TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (6): 951-956
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1009-1119

Urodynamic evaluation of acute effects of sildenafil on voiding among males with erectile dysfunction and symptomatic benign prostate

Fatih Rüştü YALÇINKAYA, Mürsel DAVARCI, Soner AKÇİN, Ahmet GÖKÇE, Eşref Oğuz GÜVEN, Mehmet İNCİ, Mevlana Derya BALBAY

Aim: To evaluate the acute effects of sildenafil citrate on micturition of men with erectile dysfunction and symptomatic benign prostatic hyperplasia using urodynamic parameters.

Materials and methods: Between June and December 2009, a total of 50 patients over the age of 40 participated in the study. The patients were admitted to our hospital with erectile dysfunction and moderate to severe lower urinary symptoms with benign prostatic hyperplasia. To examine the sexual function of the participants, we used the IIEF-5 Sexual Health Inventory for Men questionnaire. Patients were randomly divided into 2 groups: a treatment group and a control group. A basal urodynamic evaluation was performed in both groups. After the urodynamic evaluation, 50 mg of sildenafil was given to the patients in the control group and 1 h later a second evaluation was performed. Following the urodynamic evaluation, a placebo was given to the patients in the control group and then a second evaluation was performed after 1 h.

Results: A statistically significant increase was seen in maximal flow and average flow (Qmax and Qave) after 1 h in the treatment group. The increase in the control group was not significant.

Conclusion: Based on the study findings, we suggest that sildenafil has an effect on micturition in the short term. However, to determine the role of sildenafil in the treatment of BPH/LUTS, further studies with larger patient groups are needed.

Key words: Benign prostatic hyperplasia, lower urinary tract symptoms, phosphodiesterase inhibitors, sildenafil, uroflowmetry, urodynamics

Introduction

Benign prostate hyperplasia (BPH) is enlargement of the prostate (1). Erectile dysfunction (ED) is defined as a deficiency in sustaining or maintaining enough penile erection for sexual intercourse for at least 6 months (2). BPH and ED are common disorders among aging males (3,4). The presence of lower urinary tract symptoms (LUTS) related to BPH is defined as an independent risk factor for the development of ED (5). In BPH, lower urinary tract symptoms develop partly as a result of partly fast growing prostate and bladder outlet obstruction (static component), and partly due to bladder decompensation and hyperfunction (dynamic component) (3).

Several studies have demonstrated that treatment of ED patients with sildenafil such as phosphodiesterase 5 (PDE5) not only treats ED symptoms but also LUTS (6,7). The highest PDE5 expression, after the corpus cavernousum, is in the bladder. However, there is also an important PDE5 expression in the prostate (8). For this reason, it is thought that PDE5

Received: 07.09.2010 – Accepted: 11.10.2011
Department of Urology, Faculty of Medicine, Mustafa Kemal University, Hatay - TURKEY.
Correspondence: *Fatih Rüştü YALÇINKAYA, Department of Urology, Faculty of Medicine, Mustafa Kemal University, Hatay - TURKEY*
E-mail: frykaya@hotmail.com

has a functional effect on these tissues (9). Uckert et al. demonstrated PDE5 presence in the human prostate transitional zone (10). PDE5 inhibitors clearly cause relaxation in the bladder, prostate, and urethral tissues. This seems more effective in the prostate and urethra. The relaxation of the prostate and urethra can decrease urinary outflow resistance and can regulate urine flow (6,9). In previous studies, chronic treatment of BPH patients with PDE5 inhibitor has been the focus. Consequently, the acute effect of PDE5 inhibitors was not evaluated. In a study carried out with uroflowmetry, it was shown that sildenafil has a positive effect on low urinary system obstruction when it is at maximum blood rate (11). Uroflowmetry (though it is the most common, practical, and objective lower urinary system obstruction evaluation tool) has a wide unstable range and no reproducibility. Pressure-flow studies, an invasive type of urodynamic studies, are carried out by calculating flow-rate during voiding on uroflowmetry along with calculating detrusor pressure. At present, pressure-flow study is accepted as the gold standard in the diagnosis of infravesical obstruction (12).

Therefore, our aim was to investigate the effect of sildenafil citrate on LUTS in BPH patients with ED.

Materials and methods

The study was planned as single center, prospective, randomized, and placebo controlled, after obtaining permission from the Ethical Committee of Mustafa Kemal University Medical School. Between June and December 2009, 50 patients over the age of 40 who had ED and lower urinary symptoms, ranging from medium levels to acute levels, according to the International Prostate Symptom Score (IPSS), were included in the study. A signed, written informed consent, approved by the local Ethical Committee, was obtained from all subjects before the study.

Detailed medical history of each patient was obtained for basal evaluation. A full physical examination, including a digital rectal examination, was performed. Total and free serum prostate specific antigen (PSA) levels were determined. Abdominopelvic ultrasonography was also performed. LUTS were evaluated with IPSS. To determine the sexual functions of the patients, the IIEF-5 Sexual Health Inventory for Men survey was used by summing up the International Index of Erectile Function (IIEF) survey (13). This survey is useful because it has 5 questions and can be answered by the patients in a few minutes. The IIEF, which was developed by Rosen et al., is one of most common forms used for evaluating sexual problems in men (14).

To be involved in the study, the IIEF-5 score had to be below 21 and the total IPSS score had to be over 7. Exclusion criteria were as follows: history of erectogenic treatment, any treatment for LUTS (α-blocker or 5 α-reductase inhibitor), urethral stricture, bladder tumor, renal insufficiency, neurogenic bladder, cardiovascular and pulmonary disorder, urinary infection, urinary stone disease, diabetes mellitus, previous prostate operation, previous pelvic operation, elevated levels of prostate specific antigen (PSA), and abnormal digital rectal examination.

The patients were randomly separated into treatment and control groups (30 patients taking 50 mg of oral sildenafil in the first group and 20 patients taking a placebo in the second group). In both groups, basal urodynamic evaluations were performed. In the treatment group, following the urodynamic evaluation, 50 mg oral sildenafil citrate tablets were given, and 1 h later a second urodynamic evaluation was performed. On the other hand, in the control group, a placebo was given after the first urodynamic evaluation, and 1 h later a second evaluation was performed. All patients, before urodynamics, were subject to uroflowmetry and postmicturition residual urine determination following spontaneous voiding. Following this, the patients underwent pressure flow studies in both sitting and standing postures. Detrusor contractility pressure during the maximum flow voiding, maximum urinary flowing speed, average flowing speed, and electromyography activity during voiding were recorded (Table 1).

Statistical analysis

A t-test was used to compare the ages, prostate volumes, PSA, duration of symptoms, IPSS, quality of life, and IIEF of all patients. Differences between

Table 1. Patients' characteristics for both groups.

	Group 1 (n = 30) mean ± SD	Group 2 (n = 20) mean ± SD	P value (<0.05 significant)
Age	58.63 ± 10.56	55.2 ± 9.19	0.376
Prostate volume (cm^3)	51.93 ± 15.01	46.3 ± 12.12	0.084
PSA (ng/dL)	1.89 ± 1.07	1.61 ± 0.77	0.84
Symptom duration (month)	3.43 ± 0.5	3.4 ± 0.5	0.641
IPSS	19.16 ± 6.06	16.9 ± 4.08	0.139
Quality of life	3.3 ± 0.74	2.75 ± 0.71	0.058
IIEF	10.83 ± 5.88	9.45 ± 4.99	0.065

predrug basal urodynamic parameters and postdrug urodynamic parameters were evaluated using a nonparametric test (Wilcoxon marked rank test). P < 0.05 considered significant.

Results

In the treatment group, the predrug basal mean Qmax (maximum flow rate) was 8.7 ± 3.54 mL/s, while it was 11.56 ± 6.82 mL/s in the first hour postdrug. This difference was statistically significant (P < 0.05). In the control group, the basal mean Qmax was 7.35 ± 2.73 mL/s, while it was 7.6 ± 3.26 mL/s in the first hour postdrug. The difference was not significant (P > 0.05) (Figure 1).

In the treatment group, the predrug mean Qave (average flow rate) was 4.72 ± 1.88 mL/s, while it was 5.8 ± 2.7 mL/s in the first hour postdrug. This difference was statistically significant (P < 0. 05). In the control group, the mean Qave predrug was 3.8 ± 1.28 mL/s, while it was 3.9 ± 1.44 mL/s in the first hour postdrug. The difference was not statistically significant (P > 0. 05) (Table 2).

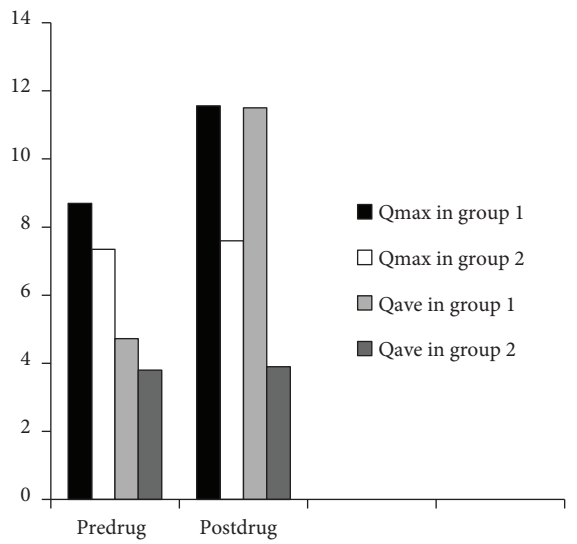

Figure 1. Pre- and postdrug flow rate in both groups.

According to the nonparametric Wilcoxon marked rank test statistical analysis (P > 0.05), there was no statistical significance between the groups, regarding first urine feeling, first jamming feeling, bladder volume, bladder compliance, vesicle pressure in discharging, abdominal pressure, detrusor pressure, electromyography, predrug basal urodynamic rate, and postdrug urodynamic rates in terms of voiding volume.

Discussion

Both LUTS and BPH are seen in similar groups. Along with this, the mechanisms to explain the process of these diseases are not well known. Chang et al. drew attention to the possible mechanisms of ED development in BPH patients based on a rabbit model, which had partial bladder outlet obstruction (15).

The beneficial effects of PDE5 inhibitors on bladder hyperactivity are clearly reported (6,9,16).

The LUTS patients with ED are still looking for medical help. The first step in treatment for ED is oral PDE5 inhibitors. Treatment with phosphodiesterase type 5 (PDE5) is an effective and reliable treatment for erectile dysfunction (17-19).

Table 2. Pre- and postdrug flow rate in both groups.

		Predrug	Postdrug	
Group 1 (mL/s)	Qmax	8.7 ± 3.54	11.56 ± 6.82	P ≤ 0.05
	Qave	4.72 ± 1.88	11.5 ± 2.7	
Group 2 (mL/s)	Qmax	7.35 ± 2.73	7.6 ± 3.26	P ≥ 0.05
	Qave	3.8 ± 1.28	3.9 ± 1.4	

Sildenafil is the first PDE5 inhibitor. The suggested starting dose is 50 mg, and this should be regulated according to the patient's response and side effects (20).

To date, 11 members of PDE type have been described. cAMP and cGMP constructed with PDE inhibitors mediate prostatic smooth muscle relaxation (21,22).

When compared with the corpus cavernosum, there was high PDE5 mRNA expression in the bladder and urethra. However, at the same time, there was a significant amount of PDE5 expression in the prostate (8), which is why the functional role of PDE5 can be seen in these tissues (9).

Uckrert et al. showed the effect of PDE5 in the prostate transitional zone. Most commonly found was PDE4, while the second most common was PDE5. They also showed that sildenafil is a relaxant mediated by an agent in the transitional zone bands of the prostate (10). These findings make us think that sildenafil has a positive effect on the prostate smooth muscle cells.

The other cause of the obstruction is a growing prostate. Obstruction is a mechanized cause. New reports make us think that cGMP accumulation has an antiproliferative effect on the smooth muscle cells of the prostate (23,24). A previous study showed that Zaprinast can decrease proliferation in smooth muscle cells and prostatic stromal cells of patients with BPH (25). The PDE5 inhibitors on the market were shown to have an antiproliferative effect on BPH smooth muscle cells (8,23). In a study carried out by Dokita et al., it was found that Zaprinast, a PDE5 inhibitor, increases urethral relaxation in rabbits (26).

Qui et al. found that sildenafil caused a small but meaningful increase in cGMP on the detrusor muscle in rabbits. At the same time, the cGMP level alone is not enough. The detrusor smooth muscle is usually mediated by cAMP. The researchers accepted that sildenafil probably caused the relaxant effect through PDE1 inhibition. At the same time, they stated that they could not ignore cGMP necessity for effective relaxation (27).

Another mechanism claimed to decrease LUTS is to increase nitric oxide (NO) transmission with PDE5 inhibitors and, in this way, to regulate nonvoiding contractions (hyperactivity) (16,28,29).

Although there is increasing proof of the positive effects of PDE5 inhibitors on LUTS, in none of these studies has the short-term effect of these drugs on the voiding of men with BPH been found.

In the study by Kaplan et al., Qmax results showed a positive improvement although it was not statistically significant (30). The common point in clinical studies that showed the positive effect of sildenafil on LUTS is that all of the findings were collected from patients who used sildenafil for at least for 1 month (7).

These long-term positive effects indicate that PDE5 depended on antiproliferative and relaxant effects, and relaxant effects on the bladder and urethra. NO is an important mediator on isolated bladder and urethra smooth muscle and, at the same time, it regulates prostatic smooth muscle tones. For this reason, the increasing level of NO after sexual functions can be responsible for the improvement in LUTS. Independent from these factors, it is known that improvement in the sexual lives of the patients increases quality of life and this can indirectly improve LUTS.

It has been shown that sildenafil increases the prostate blood flow by 75% (31). The stimulation of an erection can cause prostatic congestion, and this unwanted condition may cause sudden voiding trouble.

In all of these studies, the focus has been on the chronic treatment of BPH patients with PDE5 inhibitors. Incidentally the acute effects of PDE5 inhibitors were not wholly evaluated. In our study, we aimed to show the acute effect on urodynamic parameters of 50 mg oral sildenafil in patients who have BPH-LUTS and ED combinations. Since our patients took only one dose of sildenafil, it is difficult to comment on the positive effects on IPSS, possible side effects, or effects if used in combination with other drugs.

In a pilot study carried out on 38 BPH patients and 15 healthy volunteers the acute effects of sildenafil on uroflowmetric parameters (32) were examined. The participants were asked to hold their voiding until the bladder was full, and they were then given 100 mg of oral sildenafil. Half an hour later, uroflowmetric evaluations were performed. Maximum and average flowing rates were remarkably high in patients with BPH after sildenafil treatment. Moreover, after sildenafil treatment, average voiding duration was clearly shorter. In the control group, there were no evident changes in uroflowmetric parameters before and after sildenafil treatment.

Pressure-flowing, an invasive urodynamic study, is carried out by measuring flowing speed lost in uroflowmetry during voiding along with measuring detrusor pressure. Nowadays, pressure-flowing studies are accepted as the gold standard for infravesical obstruction diagnosis (12,33).

In our study, the basal and first-hour urodynamic parameters of the sildenafil group (group 1) and placebo group (group 2) were evaluated. In the first group, Qmax and Qave rates were clearly increased after 1 h and this increase was statistically significant ($P < 0.05$). In the second group, these rates also increased, but they were not statistically significant ($P > 0.05$). There was no statistically significant difference between predrug basal urodynamic values and postdrug first-hour urodynamic values ($P > 0.05$). These results were similar to those of 2 previous pilot studies. In both of the groups, regarding first voiding feeling, bladder volume, bladder compliance, vesical pressure in outflowing, detrusor pressure, electromyography, abdominal pressure, and voiding volume, there was no significant difference between predrug basal urodynamic values and postdrug first hour urodynamic values ($P > 0.05$).

Our study differed from other long-term studies in that no difference in Qmax was found when the urodynamic calculations were carried out when the drug reached its maximum blood concentration. This may be a possible explanation for why the Qmax improved.

Conclusion

In this study, the acute effect of sildenafil citrate on the voiding of patients with ED having BPH/LUTS was evaluated with urodynamic parameters. In patients who took sildenafil, both the Qmax and the Qave showed significant increases 1 h after the drug intake. The increases in the placebo group were not found to be significant. For this reason, we claim that sildenafil has an effect on voiding in the acute stage. The improvement in the sildenafil group, when compared with the findings from the placebo group, is supported and is not a measurement variation. It was seen that sildenafil was not harmful during voiding, and it even helped patients with ED-BPH (LUTS) to void. Hence, it can be safely recommended for this patient group for daily application. Finally, more research with larger patient groups is needed in order to define the role of sildenafil in BPH-LUTS treatment.

References

1. Yalçınkaya FR, Gökçe A, Davarcı M, Güven EO, İnci M, Kartal SB et al. The impact of NIH-IV prostatitis on early post-operative outcomes of the impact of NIH-IV prostatitis on early post-operative outcomes of transurethral resection of the prostate in patients with symptomatic benign prostate hyperplasia. Turk J Med Sci 2011; 41: 515-519.
2. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993; 7: 270: 83-90.
3. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev 2004; 84: 935-86.
4. Gacci M, Bartoletti R, Figlioli S, Sarti E, Eisner B, Boddi V et al. Urinary symptoms, quality of life and sexual function in patients with benign prostatic hypertrophy before and after prostatectomy: a prospective study. BJU Int 2003; 91: 196-200.
5. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Thomas S et al. Correlates for erectile and ejaculatory dysfunction in older Dutch men: a community-based study. J Am Geriatr Soc 2001; 49: 436-42.
6. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB, Hanbury DC. Sildenafil influences lower urinary tract symptoms. BJU Int 2002; 90: 836-39.
7. Mulhall JP, Guhring P, Parker M, Hopps C. Assessment of the impact of sildenafil citrate on lower urinary tract symptoms in men with erectile dysfunction. J Sex Med 2006; 3: 662-667.
8. Rostaing L, Tran-Van T, Ader JL. Increased glomerular filtration rate in kidney-transplant recipients who take sildenafil. N Engl J Med 2000; 342: 1679-80.
9. Tinel H, Stelte-Ludwig B, Hutter J, Sandner P. Pre-clinical evidence for the use of phosphodiesterase-5 inhibitors for treating benign prostatic hyperplasia and lower urinary tract symptoms. BJU Int 2006; 98: 1259-63.
10. Uckert S, Kuthe A, Jonas U, Stief CG. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol 2001; 166: 2484-90.
11. Guven EO, Balbay MD, Mete K, Serefoglu EC. Uroflowmetric assessment of acute effects of sildenafil on the voiding of men with erectile dysfunction and symptomatic benign prostatic hyperplasia. Int Urol Nephrol 2009; 41: 287-92.
12. Kojima M, Inui E, Ochiai A, Naya Y, Ukimura O, Watanabe H. Noninvasive quantitative estimation of infravesical obstruction using ultrasonic measurement of bladder weight. J Urol 1997; 157: 476-9.
13. Davis-Joseph B, Tiefer L, Melman A. Accuracy of the initial history and physical examination to establish the etiology of erectile dysfunction. Urology 1995; 45: 498-502.
14. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54-61.
15. Chang S, Hypolite JA, Zderic SA, Wein AJ, Chacko S, DiSanto ME. Enhanced force generation by corpus cavernosum smooth muscle in rabbits with partial bladder outlet obstruction. J Urol 2002; 167: 2636-44.
16. Filippi S, Morelli A, Sandner P, Fibbi B, Mancina R, Marini M et al. Characterization and functional role of androgen-dependent PDE5 activity in the bladder. Endocrinology 2007; 148: 1019-29.
17. Lue TF. Erectile dysfunction. N Engl J Med 2000; 342: 1802-13.
18. Gülkesen KH, Köksal IT, Özdem S, Saka O. Prediction of prostate cancer using decision tree algorithm. Turk J Med Sci 2010; 40: 681-686.
19. Doğan H, Canbaz S, Tander B, Pekşen Y, Cantürk F, Oruç NO. The prevalence of home injuries among elderly people in Samsun, Turkey, and the influencing factors. Turk J Med Sci 2010; 40: 651-658.
20. Wespes E, Amar E, Hatzichristou D, Hatzimouratidis K, Montorsi F, Pryor J et al. EAU Guidelines on erectile dysfunction: an update. Eur Urol 2006; 49: 806-15.
21. Takeda M, Tang R, Shapiro E, Burnett AL, Lepor H. Effects of nitric oxide on human and canine prostates. Urology 1995; 45: 440-6.
22. Avcı A, Atlı T, Ergüder BI, Varlı M, Devrim E, Demir O et al. Effects of grape consumption on plasma and erythrocyte antioxidant parameters in elderly subjects. Turk J Med Sci 2010; 40: 525-529.
23. Cook AL, Haynes JM. Protein kinase G II-mediated proliferative effects in human cultured prostatic stromal cells. Cell Signal 2004; 16: 253-61.
24. Gökçe A, Aslan S, Yalçınkaya FR, Davarcı M, Kaya YS, Savaş N et al. Improvement of monosymptomatic enuresis aft er adenotonsillectomy in children with obstructive sleep apnea syndrome. Turk J Med Sci 2012; 42: 757-761.
25. Dokita S, Morgan WR, Wheeler MA, Yoshida M, Latifpour J, Weiss RM. NG-nitro-L-arginine inhibits non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle. Life Sci 1991; 48: 2429-36.
26. Adolfsson PI, Ahlstrand C, Varenhorst E, Svensson SP. Lysophosphatidic acid stimulates proliferation of cultured smooth muscle cells from human BPH tissue: sildenafil and papaverin generate inhibition. Prostate 2002; 51: 50-58.
27. Qiu Y, Kraft P, Craig EC, Liu X, Haynes-Johnson D. Cyclic nucleotide phosphodiesterases in rabbit detrusor smooth muscle. Urology 2002; 59: 145-49.
28. AL-Nımer MS, AL-Obaıdı SA, AL-Dulaımı KS. Serum nitric oxide and peroxynitrite levels in adult sero-positive rheumatoid arthritis treated with disease modifying antirheumatic drugs: a preliminary report. Turk J Med Sci 2010; 40: 191-197.
29. Yeni E, Ciftci H, Savas M, Verit A, Taşkın A. Is oxidative stress an etiologic factor in idiopathic male infertility? Turk J Med Sci 2010; 40: 1-6.
30. Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol 2007; 51: 1717-23.
31. Gingell C, Sultana SR, Wulff MB, Gepi-Attee S. Duration of action of sildenafil citrate in men with erectile dysfunction. J Sex Med 2004; 1: 179-84.
32. Guler C, Tuzel E, Dogantekin E, Kiziltepe G. Does sildenafil affect uroflowmetry values in men with lower urinary tract symptoms suggestive of benign prostatic enlargement? Urol Int 2008; 80: 181-5.
33. Gümüş D, Bağdatlı Y. A bacteriological examination of urine before and after urodynamic testing. Turk J Med Sci 2010; 40: 317-322.