REVIEW ARTICLE

The use of phosphodiesterase 5 inhibitors with concomitant medications

G. Corona[1,2], E. Razzoli[3], G. Forti[1], and M. Maggi[1]

[1]Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence; [2]Endocrinology Unit, Maggiore-Bellaria Hospital, Bologna; [3]Eli Lilly Italia, Medical Division, Sesto Fiorentino, Florence, Italy

ABSTRACT. The phosphodiesterase-5 inhibitors (PDE5i) sildenafil, vardenafil, and tadalafil are considered first-line therapy for the treatment of patients with erectile dysfunction (ED). In addition to the classical pro-erectile-effect, clinical findings have suggested that they can also influence vascular tone in pulmonary, coronary and other vascular tissues, as well as improving symptoms associated with benign prostatic hyperplasia. Therefore, considering the hypothetical widespread application of PDE5i, the potential for drug-drug interactions emerges as a relevant factor in determining the safety profile of PDE5i. Review of relevant literature was conducted using data sources from MEDLINE (1998, to June 2007). The use of nitrates remains the only contraindication for all 3 PDE5i. Vardenafil is also not recommended in patients taking type 1A (such as quinidine, or procainamide) or type 3 antiarrhythmics (such as sotalol, or amiodarone) while no other major limitations have been reported for tadalafil and sildenafil. In contrast to previously reported labeling, recent studies have suggested only a precaution, but not contraindication with the concomitant use of α-blockers agents. In addition, precaution is also suggested in the presence of potent CYP3A inhibitors, such as azole antifungals, antiretroviral protease inhibitors, or macrolid antibiotics. This is because sildenafil, vardenafil, and tadalafil are metabolized mainly via the CYP3A4 pathway. On the other hand, statins and testosterone seem to have synergic effects with PDE5i on sexual activity.
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INTRODUCTION

Erectile dysfunction (ED), previously defined as impotence, is the "inability of the male to attain or maintain an erection sufficient for satisfactory sexual intercourse" (1). ED affects millions of men worldwide with implications that go far beyond sexual activity alone. In fact, ED often negatively impacts in couple relationship and social life, besides the obvious reproductive and psychological consequences, such as loss of self-esteem and depression. In the meanwhile, psychological, organic, and relational determinants often simultaneously concur in causing ED (2-4). Treating ED is therefore not an easy task. However, the landscape of ED treatment was definitively revolutionized by the recent introduction in the market of phosphodiesterase 5 inhibitors (PDE5i). Phosphodiesterase-5 (PDE5) is a critical component of the nitric oxide cyclic GMP (NO-cGMP) signaling pathway, responsible, within the penis, for smooth muscle tone relaxation (5). Inhibition of PDE5, with the amplification of the NO-cGMP signaling is responsible for smooth muscle relaxation within the penile vasculature and for pro-erectile effects (5).

According to the European Association of Urology guidelines, the PDE5i sildenafil, vardenafil, and tadalafil are considered first-line therapy in the treatment of patients with ED (6). They have been shown to improve erectile function in several clinical trials and in different ED patient subsets, including those with a more severe ED, such as in the presence of diabetes mellitus or after radical prostatectomy (6, 7). These trials have also largely dispelled doubt about the safety and tolerability of PDE5i. Despite initial reports suggesting a higher prevalence of myocardial infarction and sudden death in men who had taken sildenafil (8), the post-marketing data on sildenafil, vardenafil, and tadalafil did not confirm these suspicions (6, 7, 9). In particular, both double blind and open-label studies did not provide evidence of an increased risk in the occurrence of myocardial infarction, stroke or any other serious cardiovascular adversity in subjects taking PDE5i (9). The commonest adverse side effects include headache, flushing, and rhinitis, consistent with the vasodilatatory proprieties of PDE5i (6, 7). In addition to the effects of NO-cGMP signaling pathway on cavernosal smooth muscle, clinical findings have suggested that this signaling transduction mechanism can also influence the vascular tone in the pulmonary, coronary, and other vascular tissues (7, 10). Accordingly, sildenafil has been recently approved for the treatment of idiopathic pulmonary hypertension (11) and several reports have suggested that PDE5i may improve arterial function [see (7) for review]. Moreover, the improvement of lower urinary tract symptoms associated with benign prostatic hyperplasia as well as an increase of the ejaculatory latency in patients with premature ejaculation have been documented (7).

Therefore, considering the hypothetical widespread application of PDE5i, the potential for drug-drug interactions emerges as a relevant factor in determining the safety profile of PDE5i.

The aim of the present article is to increase awareness of differences that could help clinicians in selecting appropriate PDE5i for long treatment of their patients. To do

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Correspondence: M. Maggi, MD, PhD, Andrology Unit, Department of Clinical Physiopathology, Viale Pieraccini 6, 50139 Florence, Italy.

E-mail: m.maggi@dfc.unifi.it

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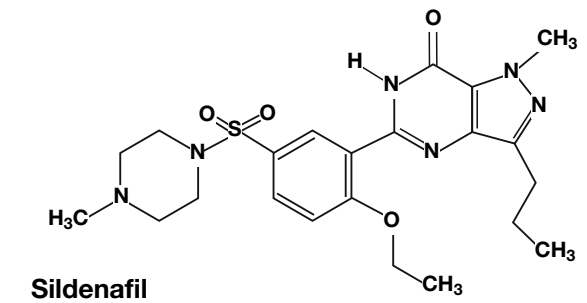
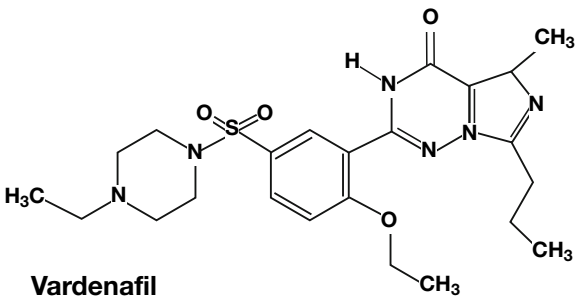
so, a MEDLINE search was conducted on PDE5i between 1998 and 2007, for interpretation and critical analysis of the available clinical data.

CLINICAL PHARMACOLOGY OF PDE5I

Absorption

Sildenafil and vardenafil are very similar in their chemical structure, whereas tadalafil, with its methildione structure, differs markedly (Fig. 1). These chemical characteristics reflect the clinical pharmacokinetics of PDE5i (Table 1).
All 3 PDE5i are rapidly absorbed after oral administration, with peak concentration reached slightly earlier for vardenafil when compared to sildenafil and tadalafil. Sildenafil and vardenafil have only a limited oral bioactivity (about 40 and 15% respectively), because of extensive presystemic metabolism in the gut wall and liver via CYP3A4 and/or CYP3A5 pathways (12-16). Although the absolute oral bioavailability of tadalafil has not been reported, at least 36% of the dose is absorbed from an oral solution (17) [see (14-16) for review]. The mean T_{max} (time to reach the blood maximal drug concentration) is similar for sildenafil 50 mg and 100 mg (1 and 1.2 h, respectively) (18). Conversely, T_{max} is slightly longer for vardenafil 10 mg than for vardenafil 20 mg (about 0.9 and 0.7 h respectively) (18, 19). Considering tadalafil, a mean T_{max} of 2 h has been reported (18). Tadalafil has the greatest mean half life (17.5 h) when compared with sildenafil (3.8 h) and vardenafil (3.9 h) [see (14-16) for review]. The longer duration of action for tadalafil has been interpreted as advantageous by providing the option for more spontaneous sexual activity (20).
Each PDE5i demonstrated an onset of effectiveness within 30 min after a single dose; however, fewer than 50% of men had at least one erection adequate enough to complete successful intercourse despite multiple attempts (18). This would suggest advising patients to take PDE5i medications about 1 h before sexual activity (18). A high fat meal (about 910 Kcal, 57% of which from fat) had no significant effect on the rate and extent of absorption of tadalafil (21, 22), but decreased the rate of absorption for sildenafil (23) and vardenafil (24), possibly affecting the onset of effectiveness.





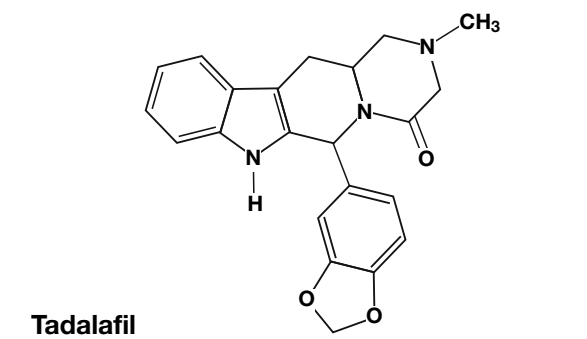


Fig. 1 - *Chemical structure of sildenafil, vardenafil, and tadalafil.*

Metabolism and elimination

Sildenafil, vardenafil, and tadalafil are metabolized mainly via the CYP3A4 pathway (Table 1). Moreover, CYP2C9, CYP2C19, and CYP2D6 contribute to sildenafil metabolism while CYP2C9 is also involved in vardenafil metabolism (12, 13, 17) [see (14-16) for review]. Both sildenafil and vardenafil have active metabolites, contributing to 20% and 7%, respectively, of the total pharmacological effects of the drugs (12, 13) [see (14-16) for review]. Conversely, no clinically active metabolites have been reported for tadalafil (17).
All 3 PDE5i are predominantly excreted as metabolites in stool (about 88%, 95%, and 61% respectively, for sildenafil, vardenafil and tadalafil) (12, 13) [see (14-16) for review].

DRUG INTERACTION

Table 2 summarizes a list of PDE5i-drug interactions potentially requiring dose adjustment. Both pharmacodynamic (i.e. at their site of action) and pharmacokinetic (i.e. absorption, distribution, metabolism, and excretion) interactions have been described. The following section is focused on available data concerning the interaction between PDE5i and the main class of drugs used in clinical practice.

Cardiovascular agents

Nitrates

Webb et al. (25), in a double blind placebo-controlled study, first described the negative interaction between sildenafil and sublingual nitroglycerin in healthy volunteers. After taking sublingual nitroglycerin, systolic blood pressure (SBP) decreased by about 20 mmHg in the sildenafil group *vs* 7 mmHg in the placebo group. Similar results were thereafter observed for tadalafil (26) and vardenafil (27). The reason derives from the PDE5i-dependent reduction in the breakdown of cGMP, induced by organic nitrates. This results in a marked increase of cGMP, leading to a concomitant decrease in blood pressure. Based on these studies, according to the Second

Table 1 - *Pharmacokinetics of the different principal phosphodiesterase 5 (PDE5) inhibitors.*

	Sildenafil	Vardenafil	Tadalafil
Available doses (mg)	25, 50, 100	5, 10, 20	10, 20
Pharmacokinetic proprieties			
Oral bioavailability	40%	15%	36%
t_{max}, min	60	60	120
C_{max}, µg/l (fasting)	560 (100 mg)	20.9 (20 mg)	378 (20 mg)
Food effect (high-fat-meal)	t_{max}, increased 1 h	t_{max}, increased 1 h	ns
AUC µg x h/l	1685 (100 mg)	74.5 (20 mg)	8066 (20 mg)
t 1/2 (h)	3-5	4	17.5
Renal excretion %	<1	1	<0.3
CYP isoenzymes	3A4 (79%), 2C9 (20%), 2C19 and 2D6 (<2%)	3A4 (major) 3A5 and 2C9 (minor)	3A4
Active metabolites	N-desmethyl sildenafil (50% potency, 20% activity contributing)	N-desmethyl vardenafil (28% potency, 7% activity contributing)	None

AUC: area under plasma concentration time curve.

Princeton Consensus Guidelines (28), all the 3 PDE5i are contraindicated in patients taking organic nitrates (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, amyl nitrate, or nitrate). The past use of nitrates (>2 weeks) is not considered a contraindication (28). Conversely, during a period ≥24 h for short acting PDE5i (sildenafil and vardenafil) and up to 48 h for long acting (tadalafil), taking nitroglycerin is not recommended (28). Finally, it should be emphasized that amyl nitrate is contained in "poppers", a recreational substance often used by young people. This suggests the importance of correct information concerning the use of PDE5i even in young subjects.

Antihypertensive agents

A significant activity of PDE5 was demonstrated in arterial and venous smooth muscle cells (29, 30). Therefore, vasodilating effects of PDE5i should be considered especially in hypertensive men, who are taking antihypertensive drugs. Studies performed in healthy volunteers, showed that sildenafil is only associated with a mild decrease in blood pressure [10 mmHg in SBP and 7 mmHg in diastolic blood pressure (DBP)] (31). Similar studies in healthy volunteers indicate that vardenafil reduces SBP by 7-8 mmHg (13) and tadalafil by 0.2-4.6 mmHg in healthy volunteers (32). However, according to the guidelines of the Second Princeton Consensus Panel (28) caution must be taken in the presence of medical conditions characterized by hypotension at baseline, such as left ventricular outflow obstruction or aortic stenosis, congestive heart failure *etc.* As a general rule, a baseline blood pressure of more than 90/60 mmHg is a prerequisite for a PDE5i to be administered (28, 33).

In hypertensive patients, the combination of PDE5i with β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics demonstrated only small and well-tolerated effects on BP, with no increase in adverse cardiovascular or other side effects (32-36) [see (37) for review]. On the other hand, in these conditions PDE5i maintained efficacy in treating hypertensive subjects with ED (32-36) [see (37) for review]. Alpha-blocker agents represent an exception, within the list of antihypertensive drugs. Doxazosin (non-selective α-antagonist) is the most common α-blocker used for hypertension. Terazosin (a non-selective agent) can also be used, along with tamsulosin (selective α-1a inhibitor) and both drugs could also be used for treating benign prostatic hypertrophy. In general, this class of drugs is used as third-line agents for hypertension, especially after the results of the National Institutes of Health-sponsored Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (38), showing an increase in incidences of heart failure when compared with chlorthalidone. The potential negative interaction between PDE5i and α-blocker has been recognized since the first Princeton Consensus Panel Guidelines (39). In an unpublished study, sildenafil (50 and 100 mg) has been shown to increase the hypotensive effect of doxazosin (4 mg) within 1 to 4 h of dosing (40). Conversely, no changes were observed with the lowest dosage (25 mg). According to the prescribing information, sildenafil at doses >25 mmHg should not be administered within 4 h after a patient takes an α-blocker (40). The concomitant administration of vardenafil (10 and 20 mg) with terazosin (10 mg) and tamsulosin (0.4 mg) in healthy subjects resulted in some individuals experiencing hypotension (SBP<85mmHg from 12.5 to 75% of cases) (41). Furthermore, vardenafil (20 mg) plus tamsulosin (0.4 mg), even separated by 6 h, resulted in 4% of healthy subjects having SBP<85 mmHg. According to these observations, the labeling for vardenafil initially stated that vardenafil was absolutely contraindicated with α-blockers. However, recent studies, performed in patients who were taking an α-blocker for a prolonged time, demonstrated that vardenafil 5, 10, and 20 mg is associated only with small incremental mean maximal reduction in SBP (about 4-6 mmHg) (42, 43). According to these recent observations, the labeling for vardenafil and α-blockers was changed from a contraindication to a precaution. However, vardenafil should not be administered within 6 h after a patient takes an α-blocker (summary of prescribing information vardenafil). Conversely, no limitations have been reported with the concomitant use of tamsulosin.

Finally, considering the interaction between tadalafil and α-blockers, initial studies demonstrated that the number of subjects with standing SBP<85 mmHg was greater af-

ter doxazosin 8 mg plus tadalafil 20 mg (28%), *vs* doxazosin plus placebo (6%) (44). Conversely, no difference was observed when tadalafil 10 and 20 mg was co-administered with tamsulosin 0.4 mg (44). More recently, Giuliano et al. (45), in a randomized double blind placebo-controlled study, demonstrated that tadalafil 20 mg showed no clinically relevant emodynamic interactions with alfuzosin 10 mg daily. In light of these studies, the labeling for tadalafil initially stated that it was contraindicated in patients taking α-blockers except for one-daily tamsulosin 0.4 mg. However, as occurred for vardenafil in April 2005, the labeling was modified to that of a precaution rather than a contraindication (28). No timing limitations have been reported (summary of prescribing information tadalafil).

In conclusion, according to the new labeling, α-blockers are no longer considered a contraindication for any of PDE5i, but precaution in the use of these drugs is still recommended. Patients should be stabilized on their α-blocker before prescribing PDE5i. In this case PDE5i

Table 2 - *Principal phosphodiesterase 5 inhibitor (PDE5i)-drug interaction and current labeling.*

Class of drugs	Type of interaction	Clinical effects	Current labeling
		CARDIOVASCULAR AGENTS	
Nitrates: Nitroglycerin Isosorbide dinitrate Isosorbide mononitrate Amyl nitrate "popper" Nitrate	PDE5i-dependent reduction in the breakdown of cGMP induced by organic nitrates leading to a marked increase of cGMP signaling	Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP<85 mmHg)	• Contraindications for all PDE5i • Past use (>2 weeks) not considered a contraindication • A period ≥24 h for short-acting PDE5i (sildenafil and vardenafil) and up to 48 h for long-acting (tadalafil) recommended against taking nitrates
Antihypertensive agents:	Possible increase of hypotensive effects	Synergic decrease in blood pressure leading to possible individual experiencing hypotension (SBP<85 mmHg)	
• α-blocker agents Doxazosin Tamsulosin Alfuzosin Terazosin Carvediol (mixed α-blocker) Labetol (mixed α-blockers)			• Precautions for all PDE5i • PDE5i should be initiated at the lowest recommended dose • Patients already taking an optimal dose of PDE5i the α-blocker should be initiated at the lowest dose
• other antihypertensives Selective β-blockers Calcium antagonists Angiotensin-concerting enzyme inhibitors Angiotensin receptor blockers Diuretics			• None
Antiarrhythmics: Quinidine Procainamide Sotalol Amiodarone	QT interval prolongation	Torsade de pointes and ventricular tachycardia	• Contraindication for vardenafil • No limitation for sildenafil and tadalafil
Anticoagulant agents: Warfarin	Substrate of CYP2C9 metabolism	Possible increase in prothrombin time and increased risk of bleeding events	• None for all PDE5i (no significant clinically interactions)
Anti-platelet aggregating agents	Sildenafil increases inhibitory effects of nitric oxide donors on ADP-dependent platelet aggregation	Possible increase in bleeding time and increased risk of bleeding events	• Precaution, in particular for sildenafil, for the high risk cardiovascular patient, commonly on multiple anti-thrombotic regimens or on warfarin
Statins:	• Increase the expression of eNOS • Activation of the serine/threonine kinase Akt which in turn, phosphorilates eNOS • Inhibition of the RhoA/RhoA-kinase pathway	Possible improvement of PDE5i outcomes	• None

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ORAL HYPOGLYCEMIC AGENTS			
Hypoglycemic drugs: Sulfonylureas Benzoic acid derivates	Not reported	Not reported	• None
Antihyperglycemic drugs: Biguanides α-Glucosidase inhibitors Thiazolidinediones	Not reported	Not reported	• None
ANTIDEPRESSANTS			
SSRI: Fluvoxamine Fluoxetine	CYP3A4 inhibitors	Increase of systemic exposure	• Precaution: starting dose of sildenafil 25 mg is suggested for patients on fluvoxamine therapy • No specific studies have been performed for tadalafil and vardenafil but similar precautions should be advised • No specific studies have been reported for fluoxetine
Citalopram Escitalopram Paroxetine Sertraline Venlafaxine	No significant effects on CYP3A4	None	• None
MAOi	Possible additive hypotensive effects	Possible individual experiencing hypotension	• Precaution for all PDE5i
ANTIEPILEPTICS			
Phenobarbital Phenytoin Carbamazepin	CYP3A4 inducers	Reduction of systemic exposure	• Potentially required higher dose of PDE5i
CHEMOTHERAPICS			
Macrolid antibiotics Erythromycin Clarithromycin Troleanddomycin	CYP3A4 inhibitors	Increase of systemic exposure	• Sildenafil: precaution and dose reduction • Vardenafil: precaution, not to exceed a single 2.5-5-mg dose of vardenafil in a 24-h period • Tadalafil: precaution not to exceed a single 10-mg dose, and should not be taken more than once for 72-h period
Azithromycin	Not involved in CYP3A4	None	• None
Rifampin	CYP3A4 inducer	Reduction of systemic exposure	• Precaution: potentially required higher dose of PDE5i
Azole antifungals Ketoconazole Itraconazole Fluconazole Voriconazole	CYP3A4 inhibitors	Increase of systemic exposure	• Sildenafil: precaution and dose reduction • Vardenafil: precaution, not to exceed a single 2.5-5-mg dose of vardenafil in a 24-h period • Tadalafil: precaution not to exceed a single 10-mg dose, and should not be taken more than once for 72-h period
Antiretroviral protease inhibitors Ritinovar Saquinovar Tipranavir Indinavir	CYP3A4 inhibitors	Increase of systemic exposure	• Sildenafil: precaution not to exceeded a single dose of 25 mg of sildenafil in 48-h period • Vardenafil: precaution, not to exceed a single2.5-5-mg dose of vardenafil in a 24-h period
Fosamprenavir			• Tadalafil: precaution not to exceed a single 10-mg dose, and should not be taken more than once for 72- h period
H_2 INHIBITOR/ANTIACID AGENTS			
H_2 inhibitors: Cimetidine	Non specific CYP inhibitor	Increase of systemic exposure	• Precaution: potentially required lower dose of PDE5i
Ranitidine	Not involved in CYP metabolism	None	• None

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Antacids Aluminum hydroxide/magnesium hydroxide	Reduction of the tadalafil absorption by 30% No effect on vardenafil and sildenafil absorption	Reduction of systemic exposure	• Precaution: potentially required higher dose of tadalafil
TESTOSTERONE			
Testosterone	Up-regulation of NOS activity Regulation of cGMP degradation and PDE5 expression	Improvement of PDE5i outcomes in hypogonadal patients	• None

SBP: systolic blood pressure; eNOS: endothelial nitric oxide synthase; SSRI: selective serotonin reuptake inhibitor; MAOi: monoamine oxidase inhibitor; cGMP: cylcic GMP.

should be initiated at the lowest recommended dose. On the other hand, for patients already taking an optimal dose of a PDE5i, the α-blocker should be initiated at the lowest dose (37). Finally, it should be emphasized that it is prudent to exert similar precautions in prescribing PDE5i to patients on mixed α-blockers, including carvediol and labetol, until more data become available (28).

Antiarrhythmics

QT electrocardiographic interval is a surrogate for prolongation of ventricular repolarization and may result in changes in cardiac contractility and ultimately *torsade de pointes* and ventricular tachycardia. Different studies published so far, using both sildenafil and tadalafil, have not demonstrated a significant alteration in QT interval prolongation (6, 7, 9). Conversely, a slightly greater impact on QT interval has been reported for vardenafil (46). According to Second Princeton Consensus Guidelines (28) vardenafil is not recommended in patients taking type 1A antiarrhythmics (such as quinidine or procainamide) or type 3 antiarrhythmics (such as sotalol, or amiodarone). In addition to Class 1A and 3 antiarrhythmics, there are other drugs, which have been established to have a causal association with QT prolongation (Table 3). The co-administration of these agents with vardenafil warrants caution. No limitations have been introduced for tadalafil and sildenafil.

Anti-platelet aggregating/anticoagulant agents

In platelet, PDE3 and PDE5 activity are significant and initial studies demonstrated that sildenafil increases inhibitory effects of nitric oxide donors on adenosine diphosphate-dependent platelet aggregation (47). This observation was thereafter confirmed by Halcox et al. (48). Conversely, *in vivo* interaction studies indicate no significant effect of PDE5i and the CYP2C9 substrate warfarin (15).

The studies published so far, together with current guidelines (28), have not reported an increased risk of clinically relevant bleeding events after PDE5i (15, 28). However, for the high-risk cardiovascular patient, commonly on multiple anti-thrombotic regiments or on warfarin for systemic anticoagulation, potential effects of reduced platelet aggregation under the influence of PDE5i should be considered. Furthermore, there is no safety information on the administration of sildenafil to patients with coagulophaties or active peptic ulcer diseases.

Statins

With the exception of pravastatin, which is transformed enzymatically in the liver cytosol, all statins undergo extensive microsomal metabolism by the CYP isoenzyme system (49). About half of statins currently available in the clinical practice (lovastatin, sinvastatin, and atorvastatin) are biotranformed primarily by the CYP3A4 system (49). Fluvastatin is primarily metabolized by the CYP2C9 enzyme and rosuvastatin has only some minor interaction with the CYP2C9 enzyme (49). The pharmacokinetics of lovastatin remained unalterated by the coadministration of tadalafil (10-20 mg), suggesting that tadalafil does not produce clinically significant changes in the clearance of drugs metabolized by CYP3A (50). On the other hand, interestingly, *in vitro* studies have shown that atorvastatin improves the sildenafil-induced vasodilatation of aortic rings through nitric oxide-mediated mechanism (51). Accordingly, Herrmann et al. (52) recently demonstrated that atorvastatin could improve the sildenafil response in men with moderate-to-severe ED, initially not respondent to the treatment.

Table 3 - *Drugs potentially involved in QT electrocardiographic interval prolungation.*

Astemizole
Arsenic trioxide
Bepridil
Cisapride
Chloroquine
Clarithromycin
Droperidrol
Erythromycin
Halofantrine
Haloperidol
Levomethadyl
Metadone
Pentamidine
Chloropromazine
Mesoridazine
Thioridazine
Pimozide
Probucol
Terfenadine

Statins are a class of drugs involved in the inhibition of cholesterol synthesis in the liver by blocking the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonate, the rate-limiting step in the cholesterol synthesis (53). Besides this classical propriety, several other functions have been attributed to this class of drugs. In particular, statins can increase the expression of endothelial nitric oxide synthase (eNOS) by endothelial cells (54). Furthermore, they demonstrated an increase of NO bioavailability through activation of the serine/threonine kinase Akt which in turn, phosphorilates eNOS (55). Finally, statins inhibit the RhoA/RhoA-kinase pathway involved in the contraction of vascular smooth muscle (56), including the penile bed (57). All the aforementioned specific mechanisms could contribute to the reported statin-improved-PDE5i outcomes.

Oral hypoglycemic agents

Current treatment options for diabetes mellitus can be subdivided into hypoglycemic drugs (sulfonylureas and benzoic acid derivates) and anti-hyperglycemic drugs (biguanides, α-glucosidase inhibitors, and thiazolidinediones). No pharmacokinetic interactions have been observed between vardenafil and glyburide, and no other specific studies are available at the moment. However, all 3 PDE5i have been extensively used to treat diabetes mellitus induced-ED. Recently, Vardi et al. (58) in a meta-analysis of double-blind, placebo-controlled studies showed that PDE5i are safe and significantly improved ED in diabetic men.

Antidepressants

Antidepressants have demonstrated numerous negative effects on male sexual function including hypoactive sexual desire, erection difficulties, and orgasm problems (59-63). Fluvoxamine is a known inhibitor of both CYP3A4 and CYP2C9. In healthy subjects who received fluvoxamine for 10 days the Area Under plasma concentration time Curve (AUC) of a single 50 mg dose of sildenafil was increased by 40% (64). A starting dose of sildenafil 25 mg is suggested for patients on fluvoxamine therapy. Although no specific studies have been performed, similar interaction should be suspected for tadalafil and vardenafil, since they are also metabolized by CYP3A4. Fluoxetine is another CYP3A4 inhibitor, which may reduce the clearance of PDE5i. However, no interaction studies have been performed. Other selective serotonin reuptake inhibitors such as citalopram, escitalopram, paroxetine, sertraline, and venlafaxine have no significant effects on CYP3A4 and are not likely to affect PDE5i pharmacokinetics.

Possible negative interactions with PDE5i should be taken into account in combination with monoamine oxidase inhibitors, due to additional hypotensive effects. However, these interactions were judged not to be clinically relevant or warrant dose adjustments. Rudkin et al. (65) recently demonstrated, in a meta-analysis of 50 randomized studies including 904 patients who had developed sexual dysfunction whilst taking antidepressants, that the treatment with PDE5i was efficient and safe. Furthermore, Segraves et al. (66), in a retrospective, pooled analysis of 19-double-blind, placebo controlled trials identified 205 men with ED receiving antidepressants and tadalafil 10-20 mg or placebo, demonstrated that tadalafil was well tolerated and significantly improved ED.

Antiepileptics

Phenobarbital, phenytoin, and carbamazepin are all potent inducers of CYP3A4, reducing the plasma concentration of tadalafil (14-16). Similar interaction should be supposed for sildenafil and vardenafil (14-16).

Chemotherapics

Different chemotherapic agents are strong inhibitors of CYP3A (the main metabolic pathway of all PDE5i). The co-administration of these agents with PDE5i requires caution due to a possible increase of systemic exposure. Erythromycin, a macrolid antibiotic, has little effect on sildenafil pharmacokinetic (increases AUC 2.8-fold but has no effects on terminal half life), probably due to CYP2C9 pathway compensation (see above) (14-16). Conversely, the labeling recommends not exceeding a single 2.5-5-mg dose of vardenafil in a 24-h period when used in combination with erythromycin. Accordingly, the labeling information for tadalafil indicates that it should be co-administered only with caution with erythromycin and clarithromycin (14-16). In particular, tadalafil treatment should not exceed a single 10-mg dose, and should not be taken more than once in 72 h, in patients taking potent CYP3A inhibitors (14-16). Azithromycin is another macrolid antibiotic not involved in CYP3A pathway and could be used safely in patients using PDE5i (14-16).

Ketoconazole (200 mg one daily) determined a 4-fold increase in vardenafil AUC when co-administered with vardenafil 5 mg in healthy subjects (14-16). The labeling recommends not exceeding a 2.5-mg or 5-mg dose of vardenafil when used in combination with ketoconazole (200 mg or 400 mg one daily, respectively) (15). Similar precaution should be taken into account for sildenafil and tadalafil (see above) and for the concomitant use of itraconazole and fluconazole (14, 15).

Antiretroviral protease inhibitors (ritonavir, saquinovar, tipranavir, indinavir) are all strong inhibitors of CYP3A-mediated metabolism. They can increase systemic exposure (AUC) of PDE5i-by 2 to 16-fold. The labeling recommends not exceeding a single dose of 25 mg of sildenafil in a 48-h period in patients with ritonavir therapy (14, 15). Similar precaution should be taken into account for vardenafil and tadalafil and for the concomitant use of other antiretrovirals (see above) (14, 15). Notably, ritonavir and indinavir, as inhibitors of CYP3A4 and CYP2C-mediated metabolism, have the greatest effect on vardenafil AUC (14, 15). Conversely, the effect on sildenafil is less pronounced when other compensatory elimination pathways are available (14, 15).

Rifampin is an antibiotic particularly useful for the treatment of tuberculosis showing a strong inducer activity on CYP3A4. The potential interaction has been clinically verified only for tadalafil (the coadministration increases tadalafil AUC by 88%). However, it is expected to reduce the systemic exposure for all PDE5i (14, 15).

Antacid/H_2 inhibitor agents

Single doses of antacids, such as aluminum hydroxide or magnesium hydroxide, did not affect the bioavailability of

sildenafil and vardenafil, while a 30% reduction of the tadalafil absorption has been reported (15).
Cimetidine (H_2 antagonist) is a non-specific CYP inhibitor that could determine an increase of PDE5i-systemic exposure potentially requiring a dose adjustment (15). Conversely, no interaction should be assumed with ranitidine, not involved in CYP metabolism (15).

Testosterone

Although PDE5i are generally considered the first-line therapy for ED, 25-50% of patients do not satisfactorily respond to them (67). Recent studies demonstrated that unrecognized hypogonadism represents an important cause in the PDE5i unsuccessful outcomes. Aversa et al. (68) first demonstrated, in a prospective, placebo-controlled trial, that in 20 sildenafil-unresponsive ED patients sildenafil responsiveness was restored and penile blood flow ameliorated by correcting an underlying hypogonadism (total T=12.8±2.1 nmol/l) with transdermal testosterone (T). This finding was later on confirmed by other authors in a randomised, double blind, placebo-controlled, multicenter study involving 75 mild hypogonadal (total T =10 nmol/l) patients (69). In that study and in a subsequent analysis (70), it was demonstrated that T administration, for 3 months, significantly improved sildenafil effect and orgasmic function. Similar findings have been reported in other small studies (71, 72) [see also (73) for review]. Interestingly, Yassin et al. (74) recently extended previous observations with sildenafil to tadalafil. In a open-label retrospective trial they demonstrated that T gel (50 mg/daily) was able to improve the responsiveness to tadalafil (up to 65%) in a consecutive series of 69 hypogonadal men (total T<12 nmol/l), non-responders to tadalafil monotherapy. The role of androgens in the regulation of NO formation is well known (4, 75-77). In particular it has been demonstrated that T, or its metabolite dihydrotestosterone (DHT), up-regulates NOS activity, acting through an increased expression of the neuronal (nNOS) or endothelial (eNOS) isoforms (4, 75-77). Moreover, a trophic effect of T on penile architecture (increase of trabecular smooth muscle and loss of connective tissue fibers) has been demonstrated in different animal species (78) and in men with ED (79). In addition, it has also been shown that T is involved in the maturation of penile tissue composition by promoting the commitment of pluripotent stem cells into the myogenic lineage and inhibiting their differentiation in adipogenic lineage (80-82). Hence, androgens play an important role not only in the formation of the main relaxing factor, cGMP, by regulating NOS activity, but also in the integrity of erectile apparatus. This could explain at least partially the T-dependent improvement of the PDE5i outcomes in hypogonadal subjects. Morelli et al. (30) recently demonstrated that androgens are also important for the regulation of cGMP degradation, by increasing PDE5 expression and activity [see also (83)]. This line of evidence suggests that PDE5i do not work if the target enzyme (PDE5) is lacking, explaining the necessity to overcome androgen deficiency to obtain full responsiveness. Although more dedicated clinical trials are needed, the studies published so far clearly indicate that detecting and appropriately treating hypogonadism in patients with ED are mandatory to have full responsiveness to PDE5i, and that hypogonadism should be carefully ruled-out before considering a patient as PDE5i-resistant and planning more invasive forms of therapy.

CONCLUSIONS

The prevalence of ED increases as a function of age. ED in the elderly is complicated by the higher chance of a coexistence of other comorbidity and chronic diseases. Elderly subjects tend to take nearly 3 times as many drugs as younger patients, receiving over 10 prescribed drugs per year (84). Physicians should be alert in this class of patients, as well as in the younger ones, that several medicaments and even non-medical product (see grapefruit) can interact with PDE5i metabolism, absorption or mechanism of action. In this review we summarize these interactions. Overall, the 3 PDE5i have been demonstrated to be safe enough. The use of nitrates remains the main contraindication for all 3. Moreover, vardenafil is also not recommended in patients taking type 1A or type 3 antiarrhythmics, while no other major limitations have been reported for tadalafil and sildenafil. Otherwise, precaution but not contraindication is suggested with the concomitant use of α-blockers agents and in the presence of potent CYP3A inhibitors, such as azole antifungals, antiretroviral protease inhibitors, or macrolid antibiotics. Conversely, statins and testosterone (only in hypogonadal subjects) seem to have a synergic effect on the PDE5i outcomes.

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