Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
September 2017, Volume: 9, Issue: 9, Pages: 5229-5232, DOI: http://dx.doi.org/10.19082/5229

Effect of periodic sildenafil dosage on intraocular pressure in patients with erectile dysfunction

Alireza Nazari[1], Yousof Taghavi Tabrizi[2], Mohammadreza Mokhtaree[3]

[1] M.D. Urologist, Assistant Professor, Department of Surgery, Physiology-Pharmacology Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2] M.D. Ophthalmologist, Assistant Professor, Department of Ophthalmology and Otorhinolaryngology, Geriatric Care Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[3] M.Sc. of Educational Psychology, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Type of article: Original

Abstract

Background and aim: Sildenafil is used to treat erectile dysfunction but it has association with some side effects. This study was conducted with the aim of investigating the effect of duration of taking sildenafil on intraocular pressure (IOP) in patients with erectile dysfunction.

Methods: The study population of this cross-sectional study were all males with erectile dysfunction referring to the urology clinic affiliated to Rafsanjan University of Medical Sciences (Kerman, Iran) over a one-year period (2015-2016) among whom 110 patients were included in the study. After medical examinations and required investigations, a weekly dose of 25-100mg sildenafil (50 mg per week on average) was prescribed for patients. IOP in these patients was measured by an ophthalmologist before, one month after and three months after taking medication respectively. Finally, data were analyzed by SPSS version 16 using repeated measures test.

Results: Mean IOP before taking medication as well as one month and three months after taking sildenafil was 14.88±1.3, 15±1.28 and 15±1.34 mmHg respectively. Analysis of results showed that the difference in IOP in various periods of measurement was significant ($p<0.001$). Mean IOP before taking sildenafil was significantly different from three months after taking it ($p<0.001$) and mean IOP one month after taking sildenafil was significantly different from three months after taking it ($p=0.002$).

Conclusion: Results of this study indicated that taking sildenafil for three months increased IOP. Although these changes may not be clinically significant.

Keywords: Sildenafil; Intraocular Pressure; Long-Term Use

1. Introduction

Phosphodiesterases (PDE) are enzymes that regulate the cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (1). The first phosphodiesterase was identified in 1970. To date, 12 types of this enzyme have been identified and investigated by researchers (3), the distribution of which, varies in different tissues (1). Type 5 of this enzyme (PDE5) was identified in 1978 (4) and it was determined that this enzyme is present in all smooth muscles, especially in the endothelium (5). Concurrent with sexual arousal, cGMP is formed in the endothelial cells of the veins in corpus cavernosa which relaxes smooth muscles in the walls of their veins and increases blood flow and erection following it. Then, the cGMP is degraded by the PDE5 enzyme and its effect disappears (6). By inhibiting PDE5, sildenafil prevents degradation of cGMP and results in its effect to continue, and this will result in relaxation of smooth muscles in the endothelium of corpora cavernosa, increased blood flow and strengthening of erection. PDE5 inhibitors were first used to increase blood flow in treatment of angina pectoris, but there was no significant effect on this (1). However, since the level of PDE5 is very high in corpora cavernosa of penis, PDE5 inhibitors have a significant effect in this organ (4). In addition, sildenafil is used in treatment of pulmonary hypertension, systemic hypertension, cardiovascular diseases and diabetes. Sildenafil also

Corresponding author:
Mohammadreza Mokhtaree, Clinical Training Unit, Moradi Hospital, Shohada St, Rafsanjan, Kerman, Iran.
Tel: +98.3434260080, Fax: +98.3434260086, Email: mrmokhtaree@yahoo.com
Received: August 10, 2016, Accepted: December 14, 2016, Published: September 2017
iThenticate screening: October 07, 2016, English editing: August 28, 2016, Quality control: September 05, 2017

has an anti-inflammatory effect by inhibiting the production of active oxygen species and inflammatory cytokines (7). Efficiency of the antioxidant system of this medication has been shown in recent studies (8). The half-life of sildenafil is 4 hours and it is metabolized and excreted through the liver. The common dose of sildenafil is 50mg and it can be used at the maximum 100mg before sexual intercourse depending on the status of patients and severity of the disease (9). Due to the effect of sildenafil on the smooth muscle of other tissues in the body, it will be associated with side effects (10). The side-effects of sildenafil on the smooth muscles of the eye include changes in blood flow, retinal function and retinal pigment epithelium as well as the impairment of IOP and glaucoma (11). The cGMP and smooth muscles play a role in the production and drainage of the aqueous humor that determines IOP (10, 11). Theoretically, at least, PDE5 inhibitors can affect IOP by affecting the production and drainage of the aqueous humor (12). Therefore, by inhibiting PDE5 and reducing cGMP following it (10), sildenafil can change the function of retina and retinal pigment epithelium (RPE) due to creating changes in ocular blood flow, and it can result in high IOP and consequently, glaucoma (13). Since most patients with erectile dysfunction are the elderly, usually require long-term medication, and concurrently may suffer from IOP disorders, it is of high importance to investigate the side effects of PDE5 inhibitors on IOP. According to what has been stated and given the relatively high consumption of this medication for some disorders (including erectile dysfunction and cardiopulmonary hypertension) (6), this study was conducted to determine the effects of long-term administration of sildenafil on IOP.

2. Material and Methods

In this descriptive and cross-sectional study, all patients with erectile dysfunction referring to the urology clinic affiliated to Rafsanjan University of Medical Sciences (Kerman, Iran) over a one-year period (2015-2016) were investigated, among whom 110 patients were included in the study. Inclusion criteria was erectile dysfunction based on the International Classification of Diseases (ICD-10) - Criteria for Male Erectile Dysfunction. Patients under 25 and over 60 years old, history of glaucoma, severe liver disease, severe renal disease, recent history of CVA and a history of taking medication used to treat sexual dysfunction were excluded from this study. Then, the cause of erectile dysfunction including diabetes, taking psychiatric medications, brain and spinal cord injury, using narcotics, methadone maintenance treatment (MMT) or other items was examined. Afterwards, the cause of erectile dysfunction was explained for patients, and if possible, was treated with the help of other specialists. Then, sildenafil was prescribed according to the common therapeutic protocol (50mg per week on average). Some explanations were provided for patients on medications including the mechanism of action and doses of medication. Then, patients were referred to an ophthalmic clinic for eye examination and IOP measurement. Ophthalmic examinations were conducted using slit lamp to view the structure and components of the eye, anterior chamber angle, as well as retinal assessment. IOP was measured using the Goldmann applanation tonometer. These ophthalmic examinations are non-invasive and safe. Then, patients were referred to an ophthalmology clinic, one month and three months after taking sildenafil for IOP measurement. Then, data were analyzed using SPSS 16 software package and repeated measures test. This study was approved by the Ethics Committee of Biomedical Research in Rafsanjan University of Medical Sciences (ethical code: IR.RUMS.REC.1394.169).

3. Results

Mean age of patients was 53.2±5.35 (range: 42-60 years). The dose of sildenafil was between 25 and 100 mg per week (an average of 50 mg per week). Mean IOP was 14.88±1.3 mmhg, 14.9±1.28 mmhg and 15±1.34 mmhg before, one month after, and three months after treatment with sildenafil respectively. To investigate the changes of IOP at different measuring times, a repeated measure test was used. Assumptions of using this analysis was assessed then the test was performed. Our findings indicated significant changes in IOP at different measuring times ($p<0.001$). To investigate the difference between different times of IOP measuring, post-hoc test was employed. Mean IOP before treatment with sildenafil was 14.88±1.3 mmHg, which was significantly different from mean IOP three months after treatment (15mm Hg±1.34) ($p<0.001$). In addition, the difference in IOP in the first month (14.9±1.28 mmHg) and the third month after taking sildenafil (15±1.34 mmHg) was significant ($p=0.002$) (Table 1).

Table 1. Results of paired comparison of stages before, one month after and three months after taking sildenafil on the scores of intraocular pressure (post-hoc test)

Stages	Compared to	Mean difference	Standard error	p-value
Before medication	One month after use	-0.024	0.029	1
	Three months after use	-0.119	0.03	<0.001
One month after medication	Three months after use	-0.095*	0.027	0.002

4. Discussion

Results of this study indicated that taking sildenafil for three months increased IOP. This has been observed in some human and animal studies too (14). Results of the study by Koksal et al. showed that a single dose of 100 mg sildenafil increased the blood flow in the ophthalmic artery, central retinal and small posterior ciliary (11). When investigating the effect of sildenafil on IOP in animal models, Gerometta et al. realized that a single dose of 50-100 mg sildenafil, along with 20 mg tadalafil increased IOP (14). The results of this study were consistent with other studies but, Grunwald et al. concluded that a maximum single-dose use of sildenafil had no significant effect on IOP of patients with chronic open-angle glaucoma (15). Ermis et al. also demonstrated that no significant changes were observed in IOP and ocular status after a single-dose use of 50-100 mg sildenafil (16). Results of the study by Yajima et al. indicated that taking sildenafil has no effect on IOP and diameter of pupil (17). Wirostko et al. demonstrated that taking over 80mg sildenafil three times per day in patients with high intrapulmonary pressure has no harmful effects on visual acuity, contrast sensitivity, color vision, visual field, examination with slit lamp, fundoscopy and finally IOP (10). It is possible that various methods and tools of measuring IOP are the cause of this difference in observed results. In addition, in this study, changes in mean IOP in different measuring times have been from 14.88 mmHg to 14.9 mmHg and finally 15 mmHg. Although these changes were statistically significant, clinically, no changes may have occurred in IOP of patients taking sildenafil (given that normal range of IOP is 12-21 mmHg (18). It is worth mentioning that mean IOP in patients under study was between 12.5 mmHg and 17.3 mmHg. An individual survey of patients showed that for example, a patient with IOP of 12.5 mmHg before treatment reached 12.7 mmHg after three months of treatment or a patient with IOP of 17.3 mmHg before treatment reached 17.35 mmHg after three months of treatment. This IOP increase was seen in all patients under the study.

5. Conclusions

Findings of this study showed that taking sildenafil for three months significantly increases IOP. Therefore, this adverse eye effect suggests that caution should be exercised in people who take sildenafil and to monitor IOP periodically. In this study, only IOP was measured. Therefore, for later studies it is suggested to examine visual acuity of patients taking sildenafil and similar medications in terms of color vision and visual field testing using perimetry.

Acknowledgments:

This project was conducted after being approved by the Research Council of the Faculty of Medicine and by the Research Deputy of Rafsanjan University of Medical Sciences. It is necessary to appreciate and thank all patients who participated in this study.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References:

1) Boswell-Smith V, Spina D, Page CP. Phosphodiesterase inhibitors. British journal of pharmacology. 2006; 147 Suppl 1: S252-7. doi: 10.1038/sj.bjp.0706495.
2) Giembycz MA, Field SK. Roflumilast: first phosphodiesterase 4 inhibitor approved for treatment of COPD. Drug Des Devel Ther. 2010; 4: 147-58. PMID: 20689641, PMCID: PMC2915539.
3) Supuran CT, Mastrolorenzo A, Barbaro G, Scozzafava A. Phosphodiesterase 5 inhibitors-drug design and differentiation based on selectivity, pharmacokinetic and efficacy profiles. Curr Pharm Des. 2006; 12(27): 3459-65. doi: 10.2174/138161206778343118. PMID: 17017939.
4) Ravipati G, McClung JA, Aronow WS, Peterson SJ, Frishman WH. Type 5 phosphodiesterase inhibitors in the treatment of erectile dysfunction and cardiovascular disease. Cardiol Rev. 2007; 15(2): 76-86. doi: 10.1097/01.crd.0000233904.77128.49. PMID: 17303994.
5) Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. International journal of impotence research. 2004; 16 Suppl 1: S11-4. doi: 10.1038/sj.ijir.3901208.
6) Gerometta R, Alvarez LJ, Candia OA. Effect of Sildenafil Citrate on Intraocular Pressure and Blood Pressure in Human Volunteers. Exp Eye Res. 2011; 93(1): 103-7. doi: 10.1016/j. exer. 2011.05.010. PMID: 21651908, PMCID: PMC3138881.

7) Moeini Moghaddam R, Shalizar Jalali A, Najafi GR, Behfar M. Protective effect of Sildenafil on contralateral epididymal sperm concentration and motility following unilateral blunt testicular trauma in pre-pubertal male mice. Journal of Shahrekord Uuniversity of Medical Sciences. 2015; 17(4): 11-6.
8) Akintunde JK, Ajiboye JA, Siemuri EO, Oyelowo SB, Sunday OJ, Abam EO, et al. Sub-chronic treatment of sildernafil citrate (Viagra) on some enzymatic and nonenzymatic antioxidants in testes and brain of male rats. J Pharm Drug Deliv Res. 2012; 1: 1-5. doi: 10.4172/2325-9604.1000105.
9) Hallowell L, Comerford KC. Nursing 2015 Drug Handbook. 35th ed. Wolters Kluwer Health. 2014.
10) Wirostko BM, Tressler C, Hwang LJ, Burgess G, Laties AM. Ocular safety of sildenafil citrate when administered chronically for pulmonary arterial hypertension: results from phase III, randomised, double masked, placebo controlled trial and open label extension. BMJ. 2012; 344: e554. doi: 10.1136/bmj.e554. PMID: 22354598, PMCID: PMC3283528.
11) Koksal M, Ozdemir H, Kargi S, Yesilli C, Tomac S, Mahmutyazicioglu K, et al. The effects of sildenafil on ocular blood flow. Br J Ophthalmol. 2008; 92(4): 469-73. doi: 10.1136/bjo.2007.131789. PMID: 18369062.
12) Kotikoski H, Vapaatalo H, Oksala O. Nitric oxide and cyclic GMP enhance aqueous humor outflow facility in rabbits. Current eye research. 2003; 26(2): 119-23. doi: 10.1076/ceyr.26.2.119.14511. PMID: 12815531.
13) Kerr NM, Danesh-Meyer HV. Phosphodiesterase inhibitors and the eye. Clin Exp Ophthalmol. 2009; 37(5): 514-23. doi: 10.1111/j.1442-9071.2009.02070.x. PMID: 19624350.
14) Gerometta R, Alvarez LJ, Candia OA. Effects of Sildenafil and Tadalafil on Intraocular Pressure in Sheep: Implications for Aqueous Humor Dynamics. Invest Ophthalmol Vis Sci. 2010; 51(6): 3139-44. doi: 10.1167/iovs.09-4862. PMID: 20089876, PMCID: PMC2891473.
15) Grunwald JE, Jacob SS, Siu K, Piltz J, Dupont J. Acute effects of sldenafil ctrate (Viagra) on intraocular pressure in open-angle glaucoma. Am J Ophthalmol. 2001; 132(6): 872-4. doi: 10.1016/S0002-9394(01)01268-5. PMID: 11730651.
16) Ermis SS, Inan UU, Samli M, Ozturk F. Acute effects of sildenafil on Humphrey visual field and intraocular pressure. Int Ophthalmol. 2004; 25(2): 69-72. PMID: 15290883.
17) Yajima T, Yajima Y, Koppiker N, Grunwald JE, Laties AM. No clinically important effects on intraocular pressure after short-term administration of sildenafil citrate (Viagra). Am J Ophthalmol. 2000; 129(5): 675-6. doi: 10.1016/j.exer.2011.05.010. PMID: 10844068.
18) Mansberger SL, Gordon MO, Jampel H, Bhorade A, Brandt JD, Wilson B, et al. Reduction in intraocular pressure after cataract extraction: the Ocular Hypertension Treatment Study. Ophthalmology. 2012; 119(9): 1826-31. doi: 10.1016/j.ophtha.2012.02.050. PMID: 22608478, PMCID: PMC3426647.