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GENERAL REVIEW

Sildenafil: From angina to SARS-CoV-2

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Summary Sildenafil was first examined as an alternative to nitrates for the management of angina pectoris and hypertension and eventually developed into an oral therapeutic agent used for the treatment of erectile dysfunction. There are appropriate indicators that PDE5 inhibitors may also modify the detrimental consequences of the immune system over-stimulation, supplying a new chance for their use in SARS-CoV2 patients. The use of sildenafil for the management of SARS-CoV2 has been suggested based on its several mechanisms of action and therapeutic effects and on the clinical features of SARS-CoV2 which similar to those of other pathologies treated with the PDE5 inhibitors. Here we review fundamental highlights in the enhancement of sildenafil for numerous scientific disorders and consider practicable new uses for this versatile drug.

Introduction

History of sildenafil discovery

Nitrates, an exogenous source of nitric oxide (NO), were and still are extensively used for the management of cardiovascular disorders, especially angina pectoris (Divakaran and Loscalzo, 2017, Marsh and Marsh, 2000). Major problem related with the use of nitrates is the speedy incidence of tachyphylaxis with extended administration (Divakaran and Loscalzo, 2017). This problem encouraged some Pfizer researchers to search alternate methods to modify NO signaling. They suggested that a downstream target in the NO/cyclic guanosine monophosphate (NO/cGMP) pathway could be modulated. Phosphodiesterase type 5 (PDE5) is exclusively catalyses the breakdown of cGMP. In 1986 Pfizer researchers succeeded in manufacturing new pyrazolopyrimidines that were extremely potent PDE5 inhibitors. It was originally termed UK-92,480, however is currently well-known as sildenafil. It designated chemically 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine, and it has been selected for additional studies. Following administration of sildenafil (75 mg/3 times/10 days), some volunteers complained of flushing, headaches, muscle pains, indigestion, and penile erections as adverse effects (Ghofrani et al., 2006). By mid-1994, at the end of two separate clinical trials, single sildenafil doses improved erectile reactions to sexual encouragement and well tolerated (Boolell et al., 1996). Once sildenafil was authorized by the U.S. FDA in 1998, it altered dramatically the therapy protocol for males with erectile dysfunction

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(ED), when reflected a psychological matter or a predictable part of aging (Goldstein et al., 2019).

Mechanism of action

The penile erection entails NO release in the corpus cavernosum (CC) through sexual encouragement. NO stimulate the guanylate cyclase to transform the guanosine triphosphate (GTP) to cGMP that stimulates a series of reactions that ultimately reduces the level of intracellular calcium, thereby encouraging the relaxation of smooth muscle (Lucas et al., 2000, Moncada et al., 1991, Pfeifer et al., 1999) in the CC and permitting blood inflow. Sildenafil is a selective, reversible and potent inhibitor of PDE5 which found in high concentrations in the CC and pulmonary arteries. On isolated human CC, sildenafil has no direct relaxant effect, but it augments the effect of NO by means of hindering PDE5, which is accountable for cGMP disintegration in the CC and prolongs cGMP actions (Barnett and Machado, 2006), resulting in smooth muscle relaxation and blood inflow to the CC. Without sexual stimulation, sildenafil has no effect at recommended doses (Bourin, 2018, Goldenberg, 1998).

PDE5 is also present in low concentrations in platelets, skeletal muscle, and pulmonary artery, vascular and visceral smooth muscle, and its inhibition by sildenafil might be improved the in vitro platelet anti-aggregatory activity of NO, and peripheral arterial-venous dilatation and inhibition of platelet thrombus formation in vivo (Bourin, 2018, Reffelmann and Kloner, 2003) and reduce the pulmonary vascular resistance (Aljanabi et al., 2017, Sebkhi et al., 2003).

Pharmacokinetics

Sildenafil was rapidly absorbed following administration of single-oral doses (25, 50, 100, and 200 mg) to 32 healthy men, reaching peak plasma levels within 1 hr. In general, its plasma levels were proportionate to the given dose. Food decreased the rate but slightly altered the degree of sildenafil absorption. First by-pass metabolism reduced sildenafil absolute bioavailability to 41%. It was quickly eliminated with a plasma clearance half-life of around 3—4 h over the dosage (25—200 mg). Sildenafil was well-tolerated over the recommended dose (25—100 mg) (Nichols et al., 2002). Sildenafil citrate's oral bioavailability could be greatly improved by formulating it as dry foam tablets. Sildenafil pharmacokinetics in ED patients were in line with a lot of data attained from volunteer studies. The common hallmarks of the patients and volunteers data include dose proportionality in the pharmacokinetics of sildenafil dose (25—100 mg) with indication of non-proportionality at higher dosage, food-linked alterations of its absorption rate and equivalent values for AUC, *T*max, *C*max, and half-life between patients and volunteers (Milligan et al., 2002).

The pharmacokinetics of the 50 mg sildenafil dose in subjects with late-stage renal disease and the maximum hemodynamic effect of the sildenafil administration after hemodialysis were evaluated (Grossman et al., 2004). They reported that hemodialysis did not eliminate either sildenafil or its primary metabolite, UK-103,320. Subsequent hemodialysis, sildenafil administration was associated with a 17% higher plasma level and earlier peak time, although the absorption level and half-life time were not affected. In hemodialysis patients, the total amount of drugs bound to plasma protein was nearly 96%.

The systemic bioavailability of dry foam tablets of sildenafil citrate was 1.5 and 1.9 times greater than that of sildenafil commercial film-coated tablets and sildenafil powder, respectively (Sawatdee et al., 2018). Compared to the commercial sildenafil citrate film-coated tablet, a 50 mg sildenafil citrate orally disintegrating tablet is bioequivalent to or meets bioequivalence requirements, indicating an acceptable alternative form of oral administration (Lv et al., 2020).

Sildenafil is eliminated primarily by the CYP3A4 (main route) and CYP2C9 (minor route) (Hyland et al., 2001). The metabolite obtained from N-desmethylation of sildenafil has a sildenafil-like PDE selectivity profile and a PDE5 *in vitro* potency of about 50% of the sildenafil. This metabolite's plasma concentrations are about 40% of the parent drug, so this metabolite accounts for about 20% of the sildenafil pharmacological actions. Sildenafil is excreted as metabolites in the faeces and in urine around 80% and 13% of the oral dose administered, respectively (Bourin, 2018).

Pharmacodynamics

Effect of sildenafil on erectile dysfunction

The treatment satisfaction, erection quality, anxiety levels, and also the sexual experience considerably enhanced by sildenafil (50-100 mg). Compared to the sildenafil 50-mg dose, sildenafil 100-mg dose enhanced the treatment satisfaction, sexual experience and anxiety levels (Loran et al., 2009). Monthly average incidence of sexual intercourse among ED patients, erectile function status, sexual satisfaction and pleasure significantly improved with sildenafil therapy. A higher dosage of sildenafil had a greater effect on the monthly average incidence of sexual activity and sexual pleasure (Li et al., 2017).

Treatment with Sildenafil for substantially improved the international index of erectile function score 5 (IIEF-5), self-esteem and relationship (SEAR) scores, erection hardness score (EHS) levels, the pleasure, happiness, and physical vigour and mental health ratings as well as frequency of sexual attempts and sexual activity (Tang et al., 2015). Regular use of sildenafil had better effect on IIEF-5 score and EHS levels than that of sildenafil on-demand (100 g), without more adverse effects (Wang et al., 2019). Sildenafil therapy increased the penetration ability, maintenance frequency and index of erectile function.in renal allograft recipients with ED (Liu et al., 2019).

Sildenafil is well tolerated acutely with minimal side effects when used for treatment of ED patients with stable chronic artery disease; it encouraged enhancements in the peak systolic strain of different myocardial ischemic zones in patients with chronic stable angina (Salem et al., 2014). It is frequently administered for ED management in hypertensive male cardiac transplant recipients (Schofield et al., 2003).

Effect of sildenafil on cardiovascular and respiratory systems

Sildenafil induced clinically insignificant reduction in the ambulatory blood pressure (BP) in active and resting normotensive and hypertensive men. It is harmless in young and old men with or without hypertension when used following treatment guidelines and the prescribing information (Vardi et al., 2002). It reduced systolic, diastolic, and mean 24-hour blood pressure (BP) and improved daytime BP levels. Regarding to the sildenafil antihypertensive activity, it may be a therapeutic alternative for treatment of resistant hypertensive (RH) (Santa Catharina et al., 2016). Coronary artery disease patients, 100 mg sildenafil dilates the epicardial coronary arteries, stops platelet activation and improves endothelial dysfunction (Halcox et al., 2002). Treatment of patients with heart failure (HF) with sildenafil (50-mg/3times/day) for 6 months endorsed a continued marked improvement in left ventricular systolic and diastolic function properties (Elhakeem and Khairy, 2019).

Sildenafil increases cardiac output and exercise capacity in patients with HF. This enhancement is attributed to the reduction in all 3 components of LV afterload: aortic and large artery stiffness, peripheral resistance, and wave reflection from peripheral sites (Hirata et al., 2005). 50 mg sildenafil is safe in hypertensive male cardiac transplant recipients and enhances BP, endothelial function and aortic augmentation index. It decreases left ventricular afterload and systolic stress by diminishing the amplitude of the reflected pressure wave and slowing its return to the heart (Schofield et al., 2003).

PDE5 has a significantly higher expression in airways and vascular smooth muscle, and is supposed to induce its effects via cGMP-PKG signaling modulation. Therefore, PDE5 inhibitors such as sildenafil are currently authorized for the treatment of pulmonary arterial hypertension (PAH) (Humbert et al., 2004). Sildenafil has developed as a vital first-line oral therapeutic agent for patients with symptomatic PAH (Barnett and Machado, 2006). Sildenafil medication over 3—4 months is successful in alleviating PAH symptoms and delaying the development of the disease in adults (Wang et al., 2014). Compared to supportive therapy alone, sildenafil with supportive therapy led to substantial changes in exercise ability (increase in 6-min walk distance), haemodynamic outcomes (reduction in mean pulmonary vascular resistance and pulmonary arterial pressure), life quality and improve in functional class in patients with PAH (Chen et al., 2009). Sildenafil substantially decreased pulmonary artery pressure and increased exercise resistance, 6-min walking distance and O2 saturation without substantial changes in heart rate and mean BP (Eskandar, 2014). Oral sildenafil is an effective therapeutic agent for management of postoperative PH and it can be used to enable stopping of inhaled and IV pulmonary vasodilators (Trachte et al., 2005).

Acute pulmonary embolism (APE) is a significant health issue arising from embolism migration to the lungs and pulmonary blood vessel obstruction. APE is a major cause of death and pulmonary hypertension, and sildenafil IV can selectively reduce changes in mean pulmonary artery pressure following APE (Dias-Junior et al., 2005). The key pathway of PDE5 inhibitors, cyclic guanosine monophosphate (cGMP)-dependent kinase (cGK), is highly expressed in platelets and sildenafil inhibits platelet aggregation by activation of the cGK pathway (Yang et al., 2019). Sildenafil has been shown to be effective in improving oxygen intake, heart failure and pulmonary hypertension at various dosages, with generally mild side effects (Galiè et al., 2005). Sildenafil is progressively used in the management of pulmonary hypertension associated with postnatal congenital diaphragmatic hernia (Hunter et al., 2009, Todd et al., 2007).

Sildenafil (50-mg) resulted in temporary dilatation of airways and decreased trapping of gas (Goudie et al., 2012). It is a potent acute pulmonary vasodilator and prolonged treatment of pulmonary hypertension with sildenafil is well tolerated and safe (Preston et al., 2005).

Immuno-modulatory and anti-inflammatory effect of sildenafil

Sildenafil may have a potential role for treatment of chronic airway disease as it can reduce airway inflammation and mucus formation in the rat model, likely via restoring of lung cGMP content, and reduced the lung NO metabolites, pro-inflammatory cytokine release, the bronchoalveolar lavage fluid leukocyte influx, diminished mucin synthesis at both mRNA and protein levels as well as declining epithelial hyperplasia and metaplasia (Wang et al., 2009).

Sildenafil reduced the pro-inflammatory cytokines levels, like interleukin (IL)-1, tumor necrosis factor alpha (TNF-α), and decreased the action of NK cells, and improved the regulatory T cells activity (Kniotek and Boguska, 2017). Sildenafil declined immunoreactivities of inflammatory markers; interleukin1β (IL-1β), fibroblast growth factor 2 (FGF-2), TNF- α and hypoxia-inducible factor 1α (HIF-1α) a model of acute radiation proctitis (Yavuz et al., 2018). Oral treatment with sildenafil inhibits polyp formation and inflammatory marker; iNOS, IFNγ, and IL-6 in azoxymethane/dextran sulfate sodium-induced colorectal cancer in mice (Islam et al., 2017).

Sildenafil and COVID-19

The WHO declared in March 2020 that severe acute respiratory syndrome infection with coronavirus 2 (SARS-CoV2) is a pandemic disease. While there is an increasing understanding of SARS-CoV2 and its clinical features, there has not yet been an effective treatment for its acute symptoms and severe complications. The use of sildenafil for the treatment of SARS-CoV2 has been suggested based on its several mechanisms of action and therapeutic effects and on the clinical features of SARS-CoV2 which similar to those of other pathologies (e.g., thrombosis, inflammation, fibrosis) which treated with the PDE5 inhibitors (Giorgi et al., 2020).

In SARS-CoV2 infection, there are various biochemical pathways that cause a cascade of inflammatory processes (Fig. 1) (Catanzaro et al., 2020, Mario et al., 2020). SARS-CoV2 infection triggers the inducible nitric oxide synthase (iNOS) with unregulated production of NO. iNOS induces injury to host cells with a subsequent pulmonary thromboembolic lung. As known, sildenafil prevents iNOS and its hemodynamic effects during acute pulmonary embolism.

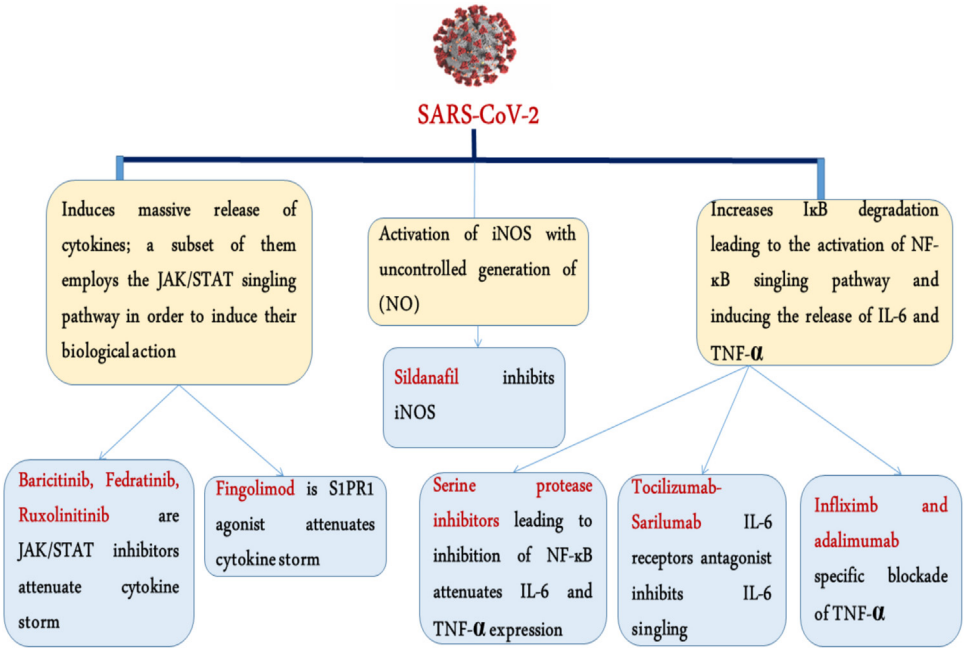

Figure 1 Diagram with the inflammatory cascade in SARS-COV2 and different potential pharmaceutical targets.

Therefore, sildenafil is hypothesized to inhibit the inflammatory cascade and thromboembolic episodes in SARS-CoV2 patients (Mario et al., 2020).

It could be postulated that COVID-19 may be more aggressive/fatal due to a high level of ''basal'' inflammation in hypertensive patients: if NO availability is impaired with a concomitant increased release of IL-6 by the dysfunctional endothelium, the effects of this coronavirus seem to be earlier and stronger than in patients with basal ''normal'' NO levels, suggesting a protective role of NO. By keeping an open mind, one could also postulate a protective role for PDE5-i (i.e., using oral Tadalafil on a daily basis) in protecting the patient population most at risk of infection, such as those hypertensive, obese and diabetic, in order to avoid or mitigate the cytokines storm and more dangerous complications (Dal Moro et al., 2020).

The potential efficiency of PDE5i against SARS-CoV2

PDE5 inhibitors can modulate over-stimulation of the immune system's harmful effects, offering a promising opportunity for their administration in patients with SARS-CoV2. In view of the overwhelming economic effects of SARS-CoV2 on national health systems globally and the expense of the intensive care units required to handle patients in critical status, the usage of PDE5 inhibitors which supply an inexpensive, readily accessible and non-experimental therapy approach to prevent the progressing of the disease from to most critical final stage, where existing therapy are inappropriate. PDE5 inhibitors have been able to regulate SARS-CoV2 by: (i) counteracting the AngII-mediated AT-1 receptor down-regulation; (ii) acting on monocyte switching, thereby diminishing pro-inflammatory cytokines release, interstitial infiltration and the vessels injury accountable for alveolar hemorrhage-necrosis; (iii) preventing the transfer of endothelial and smooth muscle cells to mesenchymal cells in the pulmonary artery, hindering thrombotic and clotting complications (Isidori et al., 2020).

Case study

In the emergency room, the patient was hypoxic with oxygen saturations of 86% on right atrium with accompanying dyspnea. He was placed on 4 to 6 l of oxygen via a nasal cannula, which led to an improvement in the oxygen saturations to low 90s. High-flow nasal cannula was attempted, which he did not tolerate. He continued to need supplemental oxygen until day 6 of his hospitalization. There was no need for mechanical ventilation. Aggressive intensive spirometry was encouraged. He was seen by the COVID-19 infections disease team and was started on hydroxychloroquine (400 mg orally twice daily for 1 day, then 400 mg PO daily to complete a 5-day course). A daily electrocardiogram was performed that did not show prolongation of his QTc interval. A 5-day PO course of azithromycin was also given. He was aggressively diuresed with intravenous furosemide. A PDE5i (sildenafil) 20 mg PO three times a day was started. With the initiation of sildenafil, there was a slow improvement in his clinical symptoms. Subcutaneous heparin for deep vein thrombosis prophylaxis was started, which was later switched to full-dose lovenox. The patient was hospitalized for 10 days and was discharged in stable condition on aspirin 81 mg PO daily and sildenafil (Ahluwalia et al., 2020).

Conclusion

Sildenafil was firstly examined as alternative to nitrates for the management of angina pectoris and hypertension,

and eventually developed into an oral therapeutic agent used for treatment of ED. Sildenafil was further improved to become a much-needed oral therapy for PAH treatment. Recently, owing to the several mechanisms of action and therapeutic effects of sildenafil and in view of the overwhelming economic effects of SARS-CoV2 on national health systems globally and the cost of the intensive care units required to handle patients in critical status, the usage of PDE5 inhibitors which supply an inexpensive, readily accessible and non-experimental therapy approach to prevent the progressing of the disease from to most critical final stage, where existing therapy are inappropriate.

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Disclosure of interest

The authors declare that they have no competing interest.

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