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Sidenafil protocols for the treatment of ICC: A literature review

Protocolos do uso de Sidenafil para tratamento da ICC: Revisão bibliográfica

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ABSTRACT
A literature search was conducted on the effects of sidenafil and the protocols used in heart failure. The phosphodiesterase-5 inhibitor stands out as a new drug in the cardiologic therapeutic arsenal, since the action of inhibiting the various types of phosphodiesterase causes an increase in cAMP and cGMP in white tissues.

Keywords: Sidenafil, Heart failure, Dysfunction, Angina, Erection, Viagra.

1 INTRODUCTION

Due to the existence of results already defined as limited in the control of symptoms and the evolution of Congestive Heart Failure (CHF), through the use of ACEI (CAPTOPRIL), DIGITAL, FUROSEMIDE, LOSARTAN, ISOSORBIDE, and HYDRALAZINE, but of consecrated use in clinical practice, research into new drugs to be incorporated into the therapeutic arsenal concerning CHF becomes necessary.

This work is based on the bibliographic survey and the results regarding the use of SIDENAFIL (VIAGRA), for the control of the symptoms and signs of this pathology. A brief review of Phosphodiesterase inhibitors is also made, in order to have an exact notion of the new indications of this class of drugs.

It is noteworthy that, because this drug is still in the research phase, it is required, as an ethical basis for its clinical use, an explanation to the patient and his family, the Clinical Service and the Physician, of the current progress of this research, the mechanism of action, the expected results and possible contraindications or unexpected effects, which is why there are few studies on the protocols of Sidenafil in CHF, considering both the national and global literature.

Besides this, there is the family impact and the surprise of the use of SIDENAFIL (VIAGRA), for being a drug used in erectile disorders, widely and folklorically known by the lay population. This fact leads the family members to contest this procedure by refusing to sign the Consent Act, and the therapy is restricted to the agents mentioned above.

Only the doctor's knowledge can overcome this doubt and carry this therapeutic method forward, convincing the patient and family members, after a detailed explanation regarding the effects, the safety in administration, the low side effects, and the gain in quality and life expectancy.

Considering that SIDENAFIL occupies deep in popular knowledge, not only because of self-medication in erectile disorders, but also because of use in healthy people for recreational purposes, the resistance to using this medication for a purpose that is not yet known is easily understood.

From the current knowledge, it becomes practically mandatory to consider the use of this agent as a control, in stopping the evolution, in the involution and in the promotion of a better quality of life to the patient (1). It is also emphasized its efficacy in young pediatric patients, in congenital heart diseases and in systolic cardiac insufficiency (2).

Its use is based on the evidence that Phosphodiesterase-5 exists not only in the penile cavernous sinus, but also in abundance in the pulmonary vascular endothelium. There is also evidence of its distribution in cardiac muscle.

Initially synthesized and studied for the treatment of hypertension and angina, this drug showed an active action in the maintenance of penile erection, which motivated and diverted the initial line of research of the study and the subsequent launch of the drug as a treatment mechanism for erection disorders (10).

Thus, we conclude that most studies, due to the particularity of the drug itself, have been conducted in male patients, lacking more information and protocols to be conducted in female patients, but this does not invalidate the observations and conclusions of these studies.

SIDENAFIL (Viagra), as a therapy for erectile disorders, is a Phosphodiesterase-5 inhibitor, available in 25, 50 and 100 mg tablets. Other Phosphodiesterase-5 inhibitors on the market are Tadalafil, Vardenafil, Avanafil, and also Lodenafil and Udenafil (19). In addition, Phosphodiesterase-5 inhibition caused by a natural product, Xanthoparmelia, is reported.

2 PHARMACOLOGY

The group of Phosphodiasterase Inhibitors is characterized by inhibiting one or more PDE subtypes, preventing the degradation of second messengers (AMPC and cGMP), resulting in higher concentrations in the cells, generating various effects in the affected tissues.

The group of these substances is divided into 8 variants (19), with varying effects and uses in the clinical management of patients, such as:

1. Non-selective PDE inhibitors: these are the methylated xanthines, bronchodilators, and anti-inflammatory drugs, used in asthma control (Caffeine, Aminophylline, Theobromine, and Theophylline);
2. Selective PDE1 inhibitor: neuroprotective, used in age-related changes, especially stroke (Vimpocetine);
3. Selective PDE2 inhibitor: reported as drugs to improve memory, to decrease endothelial permeability in inflammatory conditions, and to prevent or improve heart failure and cardiac hypertrophy [Erythro-9-(2-Hydroxy-3-Nonyl)Adenine] - EHN;
4. Selective PDE3 inhibitor: drugs that increase cardiac accounting (inotropism), heart rate (Chronotropism) and conduction velocity (Domotropism), causing vasodilation, decrease in overall vascular resistance and decrease in BP, being used in Heart Failure and Pulmonary Hypertension (20), having as side effect Ventricular Arrhythmia, being in some cases fatal (Milrinoma, Amrinone and Cilostazol and Dipiradamol). CILOSTAZOLE is indicated in the prevention of stroke, claudication and obstructive peripheral vascular disease. Cilostazol and Dipiradamol act primarily on platelets and vessels, and their use is associated with the risk of bleeding;
5. Selective PDE4 inhibitor: reduce the risk of exacerbations of chronic obstructive pulmonary disease (COPD), asthma, and rhinitis, and may have antidepressant and antipsychotic effects. They are not bronchodilators and are therefore not indicated for asthma (Cilomilast, Crisaborole, Luteolin, and Roflumilast);
6. Selective PDE5 inhibitor: is the target of this study (SIDENAFIL), which acts in the control of CHF and pulmonary hypertension. Phosphodiasterase-5 is a cGMP-specific diasterase, expressed abundantly in vascular smooth muscle. SIDENAFIL inhibits phosphodiesterase-5 by occupying its catalytic site as a pseudosubstrate, maintaining cGMP levels for a longer time interval. The drug is believed to exert its cardioprotective effect through the interaction and regulation of calcium pathway

proteins and signaling and antihypertrophic factors in cardiomyocytes. Chronic administration has been shown to improve endothelial integrity by reducing oxidative stress, by decreasing the production of superoxide ion, in pulmonary endothelial cells. Recent studies have hypothesized its use in chronic pulmonary thromboembolism.

7. Selective PDE6 inhibitor: PDE5 inhibitors (studied in this paper), also act as inhibitors of retinal phosphodiesterase-6, which is the cause of visual symptoms resulting from the use of SIDENAFIL.
8. Selective PDE7 inhibitor: has a neuroprotective effect (Quinazoline) (21).

3 PATHOPHYSIOLOGY

The dysfunction of the left ventricle, with the increase in oxytocin, causes an increase in the end-diastolic pressure, so that this ventricle contributes to the installation of Pulmonary Hypertension. The changes in the endothelium of the pulmonary vessels lead to increased endothelin and decreased nitric oxide, generating pronounced vessel changes, vasoconstriction, and proliferation of smooth muscle cells (1), causing Pulmonary Hypertension and right ventricular dysfunction.

SIDENAFIL relaxes the arterial wall, causing lower pulmonary artery pressure and resistance, reducing the overwork of the right ventricle, improving the signs and symptoms of right heart failure.

Nitric Oxide, released from endothelial cells by guanylate cyclase, stimulates the production of cGMP (cyclic Guanosine Monophosphate), which is hydrolyzed to its inactive form (Guanosine 5-Monophosphate) by PHOSPHODIESTERASE-5.

SIDENAFIL acts as an inhibitor of this phosphodiesterase, facilitating the accumulation of the Active Form i.e. cGMP (cyclic Guanosine Monophosphate) (1).

SIDENAFIL is a drug that is readily absorbed orally within 30 to 60 minutes, and is contraindicated in patients taking nitrates (treatment for coronary insufficiency), treatments for prostatic hypertrophy, such as alphablockers, Doxazosin, Tansulosin, or Alfuzosin, (18), because they share a similar mechanism of action, through peripheral vasodilation, causing the additive effect. Simultaneous use may result in drastic hypotension and sudden death.

Drugs like Omeprazole, Fluconazole, Quinidine, Amiodarone, Clarithomycin, Erythromycin, Fluoxetine, Indinavir, and Ritonvir are inhibitors of CYP3A4, decreasing the fragmentation capacity and intensifying the effect of SIDENAFIL.

This is why, according to the world literature, deaths have at first been observed in patients who were probably taking these drugs and who probably self-medicated with SIDENAFIL. The side effects of SIDENAFIL can be summarized as headache and flushing, heartburn, nasal congestion, dizziness, and photophobia in some rare cases.

The SIDENAFIL for cardiologic use is presented with the commercial name REVATIO, in a 20mg dosage, with round and white tablets (10). It was the first synthesized molecule capable of inhibiting phosphodiesterase-5 by occupying its catalytic site as a pseudosubstrate (11).

4 BIBLIOGRAPHIC SEARCH

A patient with chronic pneumopathy (COPD + mucovicidosis) (3) is reported, with development of Pulmonary Hypertension, confirmed by ultrasonography, and spirometry showing severe ventilatory disorder, with dyspnea, functional limitation for small daily tasks, and need for use of O_2 for one year.

The patient was being treated with prednisone, furosemide, carvedilol, spironolactone, ASA, and anlodipine. Sidenafil 20mg was added at the time, and she was released with O saturation$_2$ at 91%, with continuous use of O_2 3l/m at home.

Two months later, the patient returns with a significant improvement in pulmonary hypertension parameters, as assessed by ultrasound, having abandoned the use of O_2 and with a saturation of 97%.

This case illustrates well the use of SIDENAFIL in these clinical pictures.

In a study from INCOR (SP), 26 patients with CHF using SIDENAFIL were evaluated. The potential gain with this drug in CHF was evaluated (6).

Starting in 2004, numerous studies were surveyed in mixed populations that had cardiovascular disorders (12). Researchers such as ISIDORI, ROBERT KLONER (13) and ROBB KOCIOL (14) demonstrated that the drug increased not only the efficiency of the heartbeat, but also the relaxation between beats, acting as a prophylaxis of hypertrophy of the heart muscle and the consequent appearance of Heart Failure.

ROBERT KLONER has investigated, in addition to the use of SIDENAFIL in heart failure, its use in coronary heart disease and ventricular arrhythmias (15).

DAVID DURRANT has investigated the cardioprotective characteristic in patients with heart failure and cancer (16).

DAVID CHARLES HUTCHINGS reports the cardioprotective effect of Phosphodiesterase-5, as a direct effect of its action on the myocardium, independent of its vascular action (17).

Researchers from Karolinska (22), in their studies, show that SIDENAFIL decreases the probability of a new heart attack in patients with stable coronary artery disease or angina, decreasing the chances of developing Heart Failure or the need for Balloon Dilatation and Saphenous Vein bypass surgery. This protection is directly proportional to the dose and frequency of use of the drug.

Italian doctors (23) have concluded that in all cases studied, daily use of SIDENAFIL (PDE5i) is able to prevent cardiac growth in the long term, as well as improving the performance of the heart.

5 PEDIATRIC USE

In children and neonates, despite the difficulty of administration due to the absence of liquid presentations, the literature reports the protocol of 2mg-8mg/kg/day, divided into 4 times a day, reaching a maximum of 100mg/day. Most protocols report Sidenafil showing good tolerance with doubled doses (7).

An improvement has been observed, with a reduction of at least one class in the staging of CHF (from 4 to 3, and even to class 2, from class 3 to 2, or 1), in addition to a substantial increase in O saturation$_2$. This determines a decrease in the incidence of recurrent respiratory infections and low birth weight in young children or in the first year of life.

The literature also mentions the use of SIDENAFIL for up to one year in congenital heart disease before surgery.

6 CONCLUSION

SIDENAFIL was shown to be well tolerated at doses 8 times higher (800mg) than the laboratory's maximum expected dose (100mg), with no increase in the adverse effects listed for the common daily dosage.

Such a drug showed no long-term effect on spermatogenesis, nor conceptual teratogenic effects.

In view of the bibliographical research and the survey of double blind studies and protocols, it was concluded that SIDENAFIL is, in fact, a new drug to be incorporated in the arsenal of cardiologic treatment, due to its actions of control and even reversal of Pulmonary Hypertension,

existing in Congestive Heart Failure, providing an increase or normalization of oxygen saturation, with reduction or disappearance of dyspnea, recovery of physical activity, essential in work activities, in short, providing a recovery in the quality of life of patients.

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