SILDENAFIL: A REVIEW ON THE CLINICAL AND NON-CLINICAL EFFECTS

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ABSTRACT

Phosphodiesterase-5 (PDE5) inhibitors produce its effect mainly by relaxing the smooth muscle by protecting second messengers like cyclic adenosine monophosphate (c-AMP) and cyclic guanosine monophosphate (c-GMP) from inactivation. Sildenafil has got multiple effects both clinically and non-clinically in various disease conditions. The databases of Pubmed (1990-2017), Embase (2000-2017), sciencedirect (2005-2017), google scholar and Micromedex were searched using the set keywords. The keywords were “sildenafil”, “clinical effects”, “non-clinical effects”, “ADR” and “effect on semen”. It can be used mainly as an erectile dysfunction agent, but has shown evidence in medical expulsive therapy (MET), Partial unilateral ureteral obstruction (PUUO), myocardial infarction, distal ureteric stones (DUS), heart failure, stroke and as a prophylactic agent in rectum surgery. It help in the betterment of exercise capacity, and hemodynamic in symptomatic pulmonary arterial hypertension patients, enhances ovarian response, endometrial thickness and circadian responses to light. Some non-clinical effects include its use in jet-lag recovery, high altitude sickness, and also have promised its effect in enhancing sports activities. Chronic treatments of sildenafil on lab rats were found to help restore the biological markers which are responsible for erectile dysfunction. Unfavourable drug reaction using Epistaxis was found in hypertensive patients and simultaneously showed dose increment to meet the required effect due to tolerance. Sildenafil did not have notable consequences on sperm count, motility, morphology, viscosity, density or ejaculate volume. However, apart from limiting it as an effective drug for erectile dysfunction, further clinical trials should be conducted to promote its use in other disease conditions.

Key-words: Sildenafil, c-GMP, c-AMP, PDE-5, medical expulsive therapy (MET), vasodilatation, nitric oxide signalling, superoxide dismutase (SOD)

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INTRODUCTION

Sildenafil citrate, a widely used drug specifically for erectile dysfunction is particularly the phosphodiesterase type-5 (PDE-5) inhibitor in smooth muscle, which is accountable for decrement of cyclic guanosine monophosphate (c-GMP). Inhibition of PDE-5 by sildenafil increases c-GMP concentrations, which promotes vasodilatation.^[1] PDE-5 is an enzyme, which is present mainly in the lung tissue and penile tissue that degrades c-GMP to non-active compounds.^[2] Sildenafil, is well-known for its widespread actions on various types of disorders. The purpose of this study is to gather the clinical and non-clinical effects

of sildenafil in various conditions. It can be used mainly as an erectile dysfunction agent,^[3,4] but has shown evidence in medical expulsive therapy (MET),^[5-7] distal ureteric stones (DUS),^[8,9] Partial unilateral ureteral obstruction (PUUO),^[10] myocardial infarction,^[11] heart failure,^[12] stroke^[13-20] and as a prophylactic agent in rectum surgery.^[21] It improves exercise capacity,^[22] and hemodynamic in symptomatic pulmonary arterial hypertension patients,^[23,24] enhances ovarian response,^[25] endometrial thickness^[26] and circadian responses to light.^[27] These agents possess oxidative stress-protective properties (antioxidant).^[28,29] Some non-clinical effects include its use in jet-lag recovery,^[30-32] high altitude sickness,^[33] and also have promised its effect in enhancing sports activities.^[34,35]

Figure 1: Mechanism of sildenafil

MATERIALS AND METHODS

The databases of Pubmed (2010-2017), Embase (2000-2017), Sciencedirect (2005-2017), google scholar and Micromedex were searched using the set keywords. The keywords were “sildenafil”, “clinical effects”, non-clinical effects”, “ADR” and “effect on semen”. The obtained records were reviewed and sorted accordingly for the full review. The flowchart regarding study design is depicted in figure 1.

Search strategy

The scientific records were retrieved by a systematic search of different bibliographic databases, and the last update of the search was performed on August 16, 2017. The titles and abstracts of all the records retrieved by the search strategy were reviewed by two authors, and the relevant records with full-texts available were selected for full review. These papers were also included for the full review. Final corrected copy of the work was checked for plagiarism and found to be eligible for publication by the fourth author.

Figure 2: The flowchart of the study design process

Inclusion criteria

Original research works, review works, short communications, medical news and Micromedex updates regarding sildenafil and both its clinical and non-clinical effects were included for the review work. A total of 64 studies were identified and only 37 were found to be appropriate for the title after screening. Finally, only 35 studies were included apart from the Micromedex updates regarding the drug. The obtained records were reviewed and preceded for manuscript preparation.

RESULTS**Table 1: The clinical effects of sildenafil**

Sl.No	Therapeutic applications	Clinical effects
1.	Erectile dysfunction	Sildenafil maintains the level of c-GMP in the corpus cavernosum of the penis by inhibiting the enzyme PDE-5 which is accountable for the degradation of c-GMP. Thus, nitric oxide (NO) in the corpus cavernosum secures to guanylate cyclase receptors by enhancing the levels of c-GMP leading to much smoother muscle relaxation (vasodilatation) of the intimal cushions of the helicine arteries. Therefore, there will be an inflow increase of blood into the spongy tissue of penis, causing an erection. ^[3,4]
2.	Medical expulsive therapy (MET)	PDE5 was exhibited to play the major role in relaxant responses of lower urinary tract tissue mediated by nitric oxide (NO) and c-GMP pathways. PDE5 inhibitors reverse the tension of isolated human ureteric smooth muscles via c-GMP-mediated pathways. ^[5] PDE isoenzymes (1, 2, 4 and 5) are present in cytosolic supernatants prepared from human ureteral tissue. Various neurotransmitters discharged from nerve terminals (adrenergic, cholinergic, non-adrenergic, and non-cholinergic) and endogenous factors from vascular endothelial sources controls the smooth muscle tone in the lower urinary tract. ^[6,7]
3.	Distal ureteric stones (DUS)	Cyclic adenosine monophosphate (c-AMP) and cyclic guanosine monophosphate (c-GMP) are important intracellular second messengers mediating cellular responses. An increment in c-AMP and c-GMP triggers a signal transduction cascade, which leads to relaxation of smooth muscle. ^[8,9]
4.	Partial unilateral ureteral obstruction (PUUO)	PUUO helps in increment of renal tubular cell apoptosis and elevates NOS concentrations in renal tubular tissues after PUUO. PDE5 inhibitors, which are recognised as effective in ED treatment, have a protective effect against the tubular apoptosis. ^[10]
5.	Myocardial ischemia	In patients with chronic stable angina, it induced improvements in the peak systolic strain of different myocardial ischemic territories. ^[11]
6.	Heart failure	The pulmonary vascular resistance in pulmonary hypertension is reduced by increasing intracellular levels of the nitric oxide (NO). ^[12]
7.	Stroke	Slower treatment with PDE5 inhibitors that escalates neurogenesis, angiogenesis, and synaptogenesis, and helps in betterment of functional outcome post stroke in young and aged rats. ^[13-19] Safety studies are

8.	Prophylactic agent in rectum surgery	conducted in ischemic stroke patients before closely examining the neurorestorative properties of sildenafil in humans. ^[20] Improvement in wound healing was associated to increment in collagen content, maturity, epithelisation and a decline in neutrophil infiltration and oxidative stress. ^[21] Usage of sildenafil as a prophylactic agent in rectum surgery should be researched and examined in clinical settings.
9.	Pulmonary arterial hypertension	The metabolism of c-GMP can lead to growth inhibition of vascular smooth-muscle cells and inhibition of cyclic guanosine monophosphate mediated relaxation. Sildenafil inhibits PDE-5 (an enzyme that metabolizes c-GMP) in the lungs and improves nitric oxide signalling thereby increasing levels of intracellular GMP leading to relaxation of smooth muscle cells, reduction in vascular remodelling and vasoconstriction, thus improving exercise capacity, and hemodynamic in symptomatic pulmonary arterial patients hypertension. ^[22,23] In the management of pulmonary hypertensive patients who are posted for non-cardiac surgery, there is an effect in safe administration of preoperative oral sildenafil. ^[24]
10.	Enhance ovarian response	A 37 years old woman, who was unsuccessful to show any follicular growth during Controlled Ovarian Hyper-stimulation (COH) in an Intra Cytoplasmic Sperm Injection (ICSI) cycle, yielded 10 oocytes in the second cycle after addition of sildenafil 50 mg per day for a total of five doses. They concluded that adjuvant sildenafil may increase ovarian response in a woman with low ovarian response. ^[25]
11.	Increasing the endometrial thickness	Applying sildenafil in vagina increases the endometrial thickness in women who has the history of repetitive miscarriage, and also it decreases natural-killer-cell activity in such women. ^[26]

Table 2: Non-clinical effects of Sildenafil

Sl. No	Non-therapeutic applications	Non clinical effects
1.	Re-entrainment of circadian rhythms	c-GMP specific PDE-5 enzyme is in existence in the hamster (nocturnal rodents, those are active during the night) suprachiasmatic nuclei, and administration of the inhibitor sildenafil (3.5 mg/kg) enhances circadian responses to light and reduces the aggregate of time needed for reentrainment after phase advances of the light-dark cycle. ^[27]

2.	Antioxidant	These agents possess oxidative stress-protective properties. ^[28,29]
3.	Jet-lag recovery	Jet lag is a chronobiological problem, ^[30] as journey across multiple time zones, the body clock (circadian rhythm) will be no more in sync with the port of stop time in which the body's normal pattern is out of place, as the rhythms that orders times to eat, sleep, regulation in hormone, variation in body temperature, and other tasks would no longer be compatible to the environment., as it undergo morning and night contrary to the rhythms to which it has grown accustomed. Sildenafil increases levels of c-GMP, in suprachiasmatic nuclei (brain cells), which act as the body's internal clock. ^[31,32]
4.	High-altitude sickness	Increases the blood circulation to the lungs and thus reduce hypoxia. It plays a role in preventing and treating high altitude sickness suffered by mountain climbers. ^[33]
5.	Sports	Dilation of the blood vessels will enrich muscles which in turn will enhance their performances in physical activities. ^[34,35]

Disadvantages

Sildenafil showed fetotoxicity and growth suppression when applied an animal model during its developmental stage.^[36] It also enhanced production of nitric oxide (NO) in embryos which caused both damage and reduction in survival rate of such embryo if generated NO in excess.^[37-39]

Other effects

Affirmative effects of sildenafil on anastomotic leak,^[40] the feared complication succeeding colorectal surgery were reported. Some animal studies implied on bone, skin and fascial healing.^[41] Its useful effects on the process of injury healing is exerted through various mechanisms including vasodilation,^[42] improved microcirculatory hemodynamics through inhibition of platelet aggregation and adhesion,^[43] stimulation of angiogenesis,^[44] induction of apoptosis of adhesion fibroblasts, and reduction of inflammatory responses.^[45] The effects of drug on colonic healing were analyzed only in particular conditions like ischemia and infection.^[46-47]

Toxicology effects

Superoxide dismutase (SOD), an antioxidant enzyme, converts superoxide anion to hydrogen peroxide and molecular oxygen.^[48] SOD is a potential therapeutic target for erectile dysfunction (ED).^[49] Also, sildenafil was developed to reduce superoxide formation and wider levels of c-GMP, c-AMP and glutathione in corpus cavernosum of rabbits and in hypertensive rats.^[50] In addition, lab rats that went chronic treatment of with sildenafil were discovered to bring back the elevated biological markers of oxidative stress and also vasoconstrictors to their usual levels.^[51] Reactive Oxygen Species (ROS), formed during normal oxygen molecule metabolism firstly in the vascular endothelium, include H₂O₂ and peroxynitrite. Increment in ROS level was developed to restrict SOD activity which therefore reduces the bioavailable NO concentration through induction of peroxynitrite level.^[52]

Adverse drug reactions

Efficacy of sildenafil may decrease with long-term use. In patients who experienced good treatment results initially, 2 year follow-up showed that 17% had discontinued sildenafil due to loss of efficacy and 37% had required a significant dose increase (double dose) to maintain efficacy.^[52] Patients with pre-existing hypertrophic cardiomyopathy may experience a decreased preload and afterload because of sildenafil dosing which might end up in an unstable hemodynamic state in those patients and possibly sudden death.^[53] Epistaxis was reported in 9% of patients with pulmonary arterial hypertension who had been under treatment of sildenafil 20 mg 3 times daily.^[54]

Effect on the semen

There are varying reports of seminal effects with sildenafil. Some reports state that it has not been any effects observed to sperm function (eg: motility),^[55,56] where other studies found a higher motility rate.^[57] Sildenafil does not have harmful effect on sperm function. In male subjects under good health single oral doses of sildenafil 100 mg had no notable effects on sperm count, density, morphology, viscosity, motility, or ejaculate volume. Mean semen concentration of sildenafil were almost 18% of mean plasma concentrations.^[55]

CONCLUSION

PDE5 inhibitors produce its effects mainly by relaxing the smooth muscle by protecting c-AMP and c-GMP. Sildenafil has numerous effects both clinically and non-clinically in various disease conditions. It can be used mainly as an erectile dysfunction agent, but has shown evidence in medical expulsive therapy (MET), distal ureteric stones (DUS), Partial unilateral ureteral obstruction (PUUO), myocardial infarction, heart failure, and as a prophylactic agent in rectum surgery. It recovers exercise capacity, and hemodynamic in those patients having symptomatic pulmonary arterial hypertension, enhances ovarian response, endometrial thickness and circadian responses to light. Some non-clinical effects include its use in jet-lag recovery, high altitude sickness, and also have promised its effect in enhancing sports activities. Lab rats that underwent chronic treatment with sildenafil were found to bring back the biological markers responsible for erectile dysfunction. Loss of efficacy was seen in long term use and harmful effects were less. The oral administration of sildenafil does not harmfully affect sperm function. However, apart from limiting it as an erectile dysfunction agent, further clinical trials should be conducted to promote its use in other disease conditions.

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