Iran J Public Health, Vol. 52, No.5, May 2023, pp.870-879

Review Article

Phosphodiesterase-5 Inhibitors as Therapeutics for Cardiovascular Diseases: A Brief Review

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(Received 10 Dec 2022; accepted 18 Feb 2023)

Abstract

Background: Three selective and most used inhibitors of PDE-5- sildenafil, vardenafil and tadalafil- have been successfully used for the treatment of erectile dysfunction. Erectile dysfunction and cardiovascular diseases might be considered as two dissimilar clinical signs of the identical systemic disease. PDE-5 inhibitors can through different models and mechanisms induce vasodilation, decrease apoptosis and cell proliferation, and they are widely present in various tissues that make them promising targets in a range of cardiovascular diseases.

Methods: PubMed was explored to identify papers published from 1990-2019, presenting data for the most used PDE-5 inhibitors (sildenafil, tadalafil or vardenafil) in treatment of cardiovascular diseases.

Results: This article analyses the therapeutic potentials of PDE-5 inhibitors in cardiovascular diseases and discusses mechanisms, possible risks and limitations. Comparable to earlier studies, newer studies suggest cardioprotective effects of PDE-5 inhibitors, which include different models and mechanisms and do not indicate an increased rate of significant cardiovascular adverse reactions. Dissimilarity in the pharmacokinetics and pharmacodynamics of PDE-5 inhibitors are significant to their risk- benefit profile and clinical use. Some of the studies suggesting infarct size reduction after PDE-5 inhibition described the especially close dose-effect relation, other studies dosage adaptation in drug- drug interactions.

Conclusion: PDE-5 inhibitors indicate the encouraging useful effects by ischemia/reperfusion injury, myocardial infarction, cardiac hypertrophy, cardiomyopathy and systolic and diastolic congestive heart failure. Therefore, this and similar reviews can help for additional clinical targeting in the therapy of cardiovascular diseases.

Keywords: Cardiovascular disease; Cardioprotective effects; Phosphodiesterase-5 inhibitors

Introduction

Phosphodiesterases (PDEs) are metallohydrolases that play the essential role in terminating cyclic nucleotides signaling by causing the hydrolysis of 3', 5' cyclic adenosine monophosphate (cAMP) and/or 3', 5' cyclic guanosine monophosphate (cGMP), thus modulating the duration and intensity of their biological actions and controlling the intracellular concentrations (1,2). They are classified into 11 families (PDE1–PDE11) according to their sequence of homology, biochemical and pharmacological effects, and the distribution differs among dissimilar tissues (2,3). PDE families vary with respect to their primary structures, tissue distribution, and sensitivity to specific inhibitors, subcellular localization and mechanisms of regulation. There are some PDEs specified only for the hydrolysis of cAMP or cGMP, and others have combined specificity. They are building complexes by connecting to a big number of proteins that connect to each other by protein-protein interactions (4).

The most common selective inhibitors of PDE-5- sildenafil, vardenafil and tadalafil have been used for the treatment of erectile dysfunction (ED), and for the treatment of pulmonary hypertension (PH) (sildenafil and tadalafil). Numerous clinical studies have suggested potential use of PDE-5 inhibitors (PDE-5i), including ischemia/reperfusion injury (IRI), cardiomyopathy, myocardial infarction (MI), cardiac hypertrophy, heart failure (HF), stroke, neurodegenerative diseases and other circulatory disorders (5). Because of the similar risk factors, pathophysiologic pathways and potential mechanisms, patients with cardiovascular diseases (CVD) have frequently also ED (6). Therapy of ED after a first MI was related with a lower mortality and the risk was lower among men who had been treated with PDE-5i, which seemed to be dose-dependent (7).

This article reviews the therapeutic potentials of PDE5 inhibitors in different cardiovascular diseases, and discusses mechanisms, possible risks and limitations.

Methods

PubMed was explored to find papers published from 1990-2019 showing relations between 3 most frequent used PDE5i and the CVD. Here are used the following search terms: (phosphodiesterase type 5 inhibitors AND cardiovascular diseases). The search was focused to English language, humans and animals, revealing possible cardioprotective profile of PDE5 inhibitors, considering mechanisms, perspectives, and experimental restrictions of these effects. This article will focus on the 3 most frequent used PDE5i: sildenafil, tadalafil and vardenafil.

Results

Ischemia/Reperfusion Injury and Myocardial Infarction

The myocardial protection from the loss of contractile function among the patients having an acute MI presents a great health challenge. The prognosis depends on it how successful is the reduction of the infarct size (5). IRI is a multifactorial process what leads to severe tissue destruction, represents a paradoxical phenomenon that results in additional destruction, resulting in dysfunction of the organ, and occurs in previously ischemic tissues after the recovery of blood flow (8). The first that the preconditioning-like effect of sildenafil were demonstrated against myocardial IRI in an in vivo rabbit model by opening of mitochondrial K (ATP) channels (9).

Studies in animal MI demonstrated antiarrhythmic effects of PDE-5i (10,11) as well as recovery of postischemic ventricular contractile function (10,12). In IR of isolated rat hearts, sildenafil pretreatment at 0.05 mg/kg resulted in improved ventricular recovery, a reduced incidence of ventricular fibrillation (VF) and decreased MI, through increasing cGMP content in the heart. At higher doses, it caused frequently VF and at

very low without influence on cardiac function (10).

Sildenafil und vardenafil just before reperfusion have the infarct-limiting effect. They protect the ischemic myocardium against IRI through a mechanism dependent on mitochondrial K (ATP) channel opening (13,14). cGMP-dependent protein kinase (PKG) signaling plays a major role in cardioprotection, and its activation with tadalafil when given 30 min to 120 min before coronary occlusion limits MI and maintains left ventricular function through H (2)S signaling (15). Ischemic preconditioning is first described in experimental preparations in which short episodes of IR applied prior to a longer coronary artery occlusion reduce myocardial infarct size, and it have been presented in many experimental studies (16).

Sildenafil-induced cardioprotection is partly mediated by increased cGMP synthesis and PKG activation, which opens myocardial mitochondrial large-conductance Ca^{2+}-sensitive potassium (mBK_{Ca}) channels responsible for myocardial ischemic preconditioning (17).

"Postconditioning" is the adjusted ischemia-reperfusion and represents the rescue of heart tissue applied after a myocardial infarction, through protective interventions with pharmacological stimulus (pharmacological postconditioning) and with repeated short intervals of ischemia (ischemic postconditioning) (18). One further study investigated whether atorvastatin and sildenafil have synergistic effects on myocardial infarct size reduction and increase nitric oxide synthase (NOS) expression. Low-dose atorvastatin in the combination with sildenafil increased the expression of P-eNOS and iNOS and limit MI size, and had a synergistic effect on P-eNOS and iNOS expression and on myocardial protection without leading to serious hypotension or tachycardia (19). Hydrogen sulfide (H_2S) is a gaseous molecule that exerts many physiological actions in the cardiovascular system. Similar to PKG, H_2S seems to protect the heart via opening of mitoK_{ATP} channel (20). PKG activation with tadalafil restricts MI when given 30 min to 120 min before coronary occlusion and preserves left ventricular function through H_2S signaling (15). Sildenafil-induced cardioprotection depends on activating of protein kinase C (PKC) and selective translocation of three PKC isoforms (PKC-α, - θ and –δ) (21).

The pathogenesis of IRI includes activation and infiltration of neutrophils and platelets, excessive production of reactive oxygen species and release of proinflammatory and diverse proapoptotic cytokines (22-25). All these pathways are damaging mitochondrial- and intracellular calcium homeostasis, causing cardiac myocyte necrosis with additionally damage of contractile function (24) and they happen very early after restoration of flow and they are compatible with the fact that most changes related with cell death, occur during the very first minutes of reflow (26). PDE-5i have been shown to protect the heart against IRI (5,13,27).

In recent years, several studies identified the expression and the induction of nitric oxide synthases (28,29 accumulation of cGMP, activation of kinases with promotion of hydrogen sulfide production (15) and opening of mitochondrial K_{ATP} channels as part of the signaling cascade (9). Many reports document the results of animal studies that showed the ability of sildenafil to induce angiogenesis in MI model (9,10,28,30).

Sildenafil being given after early reperfusion has increased the levels of vascular endothelial growth factor (VEGF) and angiopoietin-**1** (Ang-1) mRNA, which leads to neovascularization. Sildenafil at a specific dose can reduce endothelial cell injury after ischemia and reperfusion, stimulates myocardial angiogenesis and angiogenic gene/protein expression and improve left ventricular contractile functional reserve (31). Another study has suggested the importance of the combined therapy with nitric oxide (NO) inhalation and selective PDE5 inhibition using tadalafil by persistent increase in cGMP. This treatment suggests how important that is for useful long-term structural and functional remodeling (32). Guanylate cyclase can be activated through NO and enlarge the formation of cGMP (10,12)

cGMP could activate PKG, and possibly open sarcolemmal (12) and mitochondrial ATP-sensitive K^+ (K_{ATP}) channels (9,10,12). cGMP and opening of mitochondrial K(ATP) channel play a key role in preconditioning of the heart following ischemia/reperfusion (I/R) injury. Sildenafil and vardenafil protect the ischemic myocardium against reperfusion injury through a pathway that depends on mitochondrial K (ATP) channel opening (14).

Cardiomyopathy

By doxorubicin-induced cardiotoxicity, numerous studies with sildenafil have demonstrated protective effects in vivo treatment of mice before the therapy with doxorubicin, in which sildenafil attenuated myocyte apoptosis and reduced left ventricular dysfunction and frequency of a prolonged ST segment. The sildenafil protective effects were abolished by either L-NAME (an inhibitor of NO synthase) or 5-HD (a blocker of mitochondrial K (ATP)) (33).

cGMP binds and activates cGMP-dependent protein kinase, also known as protein kinase G (PKG). One of the targets of PKG Iα is RhoA (34), and this formation activated by doxorubicin limits its interaction, and suppresses classical cGMP-PKG Iα pro-survival signaling, resulting in intensified apoptosis. PDE5 inhibition can protect from doxorubicin-induced injury by elevating cGMP, and as a result, cGMP connecting to PKG Iα reduces oxidant-induced disulfide formation (35).

Coadministration tadalafil with doxorubicin reduced oxidative stress, upgraded antioxidant capacity by upregulation of mitochondrial superoxide dismutase and prevented the depletion of prosurvival proteins including Bcl-2 and GATA-4 (36,37).

Sildenafil seems to be involved in controlling diabetic cardiomyopathy progression through interleukin-8, which is a proinflammatory C-X-C chemokine that plays significant role in inflammation. Sildenafil in diabetic cardiomyopathy seriously reduced Th1 type chemokine CXCL10 level, in blood and in human cardiomyocytes that participates in heart damage initiation and progression (38).

There are evidence that suggest the participation of long non-coding RNAs in cardiovascular illness (39) and the part of long non-coding RNAs in diabetic cardiomyopathy (40).

A bigger expression of the long non-coding RNAs metastasis associated lung adenocarcinoma transcript 1 (MALAT1) has been detected in diabetic cardiomyopathy (41) and Sildenafil can suppress the increase of those levels (42). Recovering the intracellular impact of NO signaling can be possibly relevant to controlling transcription of long non-coding RNAs involved in cardiac injury and in the development of cardiomyopathy related to dysmetabolic conditions including diabetes (42).

Sildenafil being chronic administrated right after permanent occlusion of the left anterior descending coronary artery in mice decreased ischemic cardiomyopathy (43). These cardioprotective effects are mediated by activation of PKG, increased Bcl-2-to-Bax ratio and expression of endothelial and inducible nitric oxide (NO) synthase (eNOS and iNOS, respectively) (27,28,29).

Therapy during three months with 100 mg /day sildenafil in mice with diabetic dilative cardiomyopathy, caused a reduction in circulating monocyte chemoattractant protein (MCP)-1 and tumor growth factor (TGF)-β, without the influence of any other vasodilatory or endothelial effects and as a result improved cardiac geometry and kinetics (44).

Vascular Endothelial Dysfunction

Endothelial dysfunction represents reduction of the bioavailability of vasodilators, particularly NO, and/or an increase in endothelium-derived contracting factors. This lack of balance leads to destruction of endothelium-dependent vasodilation, which is related with many of the ordinary risk factors for CVD and plays a key role in the progress of atherosclerosis and acute coronary syndromes (45, 46).

The endothelial cell dysfunction and cardiac events are well reviewed (47,48), and also the effects of PDE-5i endothelial function have been largely investigated in recent years. The presence of the PDE-5 in the systemic artery endothelium and smooth muscle cells opened a new field of investigations of conditions that affects systemic arteries. Cumulative data from numerous studies with sildenafil have showed partial recovery of endothelial function in experimental models of hypertension and hypertensive subjects. Sildenafil beneficial effects on endothelial and kidney dysfunctions are power to reduce the levels of angiotensin II and increase angiotensin 1-7 and to improve NO bioavailability in angiotensin-dependent hypertension (49).

In a meta-analysis, endothelial dysfunction was the important independent risk factor for MI, stroke, cardiac death, and the need for coronary revascularization (50).

Acute administration of sildenafil 25 and 50 mg increased endothelium-dependent flow-mediated vasodilation in the brachial artery among patients with chronic heart failure (51). Sildenafil was dilated the epicardial coronary arteries, reduced exercise-induced ischemia, improved endothelial dysfunction in the brachial artery, and suppress platelet activation in patients with coronary artery disease (52). In human sildenafil administrated oral cause's powerful protection against IR-induced endothelial dysfunction through opening of K (ATP) channels (53).

In one study, the effects of sildenafil on vascular disturbances were examined in a mouse model of Angiotensin II-induced hypertension, and sildenafil decreased the damaging effects of Angiotensin II on resistance vessels probably through restoring the balance of ROS/NO/eicosanoids (54).

Cardiac Hypertrophy and Heart Failure

Continual cardiac pressure overload induces pathological ventricular remodeling and hypertrophy that can common lead to HF. Blocking the intrinsic catabolism of cGMP with sildenafil reduces chamber and myocyte hypertrophy, and improves in vivo heart function in mice with chronic exposure to the pressure overload induced by transverse aortic constriction. Takimoto et al have showed how multiple signaling pathways activated by the pressure load are being deactivated by sildenafil, such as calcineurin /NFAT, PI3K/Akt and ERK1/2 (55).

In experimental models, cGK1 activity is being stimulated by the PDE5A inhibition to suppress numerous cardiac signaling pathways involved in HF and pathological hypertrophy (56). That refers to blockade of calcineurin/NFAT signaling (55), its activation of regulators of G-protein signaling (RGS2/4) to block Gq-activated cascades (e.g. from angiotensin or endothelin-1) (57), enhanced mitochondrial and consequent cytoprotection against ischemic injury connected to glycogen synthesis kinase 3-β and mitogen activated kinase ERK1/2 (27), improvement of the cGK1 diastolic function by phosphorylating titin to increase distensibility (58), improvement of proteasome degradation of misfolded proteins (59), inhibition of transient receptor potential canonical ion channel - type 6 (Trpc6) (60) and other mechanisms.

The cardioprotection of sildenafil through NO signaling pathway can be used for slowing the ventricular hypertrophy and remodeling as the indicators of HF (29).

Chronic treatment with sildenafil directly following MI attenuated also ischemic cardiomyopathy and reduced apoptosis in the border zone of the infarcted myocardium (61).

Activation of the sympathetic nervous system in patients with HF, particularly the cardiac sympathetic nerves, has been suggested as an isolated predictor of mortality in HF patients (62). In one study among patients with chronic HF, the acute administration of sildenafil as a bolus dose was connected with a moderate reduction in systemic arterial blood pressure and a more valuable reduction in pulmonary arterial pressure, which resulted in a 20% reduction in cardiac noradrenaline spillover (63).

HF with preserved ejection fraction represents a clinical syndrome of HF with LVEF >50% and

frequently has multiple comorbidities, including hypertension, coronary artery disease, atrial fibrillation and diabetes mellitus inducing a systemic proinflammatory state which further induces coronary microvascular endothelial inflammation. It reduces NO bioavailability and PKG activity that leads to hypertrophy development. Stiffness of myocyte and extracellular matrix components of ventricular muscle contribute to high diastolic left ventricular stiffness and HF development (64).

The prognosis of HF with preserved ejection fraction is getting worse with pulmonary hypertension (PH) and right ventricular failure development. Patients had pulmonary artery pressure (PAP) >40 mm Hg (right heart catheterisation and right ventricular systolic dysfunction, and PDE5i largely improved PAP and right ventricular function (65).

Studies with animal models support a cardioprotective effects of PDE5is, as well as improving contractile function in HF with reduced ejection fraction (HFrEF) (29,66) and regressing left ventricular hypertrophy (55,61).

The effects of PDE5i against inflammation und apoptosis have been demonstrated among the studies in animal models of left ventricular dysfunction (67). Sildenafil seriously decreases left ventricular remodeling and has the prophylactic effect by exercise intolerance in rats of chronic mitral regurgitation by reducing perivascular fibrosis, apoptosis and hypertrophy (68).

PDE-5i improve diastolic function in animal models of systolic HF and clinical studies of HFrEF by decreasing hypertrophy, fibrosis and improving chamber compliance. In the hypertensive heart after chronic renin-angiotensin aldosterone system stimulation and angiotension II-induced HF, sildenafil increased diastolic and systolic performance, and reduced left ventricular hypertrophy (67).

PDE5i suppress beta-adrenergic receptor (β-AR) stimulation in left ventricular myocytes via reduced myofilament Ca sensitivity through PKG-phosphorylation of cardiac Troponin I (69).

Sildenafil improves the ability to exercise, in patients with systolic HF with secondary PH, decreases pulmonary arterial pressure contributing to decreased pulmonary vascular resistance (70).

Possible Risks and Caution by Using Pde5

The patients receiving nitrate therapy need to be considered with attention and separately, because PDE-5i increased the hypotensive effects of acute and chronic nitrates (71). PDE-5i and glyceryl nitrate, isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil, and organic nitrates should not be used simultaneously (72).

The therapy of ED should be applied only to patients with low-risk of cardiac events, because sexual activity and treatment of ED may cause cardiac events in patients with preexisting CVD. On the other hand, men with high risk of CVD should receive cardiovascular risk assessment before attempting sexual activity and receiving ED treatment (73).

The early predominating safety concern refers to potential risk of arrhythmia, especially while many cases of unpredicted death have been described with sildenafil in patients predisposed to ischemic cardiac events. The patients that have limited cardiac repolarization reserve can be prone to arrhythmia if treated with medications that prolong ventricular repolarization. Sildenafil at therapeutic concentrations does not prolong cardiac repolarization (74) and do not modify action potential duration or QTc (75).

Even though many studies have not shown a significant distinction in the risk of severe cardiovascular events in patients treated with PDE5 inhibitors and placebo, the risks and benefits need to be valued on an individual basis.

Discussion

The reviewed studies, mostly among studies with animals, suggest cardioprotective effects of PDE-5i with various models and mechanisms. Variations in the pharmacokinetics and pharmacodynamics of PDE-5i are significant to their risk-

benefit profile and medical use. Some of the studies examining the reduction of the infarct size after PDE-5 inhibition described a particularly close dose-effect relation, other studies dosage adaptations in drug- drug interactions and special populations based on the specific demands of the patients. The progress in developing of new PDE-5I with improved selectivity, faster onset of action, increased potency, less side effects and improved tolerability should be the aim. Further researches should probably compare PDE-5i together to determine the patient groups in which the drug would be most effective.

Conclusion

The future carefully designed clinical trials should consequently lead to new applications of PDE-5i and give encouraging results with the perspective of clinical therapeutic strategies to upgrade symptoms and prognosis in CVD.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

No funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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