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Interactions between drugs for erectile dysfunction and drugs for cardiovascular disease

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The association of erectile dysfunction (ED) and cardiovascular disease is well-documented in the literature and both conditions share risk factors. Therefore, it is difficult to distinguish the effect of underlying disease and adverse effects of the drugs and/or interactions between ED drugs and drugs implemented for cardiovascular disease. The known interactions of systemic administered drugs for ED with drugs for cardiovascular disease are mainly pharmacodynamic. Thus, nitrates enhance the production of cyclic GMP and combined with phosphodiesterase type-5 inhibitors this can lead to severe hypotension. The same is the case for the treatment with phentolamine in patients treated with β-adrenoceptor antagonists. Due to increased partial thromboplastin time, the risk of bleeding is enhanced for intracavernous alprostadil injection in heparin-treated patients. Pharmacokinetic interactions of clinical importance have been described for ED drugs with other therapeutic groups such as sildenafil with the antifungal drug, ketoconazole, and apomorphine with the antiparkinson drug, entacapon. Although sildenafil and antihypertensive dihydropyridines like amlodipine are metabolized by the same cytochrome P450 enzyme, CYP3A4 in the liver, the combination of these drugs does not exhibit a synergistic blood pressure lowering action. Unfortunately documentation concerning drug interactions is often poor and occasional.
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Introduction

Male erectile dysfunction (ED) is defined as the inability to attain or maintain penile erection sufficient for satisfactory sexual performance. The prevalence was $>50\%$ in self-reported community-based respondents sampled between the ages of 40 and 70 y.[1,2] The prevalence of complete ED increases with age from 5% at 40 to 15% at 70 y.[1] The incidence rate for ED is 26 cases per 1000 man years indicating it is an important public health problem[3]

Alterations in the flow of blood to and from the penis are thought to be the most frequent causes of male ED. Therefore, erectile dysfunction can be considered to be another manifestation of vascular disease. ED is frequent in patients with other signs of atherosclerotic disease such as ischaemic heart disease and arterial leg disease,[1,4,5] and ED and cardiovascular disease share the same risk factors such as hypertension, diabetes mellitus, dyslipidemia and smoking.[1–3] The presence of several risk factors increases the risk of heart disease[6] and ED.[7,8] Moreover, low penile brachial pressure index was found to be associated with major vascular events such as myocardial infarction and cerebrovascular accidents,[9] ED is related to the presence of intermittent claudication[10] Therefore, patients seeking health care for ischaemic heart disease will often have or develop ED and doctors should be aware of general cardiovascular disease in patients with ED.

The fact that the prevalence of ED in patients with cardiovascular disease is higher than in the general population also implies that patients, in addition to treatment for ED, are also treated for both heart disease, hypertension, diabetes, and/or dyslipidemia. This increases the risk that drug treatments for ED can affect cardiovascular function and treatments for cardiovascular disease can lead to ED. Adverse effects and drug interactions accounts for approximately one-third of the cases referred to a department of internal medicine[11] and the same numbers are probably true for patients presenting with ED. The present review will focus on the effects of drugs for cardiovascular disease on erectile function and make special emphasis on the interactions of drugs for treatment of ED with drugs for treatment of heart disease.

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Drugs for cardiovascular disease and erectile dysfunction

The impact of cardiovascular drugs on erectile function is established in some cases, but in many others the evidence is anecdotal and based on case reports. Rather than improving erectile function most of these studies suggest that treatment of cardiovascular disease worsens erectile function. Thus, in epidemiological studies the relative risk for ED in hypertension and heart disease was increased, respectively, from 1.13 and 1.54 in untreated to 1.52 and 1.96 in treated patients.[3] However, these figures do not allow to distinguish whether the patients have ED due to underlying generalized vascular disease or if erectile function deteriorates as a consequence of treatment with drugs for cardiovascular disease.

Pharmacological treatment of hypertension and erectile function

Thiazide diuretics, beta-adrenoceptor antagonists, calcium channel blockers, ACE inhibitors, and angiotensin II receptor antagonists are considered as first-line drugs for treatment of hypertension (Table 1).[12] The goal of antihypertensive treatment, in addition to lowering blood pressure, is to reduce the risk of cardiovascular events. There is little trial-based evidence to indicate which of the hypertensive drugs are more likely to cause ED.

It is generally thought that diuretics have a negative impact on erectile function. ED was reported to contribute to the non-compliance with antihypertensive treatment with thiazides,[13] and in men given bendrofluazide there was an excess of complaint of ED.[14] In a study of mild hypertension a significant association between men with ED and treatment with either hydrochlorthiazide or chlorthalidone therapy was also found.[15,16] In contrast, others have found no discernable effect of thiazide diuretics on sexual function.[17–19] It is difficult to evaluate whether the dose of thiazide diuretic applied for the treatment of hypertension in these studies plays a role for the frequency of ED, but patients in the study by Chang and colleagues[15] were treated with 50 mg/day of hydrochlorthiazide or chlorthalidone which is above the 12.5–25 mg/day dose recommended for the treatment of hypertension today.[20] In the treatment of mild hypertension study (TOMHS) the patients were

Table 1 Drugs for cardiovascular disease and for erectile dysfunction

Treatment of hypertension	*Treatment of heart disease*	*Treatment of erectile dysfunction*
Reduction of cardiac output	Diuretics:	*Peroral administration*
Thiazide diuretics:	Thiazides	Dopaminergic agonists:
Hydrochlorthiazide	Loop (furosemide, bumetanide, etc)	Apomorphine SL
Bendroflumethiazide	K^+ sparing (spironolactone, amiloride)	
General β-adrenoceptor antagonist:	Vasodilators:	General α-adrenoceptor antagonists:
Propranolol	ACE inhibitor	Phentolamine
	AT_1-receptor antagonists	
	Hydralazine/nitrate	
Selective β_1-adrenoceptor antagonists:	Inotropics:	α_2-adrenoceptor antagonists:
Metoprolol, atenolol etc	Digoxin	Yohimbine
General β- and α-adrenoceptor antagonist:	Antithrombotics:	Phosphodiesterase type-5 inhibitors:
Labetalol, carvedilol	Aspirin	Sildenafil
	Clopidogrel	Vardenafil
		Taladafil
Reduction of peripheral resistance	Antiarrhythmics:	*Intracavernous administration*
Calcium channel blockers:	Amiodaron	Prostaglandin analogues:
Nifedipine, amlodipine, etc	Lidokain	PGE_1
Verapamil		
ACE inhibitors:	Anticoagulants:	Combination therapy:
Captopril, enalapril, etc	Heparin	Trimix (PGE_1, phentolamine, papaverine)
	Warfarin	Vasoactive intestinal peptide and phentolamine
AT_1 receptor antagonists:	Hypolipidemic drugs:	
Losartan, valsartan, etc	Fibrates (clofibrate, gemfibrozyl, etc)	
	Statins (simvastatin, pravastatin, etc)	
α-Adrenoceptor antagonists		
Prazosin, doxazosin, etc		

Monotherapy is first applied for hypertension, but patients are often treated with combinations of two to three drugs. In case of heart disease such as chronic heart failure patients are often treated with multiple drugs (ie one or two from each group). Combination therapy has been applied for intracavernous treatment of erectile dysfunction and is also emerging in case of combining two peroral drugs such as apomorphine and sildenafil.

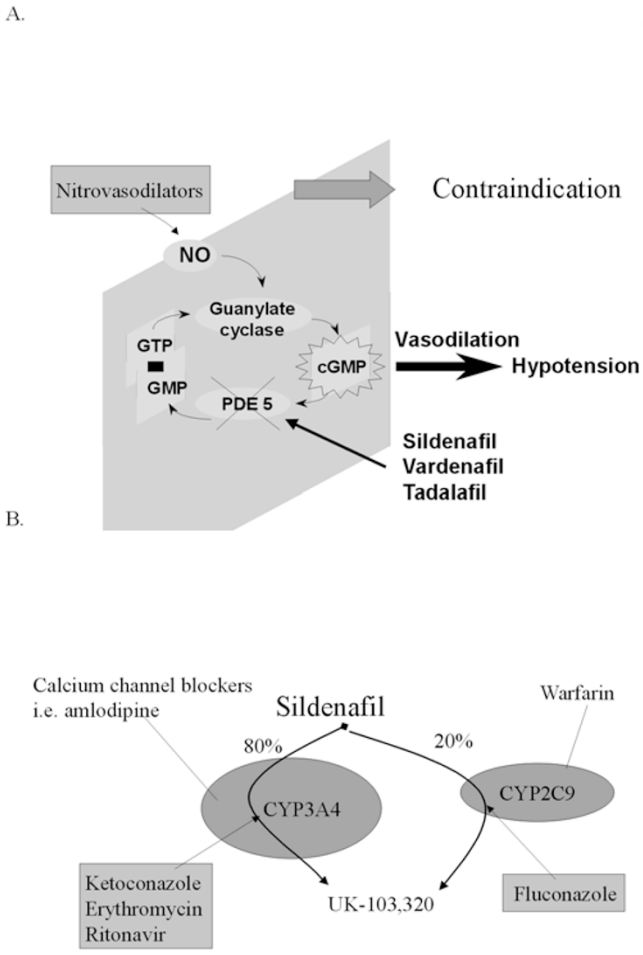

Figure 1 Pharmacodynamic and pharmacokinetic interactions of phosphodiesterase type-5 inhibitors. (A) The clinically most important interaction is for the phosphodiesterase type-5 inhibitors with nitrates. (B) The pharmacokinetic interactions with drugs which are able to inhibit the conversion of sildenafil to its principal circulating metabolite, UK-103,320.

treated with 15 mg/day of chlorthalidone,[16] but the frequency of ED was 18% which is comparable to the frequency of 14% in hypertensive men treated with thiazide diuretics in the study by Chang and colleagues.[15] In contrast, the dose of hydrochlorthiazide was only 6.5 or 25 mg/day in the trial studies where frequency of self-reported ED was 1.5%[18] and hence less than observed by Chang *et al*.[15] Therefore, there is at present no clear association between diuretic treatment and ED, but due to an eventual effect on sexual function high doses of thiazides should be avoided in sexually active males.

Incidence rate of erection problems were different for chlorthalidone at 24 months compared to placebo treated hypertensive patients, but were similar to the placebo group at a 48-month follow-up.[16] The lack of additional worsening in erectile function with time in a patient population treated with thiazide diuretics points toward an early effect, and also suggest that fear of ED as an adverse effect of thiazide treatment should not lead to a change in the antihypertensive medication.

The β-adrenoceptor antagonists applied for the treatment have a different pharmacodynamic profile as some of them are selective for β_1-adrenoceptors such as metoprolol, atenolol, and acebutolol, general β-adrenoceptor antagonists like propranolol, and others which block both β-and α-adrenoceptors such as carvedilol and labetalol. In erectile tissue β_2-adrenoceptors are expressed, and although the role of β-adrenoceptors in erectile function is not clarified, they probably mediate vasodilation in response to the increase in adrenaline during erection.[21–23] In patients treated with the general β-adrenoceptor antagonist, propranolol, ED occurred more frequently than in patients taking placebo[24] and was a significant reason for withdrawal from treatment.[14] Moreover, sexual dysfunction was increased from baseline on a 24-week follow-up in patients treated with propranolol.[25] In contrast, antagonists selective for β_1-adrenoceptors

such as acebutolol and bisaprolol do not appear to increase the frequency of ED compared with untreated patients.[16,18,26] Therefore, there seems to be a relation to antagonism of β_2-adrenoceptors by β-adrenoceptor antagonists and ED.

Erection problems in hypertensive patients treated with calcium channel blockers such as amlodipine appear to be similar to placebo-treated patients,[18] and with a less deteriorating effect on male erectile function compared with propranolol.[27] Although calcium channel blockers can affect ejaculation,[28] they have little impact on erectile function.

Angiotensin converting enzyme inhibitors such as enalapril did not affect erectile function in hypertensive patients compared with placebo-treated patients.[16] However, compared with patients treated with propranolol, enalapril, had a favorable effect,[25] and in cross-over studies where either the ACE-inhibitor, lisinopril, or the angiotensin II receptor antagonist, valsartan, were compared to β-adrenoceptor antagonist, the number of sexual intercourses were higher in the groups of patients treated with lisinopril and valsartan.[29,30] These results so far suggest that ACE inhibitors and angiotensin II receptor antagonists are not associated with ED. Whether these drugs have a favourable effect on erectile function similar to α_1-adrenoceptor antagonists such as doxazosin and moxisylyte,[16,31,32] awaits studies properly designed for evaluation of their impact on sexual function.

In most cases, the mechanisms underlying ED associated with antihypertensive drugs are unknown.[33] However, animal studies provide us with some understanding of the pathophysiology. Decreased erectile function has been observed in cholesterol-fed rabbits,[34] diabetic[35] and hypertensive[36] rats and can be ascribed to impaired vasodilation and hence reduced blood flow to penis. Thus, in animal models the arterial risk factors of hypertension, diabetes, dyslipidemia, and ageing reduce both the neurogenic and endothelium-dependent relaxation in the corpus cavernosum[37–39] and penile arteries.[36] Structural changes of the penile vasculature or erectile tissue also contribute to the reduced vasodilation, since proximal atherosclerotic lesions lead to reduced increases in intracavernous pressure after infusion of papaverine,[34] while lumen narrowing in the arteries feeding the penis is an explanation for increased penile vascular resistance and less increase in intracavernous pressure in spontaneously hypertensive rats (SHR).[40,41] In the case of stenotic atherosclerotic lesions in the arteries supplying penis, the blood flow to the penis is mainly determined by the systolic pressure. Lowering of the blood pressure by any kind of antihypertensive treatment would lead to reduced systolic blood pressure and divert blood away from the penis, and could hence result in decreased blood flow and ED. In the case of increased penile vascular resistance the mechanisms of blood pressure lowering of the different groups of antihypertensive drugs probably play a role. Thus, the blood pressure lowering effect achieved with thiazide diuretics and β-adrenoceptor antagonists can mainly be ascribed to a lowering of cardiac output, while calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, and α-adrenoceptor antagonists lower blood pressure mainly through reduction of peripheral vascular resistance. The latter groups of antihypertensive drugs, in addition to the systemic vasodilator effect, will also lower penile vascular resistance and that will probably compensate for the lowering of systemic blood pressure and result in unaltered penile blood flow during erection, unless there is a proximal stenosis. Apart from functional lowering of penile vascular resistance by inhibition of the angiotensin II pathway, recent evidence has suggested that treatment of SHR rats with inhibitors of angiotensin converting enzyme, in contrast to a vasodilator of the systemic vasculature, hydralazine, also result in reversal of structural changes both in the systemic arteries and the penile resistance vasculature.[42] There is a lack of studies addressing how antihypertensive drugs affect erectile function in diseased animals, and the above-mentioned suggestions need to be properly examined. An understanding of the mechanisms leading to ED in treated hypertensive patients will increase compliance and lessen the devastating effects of this arterial risk factor on heart and erectile function.

Treatment of heart disease and erectile dysfunction

An array of drugs are applied for the treatment of heart disease. In most cases a multiple drug regimen is applied for conditions such as chronic heart failure, where patients are treated with diuretics for removal of surplus liquid, ACE inhibitors and/or AT_1 receptor antagonists to cause peripheral vasodilation, digoxin as positive inotropic agent, antithrombotics, antiarrhythmics, anticoagulants, and hypolipidemic drugs (Table 1).[43] In addition, the aldosteron receptor antagonist, spironolactone, and β-adrenoceptor antagonists such as metoprolol, bisaprolol, and carvedilol were recently found to enhance survival in patients suffering from heart failure.[44–46] Nitrates relieve pain, but they have not been shown to prolong survival in chronic heart failure unless they are taken in combination with the peripheral vasodilator, hydralazine.[47] Evidence regarding the effect on erectile function of most of these drugs is sparse.

Digoxin is indicated for treatment of atrial fibrillation and heart failure in functional stage III–IV according to the New York Heart Association (NYHA). However, digoxin has no life prolonging

effect in patients with chronic heart failure, although it reduces the need for hospitalization.[48] In therapeutic concentrations (0.5–0.7 ng/ml) digoxin inhibits erectile function measured by visual sexual stimulation and by nocturnal penile tumescence in healthy volunteers.[49] The mechanism can probably by ascribed to the reported inhibitory effect of digitalis glycosides on NO-evoked vasodilation in isolated penile arteries[50] and corpus cavernosum strips.[51] In addition, a relation of digoxin to low plasma testosterone levels and decrease in sexual desire has been found.[52] Therefore, in the case of ED in patients treated with digoxin, they should consult a cardiologist to evaluate whether treatment with digoxin is necessary.

Lipid-lowering therapy in hyperlipidemic patients with either fibrates[53,54] and statins[55,56] yield substantial health benefits such as diminished coronary events and deaths. High levels of total plasma cholesterol and low levels of high density lipoprotein are associated with an increased prevalence of ED.[1,57] However, ED was reported to be a frequent side-effect of treatment of hyperlipidaemic subjects using clofibrate[58] or gemfibrozyl.[59] In patients referred to a clinic for primary hyperlipidaemia an increased risk of ED was also observed in patients treated with one of four fibrate derivatives (fenofibrate, ciprofibrate, bezafibrate and gemfibrozyl).[60] The mechanisms by which fibrates lower lipoprotein levels remain unclear, but they interact with peroxisome proliferator-activated receptors (PPARs),[61] which regulates gene transcription. In the liver activation of PPARα by clofibrate and gemfibrozyl stimulates liver microsomal esterification of estradiol and testosterone.[62] Further studies must show whether the latter mechanism of action is an explanation for the increased prevalence of ED reported in patients treated with fibrates.

In patients with hyperlipidemia and treated with statins such as simvastatin and pravastatin and referred to a clinic for primary hyperlipidaemia, an increased risk for ED was reported.[60] Moreover, five patients with coronary artery disease developed ED one week after starting treatment with simvastatin, and sexual function was restored after stopping the treatment, but ED recurred when two of the patients were rechallenged.[63] No control patients were included in the latter study. In contrast, others in a cross-over study of 22 men with hypercholesterolemia randomized for placebo, simvastatin, or lovastatin, found an increase in nocturnal tumescence after 2 weeks, although the increase was not significant after 6 weeks treatment.[64] Evaluation of the frequency of ED reported in the Scandinavian simvastatin survival study, where 4444 patients with coronary heart disease were randomized to treatment with simvastatin or placebo for up to 6 y, ED was found in 28 placebo-treated patients with eight resolved cases, while ED was present in 37 simvastatin-treated patients with 14 resolved cases.[65] Therefore, in patients treated with statins an underlying diseased vasculature rather than the drug appears to be the cause of ED.

The information regarding the effects of anticoagulants on erectile function is sparse. There are several case-reports suggesting heparin therapy is associated with priapism,[66] and in a review of 121 cases of priapism, four of the patients were in treatment with heparin.[67] The prognosis for preservation of potency after treatment for priapism asssociated with heparin treatment is poor compared with the overall average with preserved erectile function in patients who have experienced priapism.[67] Treatment with the coumarin derivative, warfarin, was suggested to be associated with an increased risk of ED in elderly men, but in this study only a few patients were actually treated with warfarin.[68] Therefore, although information regarding anticoagulants and erectile function is lacking, these drugs do not appear to impose a major risk for ED.

In summary, diuretics which lower cardiac output seem to be associated with worsening in erectile/sexual function, although it needs to be established whether this is a dose-related adverse effect. General β-adrenoceptor antagonists which also block β_2-adrenoceptors seem to be associated with ED, while this is less clear for selective β-adrenoceptor antagonists. There is evidence suggesting that α_1-adrenoceptor antagonists improve erectile/sexual dysfunction, but whether ACE inhibitors and AT_1 receptor antagonists have a favourable effect on erectile function awaits studies designed for evaluation of their impact on sexual function. Evidence regarding effect on erectile function of lipid-lowering drugs, anticoagulants, antithrombotics, and antiarrhythmic therapy is sparse and not conclusive.

Interactions between drugs for erectile dysfunction and for cardiovascular disease

There are several treatment options for ED as outlined in Table 1. Although these drugs have different mechanisms of action, all drugs for ED reaching sufficiently high plasma concentrations have in common the potential of inducing systemic hypotension. Therefore, pharmacodynamic interactions enhancing the systemic vasodilator effect or pharmacokinetic interactions leading to accumulation of the drug applied for treatment of ED are of major concern.

Apomorphine and drugs for cardiovascular disease

Apomorphine is an agonist at D_1- and D_2-like receptors and was found to cause erections in

animals and man,[69,70] but nausea was a prevalent side effect when it was administered subcutaneously.[70] However, development of apomorphine in a sublingual formulation reduced side effects such as nausea, vomiting, drowsiness, arterial hypotension, and yawning, and the efficacy of apomorphine for the treatment of ED was maintained.[71,72] Arterial hypotension is probably mediated by vascular D_1 receptors activated by (−)-apomorphine in the racemic apomorphine formulations.[73] A potential interaction between sublingual apomorphine and antihypertensives to consider, is therefore greater orthostatic decreases in systolic blood pressure. However, in patients in treatment with α_1-adrenoceptor antagonists and calcium channel blockers systolic blood pressure was lowered by 10 and 6 mmHg, respectively, *vs* placebo, while there were no changes in blood pressure in patients treated with ACE inhibitors, β-adrenoceptor antagonists, or diuretics.[74] These changes in blood pressure do not appear to be of clinical importance.

One of the significant adverse events occuring in the double-blind studies of sublingual apomorphine was syncope, but the patients recovered rapidly.[75] The authors found the syncopes were preceded by a prodrome including nausea, vomiting, dizziness, sweating, and pallor and suggested the mechanisms of action to be vasovagal.[75] In patients receiving nitrates the prodrome of symptoms was observed in 16% of the patients and Holter monitoring revealed sinus pauses concurrent with the prodrome of symptoms.[74] An explanation for the syncopes can probably be found in animal studies. In dogs apomorphine potentiates vagal bradycardia through D_2 receptors located either on vagal nerve endings leading to enhanced acetylcholine release[76] or on sympathetic ganglia and nerve endings leading to inhibition of norepinephrine release.[77,78] The latter studies of dopaminergic agonists were performed in dogs and apart from nitrates, pharmacodynamic interactions of apomporphine with antiarrhythmics such as digoxin leading to bradycardia should be addressed. However, it should also be stressed that clinical trials performed so far,[74,75] suggest the patients are recovering rapidly from syncopes in relation to apomorphine.

Apomorphine is metabolized mainly by sulphation, glucuronidation and *N*-demethylation to norapomorphine. In addition, it is O-methylated by catechol-o-methyltransferase (COMT) and according to product information from Novartis Pharmaceutical Corporation and Roche Laboratories, apomorphine should not be administered together with inhibitors of COMT such as entacapone and tolcapone applied for the treatment of Parkinsons disease.[79] *In vitro* human hepatic microsomal studies showed apomorphine at supratherapeutic concentrations is able to inhibit several cytochrome P450 enzymes.[80] Clinically relevant pharmacokinetic interactions of apomorphine with cardiovascular drugs have not been reported.

α-Adrenoceptor antagonists and drugs for cardiovascular disease

Phentolamine evokes penile erection by blocking both α_1 and α_2-adrenoceptors in the erectile tissue, and in addition it was recently suggested also to activate NO synthase.[81] In patients with erectile insufficiency oral or buccal phentolamine has shown some success.[82,83] Phentolamine also blocks α_1 and α_2-adrenoceptors in the systemic arterial circulation and therefore, hypotension is the major adverse effect of phentolamine. The hypotensive action of phentolamine is followed by compensatory reflex cardiac stimulation by tachycardia, and the latter response is blunted in patients treated with β-adrenoceptor antagonists. Although more pronounced for α_1-adrenoceptor antagonists such as prazosin and doxazosin,[84] in patients on β-blockers the first dose administration of phentolamine can cause an exaggerated fall in blood pressure, and it is convenient to initiate treatment with lower doses of phentolamine in these patients.

The clinical pharmacology of yohimbine has recently been extensively reviewed.[85] Yohimbine and the isomeric form thereof, rauwolscine, are selective α_2-adrenoceptor antagonists, but they do also act as full agonists at 5-hydroxytryptamine 5-HT_{1A} receptors.[86] Yohimbine as monotherapy for ED possesses only modest efficacy in patients with ED.[87] The mechanisms of action is in part an explanation for the modest effect. In animal studies more selective α_2-adrenoceptor antagonist such as delequamine and atipamezole seem to improve erection,[88] while 5-HT_{1A} agonists such as 8-OH-DPAT and buspirone inhibits penile erection.[89] In contrast to other drugs for ED, yohimbine does not lower blood pressure and is remarkedly free of side effects in the dose range found to be effective for treatment of ED, although in supratherapeutic doses it increases blood pressure, anxiety, and the frequency of urination.[85] However, hypertensive patients are more sensitive to the pressor effects of yohimbine.[85,90] In addition, the spillover of noradrenaline due to yohimbine causing inhibition of prejunctional α_2-adrenoceptors at peripheral sympathetic nerve endings, results in higher noradrenaline plasma concentrations. Increased plasma noradrenaline is a concern in patients with coronary artery disease and congestive heart failure.[90] Therefore, yohimbine should be used with care in patients with cardiovascular disease. Moreover, yohimbine has a monoamine oxidase inhibitory effect and is contraindicated with tricyclic antidepressive and tyramine-containing food, since these combinations result in significant increases in blood pressure.[91]

There is no information concerning interaction of yohimbine with cardiovascular drugs.

Phosphodiesterase type-5 inhibitors and drugs for cardiovascular disease

Sildenafil and other selective phosphodiesterase type-5 inhibitors such as vardenafil and tadalafil by inhibition of type-5 cyclic GMP phosphodiesterase, enhances the duration of action of the increase in GMP elicited by nerve- and endothelium-derived NO released during erection.[92] Sildenafil has clinical efficacy in the treatment of male impotence following oral administration.[93] The most common side effects of sildenafil include headache, flushing, dyspepsia, rhinitis and visual disturbances.[94] The cardiovascular side effects of sildenafil are important because of the frequent presence of underlying cardiac disease in men with ED. Post-marketing surveillance data after approval of sildenafil by the Food and Drug Administration (FDA) revealed a number of cardiovascular events, including myocardial infarction and sudden death from cardiac causes, and although the number of events were not unexpected in the population of men which received sildenafil,[95] some of the cases were even before any attempt of sexual intercourse.[96] However, in a retrospective study the incidence of cardiovascular events were similar in patients receiving placebo compared with men treated with sildenafil,[97] and in men with known severe coronary artery disease, sildenafil (100 mg) produced only small decreases in systemic arterial and pulmonary pressure and had no effect on heart rate or cardiac output.[98] Moreover, sildenafil does not exacerbate myocardial ischaemia in canine models of coronary artery stenosis.[99] Therefore, these studies do not support a worsening of cardiovascular disease in connection with sildenafil treatment for ED.

The clinically most important interaction for phosphodiesterase type-5 inhibitors is with nitrates (Figure 1). Nitrates such as nitroglycerin increases cyclic GMP content in the vascular smooth muscle in systemic arteries,[100] and sildenafil by inhibition of phosphodiesterase type-5 prolongs the duration of action of cyclic GMP and results in large and prolonged decreases in systemic blood pressure in man[101] and decreases coronary blood flow in vessels with critical stenosis in dogs.[102] Therefore, phosphodiesterase type-5 inhibitors such as sildenafil are contraindicated in patients taking nitrates. On the other hand, nitrates should be avoided in patients in treatment with sildenafil for ED, since most of the cardiac deaths attributed to sildenafil can probably be ascribed to concomitant administration of nitrates and sildenafil.[95]

The potential exists for interaction between sildenafil and antihypertensive medication. However, treatment with sildenafil in hypertensive patients receiving diuretics or ACE inhibitors did not result in a change in blood pressure. Sildenafil (25–100 mg) only induced insignificant decreases in blood pressure of 2–5 mmHg in patients treated with α- and β-adrenoceptor antagonists and calcium channel blockers.[103] Therefore, sildenafil does not have clinically significant interactions with current antihypertensive drugs.

In addition to inhibition of phosphodiesterase type-5, sildenafil has been suggested to have other mechanisms of action which could play a role both for the therapeutic effect and adverse effects of sildenafil. Firstly, sildenafil is more selective against phosphodiesterase type-5 than against several other human phosphodiesterases, but only 7.7–16.6-fold greater against human phosphodiesterase type-5 than phosphodisterase type-6.[104] Inhibition of phosphodiesterase type-6 by sildenafil probably explains the dose-related impairment of color (blue/green) discrimination seen with sildenafil.[94] Secondly, in rabbits injected intracavernosally, sildenafil increased the intracavernosal pressure independently of the NO/cyclic GMP pathway.[105] In the latter study the authors did not exclude sildenafil increased intracavernosal pressure by enhancing the vasodilator action of endothelium-derived natriuretic peptide as described for the pulmonary circulation.[106] While inhibition of phosphodiesterase type-6 appears to be linked to visual color disturbances, the second mechanism of action of sildenafil could be of therapeutic relevance, but it has so far not been related to the adverse effects of sildenafil.

Unexpected electrophysiological effects on cardiac repolarization through modulation of K^+ channels might provide an alternative explanation for an increased risk of sudden death. *In vitro* it was reported that high concentrations (1–100 μM) of sildenafil prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current (I_{Kr}),[107] and sildenafil inhibited exitatory neurotransmission through a direct interaction with prejunctional Ca^{2+}-activated K^+ channels in the vas deferens in humans.[108] Moreover, sildenafil was reported to increase the basal cyclic AMP content in cardiac myocytes.[109] Arrhythmias observed in connection with phosphodiesterase 3 inhibitors such as milrinone in patients with congestive heart failure have been attributed to increased cyclic AMP levels which, via protein kinase A, stimulate a slowly activating delayed rectifier potassium current (I_{Ks}).[110] However, a recent study performed by infusing sildenafil and reaching high supratherapeutic plasma concentrations in dogs did not reveal any changes in the cardiac electrocardiogram.[111] Therefore, there is not much evidence to support the fact that

sildenafil has a proarrhythmic effect or should influence the pharmacodynamic effect of antiarrhythmic drugs.

Sildenafil is metabolized by the cytochrome P450 enzymes, CYP3A4 (80%) and CYP2C9 (20%),[112] and coadministration of sildenafil and drugs which inhibit these cytochrome P450 enzymes may lead to increased plasma concentrations of sildenafil (Figure 1). This may in turn, lead to an increase in adverse effects such as visual disturbances and hypotension associated with sildenafil. Inhibitors of CYP3A4 include antifungal drugs such as ketoconazole, macrolide antibiotics such as erythromycin, and the antidepressive drug, norfluoxetin.[113] Inhibition of CYP3A4 impaired sildenafil biotransformation in human liver microsomes, while inhibition of CYP2C9 did not produce detectable inhibition of formation of the sildenafil metabolite, UK-103,320.[112] Coadministration of either erythromycin or indinavir with sildenafil was found to increase plasma concentrations of sildenafil.[114,115] Other drugs are biotransformed by CYP3A4 such as the dihydropyridine class of calcium channel blockers, including nifedipine, amlodipine, and felodipine, and statins such as simvastatin and atorvastatin. However, sildenafil did not change the plasma concentration of the only drug examined in this aspect, amlodipine, and the coadministration of these drugs did not result in hypotension.[116] Therefore, in the case of coadministration of sildenafil with CYP3A4 inhibitors, the magnitude of interaction suggest a lower starting dose of sildenafil such as 25 mg may be appropriate.

Alprostadil and drugs for cardiovascular disease

Intracavernous injection of PGE_1 is an efficacious treatment for ED, but due to the inconvenience of injection, it is considered as second line treatment for this condition. Intracavernosal injection of PGE_1 has a response rate in the range of 40–70% in patients suffering from ED in clinical trials.[117–120] Adverse effects of alprostadil are related to the injection such as pain, hematoma, false injections, and fibrotic changes, while systemic side-effects such as hypotension, even with high doses ($>40\,\mu g$) of PGE_1 are rare.[118,120] This is probably due to the fact that PGE_1 is at least partially metabolized within the cavernous bodies of the penis and, in addition, undergoes rapid first pass clearance in the liver and lung tissue. Due to the rapid metabolization of PGE_1 there are only few relevant interactions with drugs for cardiovascular disease.

In connection with injection therapy of ED in patients receiving anticoagulants, a concern is the risk of bleeding. Concurrent use of infused alprostadil and heparin may result in increased partial prothrombin and thrombin time which increases the risk for bleeding.[79] The mechanism is unknown and the documentation is poor regarding this interaction, but concurrent use of alprostadil and heparin should be avoided. In contrast, vacuum therapy and intracavernous self-injection appeared to be safe in patients receiving warfarin,[121] and there are no pharmacodynamic and pharmacokinetic interactions with acetylsalicylic acid. Although the documentation is poor regarding the interaction of alprostadil and heparin, this drug combination should be avoided, while the adminstration of PGE_1 appears safe in patients treated with peroral anticoagulants and antithrombotics.

In summary all drugs for ED have the potential of inducing hypotension with the exception of yohimbine. The documentation for interactions of drugs for ED with drugs for cardiovascular disease is most extensive for sildenafil. The clinically most important interaction is for the phosphodiesterase type-5 inhibitors with nitrates.

Conclusions

ED is particularly common in patients with heart disease, because of the presence of overlapping arterial risk factors. Therefore, it is difficult to distinguish the effect on erectile function of underlying disease and of the multiple drugs the patient is treated with for cardiovascular disease. Diuretics seem to be associated with worsening in erectile function, although it needs to be established whether this is a dose-related adverse effect. General β-adrenoceptor antagonists which also block β_2-adrenoceptors seem to be associated with ED, while this is less clear for β_1-adrenoceptor selective antagonists. There is evidence suggesting α_1-adrenoceptor antagonists improve erectile/sexual dysfunction, but whether ACE inhibitors and AT_1 receptor antagonists have a favourable effect on erectile function awaits studies designed for evaluation of their impact on sexual function. The effect of other cardiovascular drugs on erectile function is largely unknown. Therefore, in connection with clinical trials with cardiovascular drugs, it is also important to address the effect on erectile function. Moreover, the mechanisms by which cardiovascular drugs affect erectile function will enhance our understanding and help us to choose the therapy with most advantages both with respect to cardiovascular disease and erectile/sexual function. With the exception of yohimbine, drugs for ED have the potential of causing hypotension. Due to the risk of pronounced fatal hypotension, coadministration of phosphodiesterase type-5 inhibitors such as sildenafil and nitrates is contraindicated. The patients with ED and in treatment with several drugs for cardiovascular disease should consult a cardiologist, before treatment with drugs for ED.

Reinforcement of education in adverse drug effects and interactions is necessary both at pre- and postgraduate level to reduce the numbers of cases referred for hospitalization as a consequence of adverse drug effects.

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