<td>...</td>
<td>16</td>
</tr>
<tr>
<td>Ciprofloxacin&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2.1</td>
<td>2.2</td>
<td>...</td>
</tr>
<tr>
<td>Tacroliumus&lt;sup&gt;19&lt;/sup&gt;</td>
<td>1.4</td>
<td>1.9</td>
<td>...</td>
</tr>
<tr>
<td>Grapefruit juice&lt;sup&gt;20&lt;/sup&gt;</td>
<td>0.8</td>
<td>2.6</td>
<td>...</td>
</tr>
<tr>
<td>P450 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir&lt;sup&gt;3,4,18&lt;/sup&gt;</td>
<td>11</td>
<td>3.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Cimetidine&lt;sup&gt;21&lt;/sup&gt;</td>
<td>1.6</td>
<td>1.5</td>
<td>...</td>
</tr>
<tr>
<td>3A4 inducers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin&lt;sup&gt;4&lt;/sup&gt;</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bosentan&lt;sup&gt;22&lt;/sup&gt;</td>
<td>0.4</td>
<td>0.4</td>
<td>...</td>
</tr>
</tbody>
</table>

AUC indicates area under the concentration-time curve; Cmax, maximum plasma concentration; 3A4, cytochrome P450 isoenzyme CYP3A4; and P450, nonspecific cytochrome P450. Numbers are fold increase (numbers <1 indicate decreases).

Conversely, inducers of P450 3A4 increase the clearance and decrease the plasma concentrations of PDE5Is<sup>2–4</sup>. Rifampin reduced exposure to tadalafil by 88%.<sup>4</sup> Although each interaction has not been studied, other 3A4 inducers, including carbamazepine, phenytoin, and phenobarbital, would likely decrease PDE5I plasma levels.<sup>2–4</sup> No initial PDE5I dose adjustment is indicated when coadministered with 3A4 inducers; however, efficacy may be reduced in some patients requiring an increased dose. Adcirca is not recommended for patients taking long-term rifampin.<sup>6</sup>

Notably, the metabolism of sildenafil was not affected by warfarin, azithromycin,<sup>16</sup> selective serotonin reuptake inhibitors, thiazides, angiotensin-converting enzyme inhibitors, calcium channel blockers, or antacid.<sup>21</sup> Vardenafil was not affected by warfarin, glyburide, digoxin, or ranitidine. Tadalafil was not affected by warfarin, midazolam, lovastatin, or theophylline.<sup>2–4</sup>

Sildenafil and vardenafil weakly inhibit several cytochrome P450 pathways at doses much higher than recommended doses (ie, plasma concentrations 20 times higher than achieved with vardenafil 80 mg).<sup>3,15</sup> There is no evidence to date that sildenafil or vardenafil affects the clearance of other commonly used drugs, including warfarin, digoxin, atorvastatin, ritonavir, amiodipine,<sup>25</sup> and slow-release nifedipine.<sup>2,3</sup> Tadalafil does not inhibit or induce cytochrome P450 pathways and had no significant effect on the pharmacokinetics of digoxin, theophylline, warfarin, midazolam, or lovastatin.<sup>4,15</sup>

### Pharmacodynamics and Dosing

Sildenafil and vardenafil each have a half-life of 3 to 4 hours, lead to peak plasma levels ~60 minutes after ingestion, and exhibit reduced absorption with a high-fat meal.<sup>13</sup> The half-life of sildenafil increases as the dose increases (25 mg, 2.6 hours; 100 mg, 3.7 hours).<sup>20</sup> Tadalafil has a half-life of 17.5 hours, which peaks at 2 hours, and its absorption is not influenced by food.<sup>15</sup> Tadalafil can be prescribed for ED as on-demand or once-daily dosing or as once daily for PHT. A dosing guide is provided in Table 2. Refer to the Physicians’ Desk Reference and its updates or product prescribing information for specific dose adjustments.<sup>2–6</sup> Higher plasma concentrations are desirable for the treatment of PHT compared with ED. Of note, some physicians prescribe higher doses of sildenafil (up to 80 mg 3 TID) for PHT than recommended (20 mg TID) on the basis of the doses used in a few clinical trials of PHT<sup>27,28</sup>. Although comparisons were made only with placebo, sildenafil 80 mg TID appeared to improve World Health Organization functional class more than 20 mg TID (placebo-corrected proportion of patients with improvement of at least 1 functional class with sildenafil 80 mg TID, 42%; with 20 mg TID, 28%).<sup>28</sup>

### Antihypertensives and PDE5Is

PDE5Is can be coadministered with most antihypertensive medications without inducing clinically significant reductions in BP.<sup>29–31</sup> Caution must be used with ß-blockers. In general, the BP reductions caused by PDE5Is are small whether they are taken alone or in conjunction with other antihypertensive medications, including ß-blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (Table 3). In most healthy subjects, BP returned to baseline values within 6 hours of sildenafil administration.<sup>34</sup> After tadalafil administration, diastolic BP decreased slightly and remained low for 12 hours,
Table 3. Interactions Between PDE5Is and Various Antihypertensive Medications

<table>
<thead>
<tr>
<th>Healthy control subjects</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with stable coronary artery disease</td>
<td>-10/-7</td>
<td>-7/-8</td>
<td>0/-5</td>
</tr>
<tr>
<td>With amlodipine</td>
<td>-8/-7</td>
<td>-8/-8</td>
<td>-1/-1</td>
</tr>
<tr>
<td>With slow-release nifedipine</td>
<td>-6/-5</td>
<td>-6/-5</td>
<td>-6/-5</td>
</tr>
<tr>
<td>With enalapril</td>
<td>-4/-1</td>
<td>-4/-1</td>
<td>-4/-1</td>
</tr>
<tr>
<td>With metoprolol</td>
<td>-4/-1</td>
<td>-4/-1</td>
<td>-4/-1</td>
</tr>
<tr>
<td>With bendrofluazide</td>
<td>-6/-4</td>
<td>-6/-4</td>
<td>-6/-4</td>
</tr>
<tr>
<td>With angiotensin II receptor blocker</td>
<td>-8/-4</td>
<td>-8/-4</td>
<td>-8/-4</td>
</tr>
<tr>
<td>With thiazide diuretics</td>
<td>No increase</td>
<td>No increase</td>
<td>4/-1</td>
</tr>
<tr>
<td>With ≥1 antihypertensive medications</td>
<td>-4/-2</td>
<td>-5/-4</td>
<td>-4/-1</td>
</tr>
<tr>
<td>With multiple antihypertensive medications</td>
<td>No increase</td>
<td>No increase</td>
<td>No increase</td>
</tr>
</tbody>
</table>

- Indicates decreased; +, increased. Numbers are the change in SBP/diastolic BP in mm Hg.

1 Mean maximum decrease from baseline.
† Mean decrease from baseline relative to placebo.
‡ Mean decrease from baseline.
§ Mean maximum decrease relative to placebo.
Thiazide diuretics included bendroflumethiazide, benzylhydrochlorothiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, indapamide, metolazone, and trichlormethiazide.
# Studies with multiple medications included diuretics, β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, and calcium antagonists.

Nitrates and PDE5Is

Penile erections and endothelium-mediated vasodilation are mediated through cGMP, which promotes trabecular and vascular smooth muscle relaxation. PDE5Is prevent the breakdown of cGMP. Nitric oxide donors (ie, nitrates) increase the production of cGMP. Because both PDE5Is and nitrates increase cGMP, coadministration can generate excess accumulation of cGMP and can trigger marked vasodilation and severe hypotension. For instance, when Emmick and colleagues evaluated nitroglycerin 0.4 mg in combination with sildenafil 50 mg, tadalafil 10 mg, and placebo, a potentially clinically significant change in BP was observed more frequently with each PDE5I than with placebo (standing SBP < 85 mm Hg: placebo, 37%; sildenafil, 47%; tadalafil, 47%; supine SBP < 85 mm Hg: placebo, 8%; sildenafil, 20%; tadalafil, 18%). Thus, PDE5Is are contraindicated with all nitrates (eg, nitroglycerin, glyceryl trinitrate,isosorbidemononitrate). Of note, recreational use of inhaled amyl nitrate or nitrite, often referred to as “poppers,” can interact with PDE5Is, causing severe hypotension. Sildenafil is not contraindicated with the anesthetic agent nitrous oxide or dietary sources of nitrates (eg, L-arginine) because neither contributes to plasma levels of nitric oxide.

Duration of Contraindication

If a patient has taken a PDE5I and then develops stable angina, unstable angina, or a myocardial infarction, when can nitrates be administered safely? The American College of Cardiology and American Heart Association suggest nitrates can be administered 24 hours (6 half-lives) after sildenafil intake to allow full clearance of the drug. The study by Emmick and colleagues evaluated nitroglycerin administration 1 day after sildenafil, tadalafil, or placebo. The incidence of a significant decrease in BP was similar between sildenafil and placebo but inconclusive for tadalafil (standing SBP < 85 mm Hg: placebo, 18%; sildenafil, 20%; tadalafil, 31%; decrease in standing SBP > 30 mm Hg: placebo, 12%; sildenafil, 4%; tadalafil, 20%). Sildenafil no longer showed evidence of an interaction with nitroglycerin 24 hours after sildenafil administration. The interaction with nitrates may be gone as early as 4 hours after sildenafil intake. When nitroglycerin was administered 4 hours after sildenafil or placebo, there was no significant difference in mean maximal change from baseline BP; however, this abstract did not report the incidence of potentially clinically significant decreases in BP. Likewise, vardenafil is suggested to lack an interaction with nitrates at 24 hours after intake (6 half-lives). Conversely, tadalafil does interact with sublingual nitroglycerin to increase the risk of hypotension at 24 hours but not at 48 hours after tadalafil intake. After receiving tadalafil 20 mg or placebo for 7 consecutive days, 150 men...
were given repeated doses of nitroglycerin 0.4 mg. At 4, 8, and 24 hours after the last tadalafil intake, nitroglycerin caused more subjects in the tadalafil group than in the placebo group to experience a potentially clinically significant decrease in BP, including a standing SBP <85 mm Hg. No significant differences were observed between the tadalafil and placebo groups at 48, 72, or 96 hours after the last tadalafil intake.\(^3\) Thus, it is recommended that nitrates be withheld for at least 48 hours after tadalafil intake and thereafter should be given with caution, supervision, and hemodynamic monitoring. It may be prudent to allow additional time to elapse in patients with conditions that increase plasma levels of PDE5Is (Table 1).\(^2\) The time frames described hold true even if the patient develops chest pain or an acute coronary syndrome. Patients prescribed PDE5Is should be counseled to inform emergency workers and physicians about their most recent PDE5I intake so that nitrates can be avoided. All other medications should be given if appropriate to the clinical condition, including the antianginal agents \(\beta\)-blockers, calcium channel blockers, and morphine, as well as aspirin, statins, oxygen, thrombolitics, and antiplatelet agents as indicated.\(^23\) Only nitrates are contraindicated.

**Treatment of PDE5I-Nitrate–Induced Hypotension**

What if a patient has taken a PDE5I, receives a nitrate, and becomes hypotensive from pronounced vasodilation? The American College of Cardiology and AHA suggest placing the patient in the Trendelenburg position, aggressive fluid resuscitation, and if necessary an \(\alpha\)-agonist (phenylephrine), a \(\beta\)-agonist (norepinephrine), and intraaortic balloon counterpulsation.\(^23\) There is no antidote to PDE5Is.

**\(\alpha\)-Blockers and PDE5Is**

“Uroselective” \(\alpha\)-blockers (tamsulosin, alfuzosin) preferentially inhibit \(\alpha_1A\) and \(\alpha_1P\) receptors found primarily in the prostate and benefit patients with benign prostatic hypertrophy. Other \(\alpha\)-blockers (terazosin) are less selective, and some (doxazosin) are used as third-line agents for hypertension because of their higher affinity for \(\alpha_1Q\) receptors, which are abundant in the peripheral vasculature.\(^40\)–\(^42\) All \(\alpha\)-blockers can cause vasodilation and orthostatic hypotension, and coadministration with PDE5Is increases the risk of a clinically significant decrease in BP. Various combinations of PDE5Is and \(\alpha\)-blockers interact to different degrees, as shown in Table 4. The degree of PDE5I–\(\alpha\)-blocker interaction depends on which drugs are coadministered, the dose of \(\alpha\)-blocker, the timing of administration, and the duration or stability of the \(\alpha\)-blocker therapy (Table 4).\(^42\) Tadalafil has fewer effects on the cardiovascular system than the other PDE5Is, as exemplified by its minimal effects on BP in healthy control subjects (Table 3).\(^35\)

**Timing of Administration**

Vardenafil was studied with terazosin and (in a separate study) tamsulosin, both simultaneously and separated by 6 hours (Table 4).\(^3\) A standing SBP <85 mm Hg or a >30-mm Hg decrease in standing SBP occurred in 9 of 24 men receiving tamsulosin and in 19 of 29 men receiving terazosin and led to the early termination of the simultaneous administration of terazosin arm. Compared with administration 6 hours apart, simultaneous administration of vardenafil and terazosin more frequently resulted in a standing SBP <85 mm Hg or a >30-mm Hg decrease in standing SBP.

**Uroselective \(\alpha\)-Blockers**

Coadministration of tadalafil with doxazosin and with tamsulosin was evaluated (Table 4).\(^43\) Tamsulosin with tadalafil decreased SBP only minimally and did not increase the risk of a potentially clinically significant decrease in BP relative to placebo. Compared with doxazosin and placebo, doxazosin and tadalafil significantly reduced standing SBP (−9.8 mm Hg) and increased the incidence of a standing SBP <85 mm Hg (28% versus 6%). So, under identical protocols, tadalafil interacted with doxazosin but not with the uroselective tamsulosin.

When sildenafil 100 mg alone was compared with sildenafil 100 mg and tamsulosin 0.4 mg coadministration, BP was not statistically different between groups in supine patients or after tilt testing.\(^35\)

When coadministration of tadalafil and alfuzosin (uroselective) was evaluated, the change in standing SBP was not statistically significant from tadalafil and placebo (Table 4).\(^41\) Although 1 asymptomatic man had a standing SBP of 83 mm Hg, no man had a supine SBP <85 mm Hg, a >30-mm Hg decrease in SBP, or a diastolic BP <45 mm Hg.

**Stability of \(\alpha\)-Blocker Therapy**

Twenty-two men with benign prostatic hypertrophy on stable tamsulosin therapy for >4 weeks were given vardenafil or placebo (Table 4).\(^44\) Small decreases in BP were observed, and the number of potentially clinically significant decreases in SBP was similar between vardenafil and placebo (1 versus 0). Of note, the study described in Timing of Administration did not specify the duration of tamsulosin therapy before vardenafil coadministration.

**Dose of \(\alpha\)-Blocker**

Forty-five men were given tadalafil (5 mg) or placebo for 28 days, and beginning on day 8, increasing doses of doxazosin (1, 2, and 4 mg/d) were administered.\(^40\) The total number of subjects experiencing a potentially clinically significant decrease in SBP or diastolic BP increased on the first day that doxazosin 4 mg was administered (9 of 39 with tadalafil and 7 of 40 with placebo) but decreased by the seventh day of doxazosin 4 mg coadministration (1 of 39 with tadalafil and 2 of 40 with placebo). Therefore, coadministration of doxazosin with long-term tadalafil appeared to have similar effects on BP as placebo; increasing the dose of doxazosin increased the incidence of potentially clinically significant decreases in BP on the first day of the 4 mg dose.

Collectively, these studies indicate that combining PDE5Is with \(\alpha\)-blockers increases the risk of a clinically significant decrease in BP. This risk is reduced with tadalafil, with uroselective \(\alpha\)-blockers, when low doses of \(\alpha\)-blockers are used, when dosing is separated by several hours (instead of simultaneously), and when patients are on stable therapy with 1 agent before the other drug class is administered.\(^42\) Consequently, for patients prescribed \(\alpha\)-blockers, current Food and
Drug Administration labeling states that PDE5Is are recommended only once a blocker-therapy has become stable. Once stability is achieved with an α-blocker, a PDE5I can be initiated at a low dose (Table 2). When starting α-blocker therapy for patients already optimized on a PDE5I, physicians should begin with the lowest α-blocker dose. Thereafter, increasing the dose of either the α-blocker or PDE5I may further lower BP.

Table 4. Interactions Between PDE5Is and α-Blockers

<table>
<thead>
<tr>
<th>Source and Study Design</th>
<th>n</th>
<th>Drug Doses</th>
<th>Change in BP, mm Hg*</th>
<th>Incidence of Hypotension† (Drug vs Placebo)</th>
<th>High- or Low-Risk Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td></td>
<td>Sildenafil 25 mg, doxazosin 4/8 mg</td>
<td>-7/-6</td>
<td>5 vs 3</td>
<td>Not uroselective</td>
</tr>
<tr>
<td>Bayer</td>
<td></td>
<td>Vardenafil 10/20 mg, terazosin 10 mg</td>
<td>-14/-23/-7</td>
<td>19 vs NR</td>
<td>Simultaneous administration,§ not uroselective</td>
</tr>
<tr>
<td>Kloner et al43</td>
<td></td>
<td>Tadalafil 20 mg, doxazosin 8 mg</td>
<td>-10/-5</td>
<td>5 vs 2</td>
<td>Not uroselective</td>
</tr>
<tr>
<td>Giuliano et al41</td>
<td></td>
<td>Tadalafil 20 mg, alfuzosin 10 mg</td>
<td>-4/-4</td>
<td>1 vs 0</td>
<td>Uroselective, tadalafil</td>
</tr>
<tr>
<td>Auerback et al44</td>
<td></td>
<td>Vardenafil 10 mg, tamsulosin 0.4 mg</td>
<td>-2/-5</td>
<td>2 vs 2</td>
<td>&gt;7 d of uroselective α-blocker therapy</td>
</tr>
<tr>
<td>Guillaume et al45</td>
<td></td>
<td>Tadalafil 5 mg, tamsulosin 0.4 mg</td>
<td>+1/NR</td>
<td>0 vs 1</td>
<td>Tadalafil, uroselective</td>
</tr>
</tbody>
</table>

2B indicates double-blind; random, randomized; —, decrease; +, increase; and NR, not reported.
*Placebo subtracted mean maximum change in blood pressure.
†Incidence of standing SBP <85 mm Hg or a decrease in standing SBP >30 mm Hg.
§One additional subject withdrew after experiencing hypotension with sildenafil and never received placebo.
More frequent when given simultaneously than when separated by 6 hours.
Results on the day that doxazosin 4 mg was given; tadalafil has a greater effect on diastolic BP than sildenafil; when diastolic parameters are included, the number of affected subjects was 9 versus 7.

Drugs for PHT and PDE5Is

Because sildenafil and tadalafil have been approved for PHT therapy and their use in combination therapy has been endorsed for certain World Health Organization class IV patients, coadministration with other PHT agents warrants investigation. Administering sildenafil to patients with PHT already taking epoprostenol, iloprost, nitric oxide, or bosentan further improves an array of hemodynamic, clinical status, and exercise capacity parameters with little or no effect on systemic BP and without increasing adverse events or hypotension. Moreover, sildenafil prolonged the effect of inhaled nitric oxide on pulmonary vasodilatation and prevented rebound pulmonary vasoconstriction after inhaled nitric oxide. Coadministration of epoprostenol reduced plasma concentrations of sildenafil by ~25%, but this interaction was not considered clinically relevant.5

Bosentan, a P450 3A4 inducer, reduced tadalafil exposure by 42%, whereas bosentan levels were unchanged. Coadministration of bosentan and sildenafil reduced sildenafil exposure by 63% and increased bosentan exposure by 1.5-fold. Coadministration with sildenafil does not increase the risk of liver aminotransferase elevation associated with bosentan. A study of 405 patients with PHT (53% also receiving background bosentan therapy) showed that tadalafil improved 6-minute walk distance, time to clinical worsening, and the incidence of clinical worsening. Interestingly, the increase in 6-minute walk distance was significant in bosentan-naive patients (44 m; P<0.01) but not for patients on background bosentan (23 m; P=0.09). The greater improvement for bosentan-naive patients may support the ceiling phenomenon hypothesis that limits additional improvements in patients on background PHT therapy or may reflect the decrease in plasma concentration of PDE5I observed with bosentan coadministration. Additional studies are underway to guide combination therapy.
In subjects given very high doses (sildenafil 800 mg), the types of adverse events were the same, but the incidences and severities of adverse events were increased. Moreover, compared with the doses used for ED, the higher doses used for PHT increased the incidences of adverse events. For example, the incidence of headache with PHT doses (sildenafil, 46%; tadalafil, 42%) was higher compared with ED doses (sildenafil, 16%; tadalafil, 11%). Co-administration with 3A4 inhibitors would likely further increase the incidences of adverse events.

There is little direct evidence on the drug interactions of nitrates and α-blockers with the higher PHT doses of PDE5Is. The higher doses increase the plasma concentrations and prolong the elimination time of sildenafil. Consequently, the contraindication with nitrates may extend beyond the previously discussed time frames derived from studies using ED doses. Conversely, combination therapy with PDE5Is and systemic nitrates could be therapeutic if the synergistic effect on cGMP and vasodilation remains relatively selective for the pulmonary vasculature as observed with PDE5Is alone.

The α-blocker data are inconclusive. In studies using different ED doses of PDE5Is with α-blockers, greater reductions in mean BP parameters and more frequent, potentially clinically significant decreases in BP were observed with higher doses, but many reports were inconclusive, and greater effects were reported with lower doses in some studies.

PDE5Is and Risk of Bleeding

The use of PDE5Is has not been evaluated in patients with bleeding disorders, with active peptic ulceration, or on multiple blood-thinning and antiplatelet agents. PDE5Is may affect bleeding by a direct action on platelets, which contain PDE5. The product inserts report that PDE5Is, alone or with aspirin, did not affect bleeding time. Berkels and colleagues reported that sildenafil 100 mg transiently prolonged bleeding time 1 hour after administration and that sildenafil 50 mg did not alter bleeding time. Compared with placebo, sildenafil increased the incidence of epistaxis in patients on concomitant vitamin K antagonists (9% versus 2%) and in patients with PHT secondary to connective tissue disease (13% versus 2%) but not in patients with primary PHT (3% versus 2%). The incidence of epistaxis in PHT clinical trials was higher with sildenafil than with placebo and minimally higher with tadalafil compared with placebo. Epistaxis has been associated with on-demand use of sildenafil and tadalafil for enhanced sexual activity. Sildenafil inhibits ADP-dependent platelet aggregation in vitro, with an additive effect when combined with nitrates. Sildenafil combined with heparin had an additive effect on bleeding time in rabbits but has not been studied in humans. Theoretically, dipyridamole, ticlopidine, and clopidogrel may interact with PDE5Is, although no studies have been conducted to evaluate a potential interaction. In conclusion, PDE5Is appear to minimally increase the risk of minor bleeding especially when combined with vitamin K antagonists or nitrates.

Miscellaneous

Unlike other β-blockers, rather than impair sexual activity, nebivolol improves erectile function. Nebivolol decreases plasma sildenafil concentration by ~20%. Co-administration with sildenafil does not potentiate the vasodilatory effect of nebivolol, and the product insert for nebivolol indicates that the effect of the drug combination on pulse and BP is additive.

The tadalafil label cautions against ≥5 U alcohol (1 U is ~1 oz of 80-proof liquor). Orthostatic hypotension was observed in patients given tadalafil and 6 U alcohol but not with 4 U. Sildenafil and vardenafil do not carry this warning. Tadalafil 100 mg increased the QT interval 2.8 ms relative to placebo (not statistically significant), which was significantly less than the active control (ibutilide) and is <5 ms, which is believed to be without significant risk.

Tadalafil and sildenafil do not carry a warning relative to the QT interval, whereas vardenafil has a precaution against co-administration with other drugs that increase the QT interval, including fluoroquinolones and class 1A (quinidine, procainamide) and class III (amiodarone, sotalol) antiarrhythmic agents. Sildenafil and vardenafil reportedly did not increase absolute QT, and each minimally increased corrected QT (by 4 to 8 ms).

The clinical implications of this small effect are unknown, and no cases of torsade de pointes are known to date.

Patient Education

Because of the potential for life-threatening hypotension, patients should be counseled appropriately on the drug interactions of PDE5Is. Patients should be warned to avoid all nitrates, including recreationally inhaled poppers and nitroglycerin from friends or family. Patients should be cautioned appropriately on α-blockers, cimetidine (which can be obtained over the counter), and grapefruit juice. If patients develop chest pain while on PDE5Is, it is crucial for them to divulge the use of PDE5Is to their healthcare providers. Patients should be instructed to contact emergency services if they experience severe dizziness, headache, or syncope that may be related to PDE5Is, and they should inform healthcare workers of their most recent PDE5I intake so that appropriate care can be given. Patients should not share PDE5Is with friends, family, or the “black market.”

Conclusions

PDE5Is are commonly prescribed and have benefited millions of men with ED and increasing numbers of patients with PHT. Although PDE5Is are safe with most antihypertensive agents, co-administration with nitrates or α-blockers poses a risk of severe hypotension. Nitrates are contraindicated within 24 hours of sildenafil and vardenafil and within 48 hours of tadalafil. Only after patients are on stable α-blocker therapy should PDE5Is be initiated, starting with a low dose. Metabolic interactions with bosentan may call for dose adjustments when combination therapy is used. Potent cytochrome P450 3A4 inhibitors, including erythromycin, clarithromycin, ketoconazole, itraconazole, and HIV protease inhibitors, increase PDE5I plasma concentrations. PDE5I drug interactions have the potential to cause life-threatening
hypotension in patients with coexisting cardiac disease requiring nitrates or α blockers. Knowledge of these potential drug interactions is needed to avoid severe side effects.

Disclosures

Dr Kloner has served as a speaker and consultant to Pfizer and Lilly. Dr Schwartz reports no conflicts.

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