INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

Less-Known Phosphodiesterase Type 5 Inhibitors – New Solutions for the Therapy of Erectile Dysfunction

GAFAROV Rushen Refatovich, DAVRONOV Oybek Otabekovich
Samarkand State Medical University, Samarkand, Uzbekistan

Abstract: Erectile dysfunction (ED) is a serious health problem that directly affects quality of males' life. In the drug treatment of ED, a group of phosphodiesterase type 5 inhibitors plays an important role (PDE-5), which is the first line of treatment for ED. This article presents the currently available data regarding the parameters of pharmacokinetics, pharmacodynamics and possible adverse events of PDE-5 inhibitors that are not so widely known or are at various stages of clinical trials. Less-known PDE-5 inhibitors, which are presented in the article, include lodenafil, mirodenafil, yokenafil, SLx-2101 and simmerafil.

Keywords: phosphodiesterase type 5 inhibitors, erectile dysfunction, lodenafil, mirodenafil, yokenafil, SLx-2101 and simmerafil.

Introduction. Erectile dysfunction (ED) is inability to achieve and maintain an erection sufficient for successful sexual performance. ED is a serious medical and social problem that affects both the psychosocial status of a man and his partner [1]. The frequency of this sexual disorder directly correlates with age: ED affects about 40% of men aged 40-50 years, at 50-60 years old - almost half (48-57%), and in the older age group more than 70% of males suffer from this problem. ED is associated with various comorbid conditions such as hypertension, hyperlipidemia, metabolic syndrome, lower urinary tract symptoms (LUTS) or benign prostatic hyperplasia (BPH), cardiovascular diseases, psychological factors, diabetes mellitus, post-radical prostatectomy, use of antidepressants and antihypertensives, etc. [2,3,4].

Penile erection occurs in response to sexual stimulation of various types (visual, tactile, auditory, olfactory). In this case, impulses from the cortex of the frontal and temporal lobes of the brain are transmitted to the amygdala, which is one of the most important centers of erection. From the amygdala impulses are transmitted to the parasympathetic erection centers in the spinal cord, located at the S2-S4 level. During sexual stimulation, the parasympathetic nervous system begins to significantly predominate, which is accompanied by the release of the main mediator of erection - nitric oxide (NO) through parasympathetic non-cholinergic, non-adrenergic nerve endings [5,7].

Nitric oxide (NO), released by nerve endings and endothelium, activates the enzyme guanylate cyclase. Guanylate cyclase increases the synthesis and intracellular concentration of the second messenger - cyclic guanosine monophosphate (cGMP). cGMP alters the activity of a number of specific protein kinases that are involved in protein phosphorylation and ion channel function. The action of protein kinases leads to the opening of potassium channels and hyperpolarization of smooth muscle cell membranes, the accumulation of calcium in the endoplasmic reticulum and blocking the entry of calcium ions into cells due to the closure of calcium channels [6,8]. This leads to a decrease in calcium concentration in the cytoplasm, relaxation of smooth muscles and the onset of penile erection.

cGMP is influenced by the enzyme phosphodiesterase type 5 (PDE5), which breaks down cGMP, resulting in penile smooth muscle contraction and detumescence. Currently, 11 types of PDE are known, which are divided into 21 subtypes. PDE isoenzymes play an important role in ensuring contractions of striated and smooth muscles, vascular tone, and the functions of endocrine and other organs [8]. Other types of phosphodiesterases are found in the corpora cavernosa, but they do not play a significant role in penile erection.

Blocking the PDE-5 enzyme increases the concentration of cGMP and promotes erection [9, 10]. Therefore, drugs related to PDE-5 inhibitors (PDE-5 inhibitors) are first-line drugs in the treatment of ED [11,12]. The most common PDE5s currently available are sildenafil, tadalafil, vardenafil, udenafil and avanafil. Less known are lodenafil, mirodenafil, yokenafil (jonkenafil), SLx-2101 and simmerafil, the clinical and pharmacological parameters of which are the subject of this article.

Materials and methods. Non-systematic literature review was performed in the PubMed, Google Scholar databases using the keywords: erectile dysfunction, phosphodiesterase type 5 inhibitors, lodenafil, mirodenafil, yokenafil (jonkenafil), SLx-2101, simmerafil.

Results. Among the phosphodiesterase type 5 inhibitors that are not so widely known or are at the stage of clinical trials include lodenafil, mirodenafil, yokenafil, SLx-2101, simmerafil.

Lodenafil carbonate (Helleva®, Cristália Produtos Químicos Farmacêuticos, Brazil). This is one of the new PDE-5 inhibitors. Developed and used in Brazil. Lodenafil carbonate is a prodrug consisting of two lodenafil molecules linked by a carbonate bridge. After taking lodenafil, carbonate breaks down into monomers and the lodenafil molecule directly has a relaxing effect on the muscles of the cavernous bodies. Lodenafil peak plasma concentration and half-life are 1.2 and 2.4 hours, respectively. In 2009, Glina S. et al. conducted a phase II clinical trial of lodenafil, which examined the effectiveness of dosages of 20, 40 and 80 mg compared with placebo and found that lodenafil at a dose of 80 mg was well tolerated and significantly more effective than placebo [13]. The same group of researchers completed a phase III clinical trial in 2010. They compared 40 and 80 mg lodenafil and placebo. Lodenafil 80 mg was significantly superior to placebo 40 mg. In general, the tolerability profile of lodenafil is similar to that of sildenafil and vardenafil. Side effects of mirolenafil included rhinitis, headache, flushing, dizziness and visual disturbances [14, 15].

Mirodenafil (Mvix®, SK Chemicals Life Science, Seoul, Korea). Mirodenafil, along with udenafil, is another PDE-5 inhibitor that originated in South Korea. Was developed in 2007. The time to reach maximum plasma concentration is 1.25 hours, the half-life is 2.5 hours. Mirodenafil is characterized by much higher selectivity compared to sildenafil, although the main pharmacokinetic parameters of these drugs are similar. Mirodenafil is 10 times more selective for PDE5 than sildenafil, while the inhibitory effect on other types of PDE is less [16]. There are clinical data confirming the same effectiveness of mirodenafil at a dosage of 50 and 100 mg [17]. There are also clinical trial results confirming the effectiveness of mirodenafil for the treatment of LUTS and ED when used simultaneously with alpha-blockers. Mirodenafil 100 mg for 8 weeks in patients already taking alpha-blockers has been shown to improve sexual function and reduce the severity of LUTS without significant episodes of hypotension [16,18]. Mirodenafil is not approved by the FDA.

Yokenafil or Yonkenafil (Zhuhai Oxforston PharmTech Co. Ltd., Zhuhai, China). Yokenafil hydrochloride is a new selective PDE5 inhibitor for the treatment of ED. Heis an analogue of sildenafil, but exhibits stronger PDE-5 inhibition and is characterized by less pronounced gastrointestinal side effects [19]. Its safety, tolerability and pharmacokinetic parameters were assessed in healthy Chinese male volunteers [20]. This study also examined the effect of food on the pharmacokinetics of yokenafil. The study was divided into 3 parts: single ascending dose (25, 50, 100, 150 or 200 mg yokenafil), multiple dose (50, 100 or 150 mg yokenafil once daily for 7 consecutive days) and food effect assessment (50 mg yokenafil (single dose): Yokenafil was found to be well tolerated after a single oral dose, but did not significantly affect the area under the plasma concentration-time curve after sequential administration. No apparent accumulation was observed over 7 days. Single doses of yokenafil up to 200 mg and multiple doses up to 150 mg were generally safe and well tolerated.

SLx-2101 (Surface Logic, Inc., USA) is a new PDE-5 inhibitor developed specifically for the treatment of ED. SLx-2101 is converted to the M1 metabolite, SLx-2081, which remains active. In preclinical studiesSLx-2101 demonstrated excellent performance on molecular, cellular, ex vivo and in vivo levels, and Pharmacokinetic studies have shown that the drug has a long-lasting effect. long lasting, maintaining therapeutic levels for more than 24 hours in rats [21]. A randomized, double-blind,

single-dose study in healthy male volunteers was conducted to preliminary evaluate safety, tolerability, pharmacokinetics, and endothelial function [22]. Five different doses were used (5, 10, 20, 40, and 80 mg), with six subjects receiving the active dose and two receiving placebo at each dose level. Blood samples were obtained within 48 hours. A positive erectile response was recorded 0–6 hours after administration without visual sexual stimulation (VSS) for doses of 10, 20, 40 and 80 mg and 24-24.5 hours after administration with VSS for 20, 40 mg. - and doses of 80 mg. There were no clinically significant effects on heart rate, blood pressure, or electrocardiogram. SLx-2101 was well tolerated in single doses up to 40 mg, with headache being the most common adverse event in active and placebo-treated subjects and visual effects noted at the 80 mg dose. The pharmacokinetic profile predicts PDE5 inhibition for at least 36-48 hours at all doses tested, allowing for confident once-daily dosing [22,23].

Simmerafil (TPN171H) (Shanghai Institute of Materia Medica, Chinese Academy of Sciences, China) is a selective PDE5 inhibitor being developed for the treatment of ED. To evaluate the efficacy and safety of TPN171H in men with ED, a multicenter, randomized, double-blind, placebo-controlled, parallel-design study was registered on the Clinicaltrials.gov platform. The study began on 31/12/2021 and completed on 14/02/2023, but we were unable to find any available publications reflecting the results of this study. However, the safety, tolerability and pharmacokinetics of Simmerafil for the treatment of pulmonary arterial hypertension (PAH) were evaluated in a study conducted by Chinese researchers. The entire study consisted of three parts: I (single dose escalation study), II (food exposure study), and III (multiple dose escalation study). 63 healthy people took part in the study. Compared to other PDE-5Is, TPN171H was found to have no effect on blood pressure and color discrimination. TPN171H was safe and generally tolerated by healthy individuals [24].

Discussion.

PDE-5 inhibitors have demonstrated high efficacy in randomized placebo-controlled trials with limited side effects, which has led to their widespread use in clinical practice. However, a number of side effects of type 5 PDE inhibitors are group-specific, so research continues to eliminate adverse events and increase the effectiveness of these ED treatments. PDE-5Is are considered the first-line treatment for ED. While most of the side effects of PDE-5I are mild, these drugs can also be associated with more serious problems such as vision impairment, hearing loss, priapism, and others [25].

As first-line drugs in the treatment of ED, PDE-5Is have several limitations for use. Drugs in this group cannot be taken together with nitrates due to the potentiation of the hypotensive effect of PDE-5I. According to the recommendations of the American Heart Association, nitrates can be used no earlier than 24 hours after taking short-acting PDE-5I and no earlier than 48 hours after taking tadalafil. When using PDE-5, the possible risk of complications associated with sexual activity should be taken into account:

- within 3 months after myocardial infarction;
- with unstable angina or angina that occurs during sexual intercourse;
- with heart failure of functional class II or higher, which has developed within the last 6 months, uncontrolled heart rhythm disturbances, arterial hypotension (blood pressure below 90/50 mm Hg) or uncontrolled arterial hypertension,
- within 6 months after stroke [26, 27, 28].

A combination of PDE-5 inhibitors with other drugs is possible.

Conclusions. With all the diversity of PDE-5, the choice of drug depends on the frequency of planned sexual intercourse and the patient's personal perception of the drug. Although safe and tolerable in patients with ED, these drugs should be used only for specific indications and under medical supervision. Patients should be counseled about the duration of action of the drug, possible side effects and principles of use. Data on the pharmacokinetics and pharmacodynamics of PDE-5I should be updated and always taken into account when managing patients with ED.

Less-known phosphodiesterase type 5 inhibitors can be also used for the therapy of erectile dysfunction but further clinical investigations are required.

REFERENCES

1. Wiley K. Erectile dysfunction. Adv Psychosom Med. 2008;29:33-49.
2. Chaly M.E., Akhvlediani N.D., Kharchilava R.R. Erectile disfunction. Russian clinical guidelines. Urology. 2017; 2 (Appendix 2): 20-30 (in Russian).
3. Ding R.K., Liu T.F. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clean North Am. 2005;32(4):379-95.
4. Cho MC, Paik JS. Udenafil for the treatment of erectile dysfunction. Ther Clin Risk Manag. May 14, 2014; 10: 341-54.
5. Pastushak AV. Current diagnosis and treatment of erectile dysfunction. Curr Sex Health Rep. 2014;6(3):164-176.
6. Liu T.F. Erectile disfunction. N Engl J Med. June 15, 2000; 342(24):1802-13.
7. McVary K.T. Erectile disfunction. New English J. Med. 2007; 357:2472-2481.
8. Yafi F.A., Jenkins L., Albersen M., Corona G., Isidori A.M., Goldfarb S., Maggi M., Nelson S.J., Parish S., Salonia A., Tan R., Mulhall JP, Hellstrom WJ. Erectile disfunction. Primers Nat Rev Dis. February 4, 2016; 2:16003.
9. Perelman MA. The influence of relationship variables on the etiology, diagnosis and treatment of erectile dysfunction. Adv Primary Care Med: Clin Update. 2007;3:3-6.
10. Porst H, Burnett A, Brock G, Ganem H, Giuliano F, Glina S, et al. SOP for conservative (medical and mechanical) treatment of erectile dysfunction. Jay Sex Med. 2013;10(1):130–71.
11. Tsertsvadze A., Fink H.A., Yazdi F., McDonald R., Bella A.J., Ansari M.T. et al. Oral phosphodiesterase-5 inhibitors and hormonal treatment of erectile dysfunction: a systematic review and meta-analysis. Ann, intern, med. 2009;151(9):650-61.
12. Gafarov R.R., Shodmonova Z.R., Allazov S.A., Khamroev G.A., Tukhtaev F.M. Phosphodiesterase type 5 inhibitors are the first line of treatment for erectile dysfunction. Achievements of science and education. 2020;5(59):103-108 (in Russian).
13. Glina S, Toscano I, Gomacki S, de Goes PM, Junior AN, Claro JF, Pagani E. Efficacy and tolerability of oral lodenafil carbonate for erectile dysfunction: a phase II clinical trial . Jay Sex Med. 2009;6(2):553-7.
14. Glina S., Fonseca G.N., Bertero E.B. et al. Efficacy and tolerability of lodenafil carbonate for oral therapy of erectile dysfunction: a phase III clinical trial. J Sex Med 2010;7(5):1928-36.
15. Pick TK, Yafi FA, Sangkum P, Hellstrom WJ. New drugs for the treatment of erectile dysfunction. Expert opinion on emergency medications. 2015;20(2):263-75.
16. Park HJ, Moon KH, Lee SW, Lee WK, Kam SK, Lee JH, Park NC. Mirodenafil for the treatment of erectile dysfunction: a systematic review of the literature. World Jay Men's Health. 2014;32(1):18-27.
17. Paik JS, Ahn TY, Choi HK. et al. Efficacy and safety of mirodenafil, a new oral phosphodiesterase type 5 inhibitor, for the treatment of erectile dysfunction. J Sex Med 2008;5(11):2672-80.
18. Lee J.I., Cho S.I., Oh S.I. et al. Efficacy and safety of combination therapy with mirodenafil and an alpha1-blocker for lower urinary tract symptoms caused by benign prostatic hyperplasia, accompanied by erectile dysfunction: a multicenter, open-label, prospective study. Int J Impot Res 2011;23(6):249-56.

19. Wang K, Ding J, Li H, Guo W, Zhu X, Su Y, Sun L, Zhou H, Ding L. Effects of itraconazole and rifampicin on the pharmacokinetics and safety of ekenafil, a novel phosphodiesterase type 5 inhibitor, in healthy subjects. Chinese items. Eur J Pharm Sci. 2022; 1(175):106213.
20. Liang B, Wang J, Bai N, Chi Y, Wang R, Cai Y. Safety, tolerability, and pharmacokinetics of single and multiple escalating oral doses of ekenafil hydrochloride, a phosphodiesterase type 5 inhibitor, in healthy Chinese male volunteers. Clin Pharmacol Drug Dev. 2022;11(10):1184-1190.
21. Sweetnam P, Campbell S, Grogan M, et al. SLx-2101, a novel long-acting phosphodiesterase-5 (PDE5) inhibitor for erectile dysfunction: in vivo and in vitro studies [abstract no. 51]. Jay Sex Med, 2006; 3 Add. 1:30 60.
22. Prince WT, Campbell AC, Tong W, et al. SLx-2101, a novel long-acting PDE5 inhibitor: preliminary safety, tolerability, pharmacokinetics, and effects on endothelial function in healthy subjects. Jay Sex Med, 2006; 3 Add. 1:29-30.
23. Hatzimouratidis K., Hatzichristou D.G. A look into the future of erectile dysfunction treatment. Drugs. 2008;68(2):231-50.
24. Qian H, Chen Q, Liang L, Zou Y, Pu H, Xin L, Song R, Li T, Zhu H, Wang Y, Tian G, Shen J, Jiang X, Yu X, Wang Zi, Jia J. Phase Ya studying the safety, tolerability, and pharmacokinetics of TPN171H, a novel phosphodiesterase type 5 inhibitor, in healthy subjects. The drug Des Devel Ter. 2021; 6(15):2947–2959.
25. Yafi F.A., Sharlip I.D., Becher E.F. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. Sex Med Ed. 2018;6(2):242-252.
26. Shodmonova Z.R., Gafarov R.R., Allazov S.A., Giyasov S.I. Phosphodesterase type 5 inhibitors - clinical efficiency and role in therapy for erectile dysfunction // Urologiia. - 2021. - N. 2. - P. 135-140. doi: 10.18565/urology.2021.2.135-140.
27. Гафаров Рушен Рефатович, Шодмонова Зебунисо Рахимовна, Аллазов Салах Аллазович, Хамроев Гулом Абдуганиевич, Тухтаев Фирдавс Мухиддинович Ингибиторы фосфодиэстеразы 5 типа – первая линия терапии эректильной дисфункции // Достижения науки и образования. 2020. №5 (59).
28. РР Гафаров, НА Бобокулов, ХФ Файзиев Ингибиторы фосфодиэстеразы 5 типа–побочные эффекты и нежелательные явления, связанные с применением. European journal of molecular medicine. 2024; (4)1: 40-45.