Clinical and hemodynamic effects of using sildenafil in patients with heart failure due to left ventricular systolic dysfunction

Thesis

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Abstract

Objectives: In randomized cross over design , we compared the efficacy of sildenafil in relatively small doses with placebo in patients with left ventricular systolic dysfunction secondary to dilated or ischemic cardiomyopathy , The primary end point was change in exercise duration time on treadmill using naughton protocol , secondary end points were change in the left ventricular dimensions , left ventricular systolic function and pulmonary artery systolic pressure as assessed by echocardiography .

Background : The goals of heart failure treatment are (1) symptomatic relief of dyspnea and improvement in exercise capacity of the patient, (2) reduction of mortality and adverse outcome .Sildenafil was discovered in 1989 as a selective inhibitor of phosphodisterase enzyme (PDE) -5 which emerged as a safe and effective treatment of erectile dysfunction. It was approved by U.S food and drug administration as oral effective treatment of primary pulmonary hypertension .Many studies had shown sildenafil to be beneficial in treatment of heart failure due to left ventricular systolic dysfunction.

Methods: After initial clinical evaluation, Doppler echocardiography and treadmill exercise test using Naughton protocol, 50 patients with left ventricular systolic dysfunction secondary to dilated or ischemic cardiomyopathy were randomized to placebo or sildenafil at dose of 25 mg twice daily.The evaluation was repeated after 6 weeks .After 2 weeks of wash out period , the patients were crossed over to alternate therapy. Final evaluation was performed after another 6 weeks of treatment.

Results: 50 patients completed the study, in both groups together, the exercise duration time increased from 382.24 sec to 396.06 at the end of placebo stage which is statistically non significant and then increased to 511.58 sec at the end of sildenail stage ((P =0.002).In both groups together the functional capacity increased from 4.34 METS to 4.41 METS at the end of placebo stage which is statistically non significant and then increased to 5.59 METS at the end of sildenail stage ((P =0.000).In both groups together there is no significant difference as regard the the left ventricular dimensions , left ventricular systolic function and pulmonary artery systolic pressure after sildenafil therapy compared with baseline and after placebo measures

Conclusion: Sildenafil in relatively small doses significantly improves exercise duration time and functional capacity in patients with left ventricular systolic dysfunction secondary to dilated or ischemic cardiomyopathy without significant improvement of the left ventricular systolic function regardless of presence of significant pulmonary hypertension.

Key words (Sildenafil, cardiomyopathy, systolic dysfunction, functional capacity, endothelial dysfunction)

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Abbreviations

Abbreviation	Meaning
NO	Nitric oxide
c GMP	cyclic guanosine monophosphate
PDE5	phosphodiesterase type 5
ACE	Angiotensin converting enzyme
FMD	Flow mediated dilatation
PASP	pulmonary artery systolic pressure
SVR	systemic vascular resistance
PCWP	pulmonary capillary wedge pressure
CYP	cytochrome P
PAH	Pulmonary arterial hypertension
ADH	Antidiuretic hormone
TGF-beta	Transforming growth factor beta
EGF	Epidermal growth factor
NYHA	New York heart association
ARB	Angiotensin receptor blocker
PPH	Primary pulmonary hypertension
ED	Erectile dysfunction
IPC	Ischemic preconditioning
PPC	pharmacological preconditioning
K_{ATP} channels	ATP sensitive potassium channels
PKC	protein kinase C
LVEF	Left ventricular ejection fraction
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
HR	Heart rate
FC	Functional capacity
EX	Exercise
LVED	left ventricular end diastolic dimension
LVES	left ventricular end systolic dimension
MR	Mitral regurgitation
1	Measures taken at base line
2	Measures taken atfter sildenafil
3	Measures taken after placebo
RRR	Relative risk reduction

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Introduction

Sildenafil was discovered in 1989 as a selective inhibitor of phosphodisterase enzyme (PDE) -5 which emerged as a safe and effective treatment of erectile dysfunction. It was approved by U.S food and drug administration as oral effective treatment of primary pulmonary hypertension (1).

Sildenafil is a selective inhibitor of phosphodisterase enzyme (PDE) -5 which is abundant in pulmonary vasculature. It catabolizes C. GMP, the second messenger of nitric oxide (NO). Inhibition of phosphodiesterase enzyme was found to lower pulmonary artery systolic pressure in patients with congestive heart failure and pulmonary hypertension (2).

It was found that both use of ACE inhibitors and phosphodiesterase inhibitors improve endothelial function in patients with heart failure. Sixty patients with congestive heart failure were randomized to receive 10 mg ramipril, 50 mg sildenafil and placebo. Flow mediated dilatation (FMD) is measured at 1, 2, 4 hours after drug administration. Ramipril increases (FMD) at 4 hours compared with placebo (2.3%). Sildenafil increases (FMD) at 1, 2, 4 hours compared with placebo (3.9%).Combined sildenafil and ramipril improve (FMD) with additive effects at 4 hours(3).

It was also found that the use of sildenafil in patients with congestive heart failure lowers pulmonary artery systolic pressure (PASP), systemic vascular resistance (SVR), pulmonary capillary wedge pressure (PCWP) and increases cardiac index and cardiac output. Eleven patients with left ventricular systolic dysfunction secondary to ischemic cardiomyopathy or idiopathic dilated cardiomyopathy administered 50 mg sildenafil, inhaled 80 ppm nitric oxide (NO) with the following results: sildenafil decreases (PASP) by 12%,(SVR) by 15% , (PCWP) by 12% and increased cardiac index by 14 %.Combined NO and sildenafil decreases pulmonary vascular resistance by 50 % and systemic vascular resistance by 24% and increased cardiac index by 30 % without change in systemic blood pressure. So use of sildenafil was found to increase cardiac output by balanced pulmonary and systemic vasodilatation in addition it augments and prolongs the homodynamic effects of nitric oxide in patients with congestive heart failure (4).

Use of sildenafil was found to protect against apoptosis of cardiac myocytes and left ventricular systolic dysfunction.

A study done on male ICR mice randomized to one of four medications: saline, sildenafil, doxorubicin, (saline and

doxorubicin). Doxorubicin causes significant increase in apoptosis while prophylactic use of sildenafil prevented apoptosis and left ventricular dysfunction (5).

Aim of the work

To study the added clinical and hemodynamic effects of using sildenafil in patients with heart failure due to left ventricular systolic dysfunction recieving conventional anti failure treatment including angiotensin converting enzyme inhibitors.

Pharmacology of Sildenafil

Sildenafil was initially studied for use in hypertension and angina pectoris. The first clinical trials were conducted in Morriston Hospital in Swansea (6). Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina, but that it could induce marked penile erection (7) (8). Therefore, it was decided to market it for erectile dysfunction, rather than for angina. The drug was patented in 1996, approved for use in erectile dysfunction by the Food and Drug Administration on March 27, 1998, becoming the first oral treatment approved to treat erectile dysfunction in the United States, and offered for sale in the United States later that year (9).

Mechanism of action

The mechanism of action of Sildenafil citrate involves the release of nitric oxide (NO). NO binds to the receptors of the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilatation). (10)

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP . The molecular structure of sildenafil is similar to that of cGMP and acts as a competitive binding agent of PDE5 resulting in more cGMP . (10)

Pharmacokinetic Data

Sildenafil is metabolised by liver enzymes and excreted by both the liver and kidneys. If taken with a high-fat meal, absorption is reduced; the time taken to reach the maximum plasma concentration increases by around one hour, and the maximum concentration itself is decreased by nearly one-third.(11)

Bioavailability	40%
Metabolism	Hepatic (mostly CYP3A4, also CYP2C9)
Half life	3 to 4 hours
Excretion	Fecal (80%) and renal (around 13%)

Uses

Sexual dysfunction

The primary indication of sildenafil is treatment of erectile dysfunction (inability to sustain a satisfactory erection to complete intercourse). Its use is now standard treatment for erectile dysfunction in all settings, including diabetes. (12)

Pulmonary hypertension

As well as erectile dysfunction, sildenafil citrate is also effective in pulmonary arterial hypertension (PAH). It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure. This in turn reduces the workload of the right ventricle of the heart and improves symptoms of right-sided heart failure. (13)

Altitude sickness

Sildenafil has been shown to be useful for the prevention and treatment of High altitude pulmonary edema associated with altitude sickness such as that suffered by

mountain climbers. (14)(15)While this effect has only recently been discovered, sildenafil is already becoming an accepted treatment for this condition, particularly in situations where the standard treatment of rapid descent has been delayed for some reason. (16)

Use in sports

Professional sports players have been using drugs such as sildenafil thinking that the opening of their blood vessels will enrich their muscles, therefore enhancing their performance. (17)

Contraindications

*When taking nitric oxide donors, organic nitrites and nitrates, such as glyceryl trinitrate (nitroglycerin), sodium nitroprusside, amyl nitrite to avoid hypotension (18).

*In men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.

-Severe hepatic impairment (decreased liver function).

-Severe impairment in renal function.

-Hypotension (low blood pressure).

-Recent stroke or heart attack.

-Hereditary degenerative retinal disorders (including genetic disorders of retinal phosphodiesterases).

Side effects

In clinical trials, the most common adverse effects of sildenafil use included headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision. (19) Some sildenafil users have complained of seeing everything tinted blue (cyanopsia). Some complained of blurriness and loss of peripheral vision. In May 2005, the U.S. Food and Drug Administration found that sildenafil could lead to vision impairment (20) and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy.(21) (22)(23)(24)(25)(26)

Rare but serious adverse effects found through postmarketing surveillance include priapism, severe hypotension, myocardial infarction (heart attack), ventricular arrhythmias, stroke, increased intraocular pressure and sudden hearing loss. (19) In October 2007, the FDA announced that the labeling for all PDE5 inhibitors, including sildenafil, required a more prominent warning of the potential risk of sudden hearing loss as the result of these Postmarketing reports. (27)

Interactions

Care should be exercised by patients who are also taking protease inhibitors for the treatment of HIV. Protease inhibitors inhibit the metabolism of sildenafil, effectively multiplying the plasma levels of sildenafil, increasing the incidence and severity of side-effects. It is recommended that patients using protease inhibitors limit their use of sildenafil to no more than one 25 mg dose every 48 hours.