CHOOSING THE 5TH TYPE PHOSPHODIESTERASE INHIBITORS FOR TREATMENT THE PATIENTS WITH ERECTILE DYSFUNCTION AND CHRONIC PROSTATITIS

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ABSTRACT

The study of the genital system' vessels in patients with erectile dysfunction and chronic prostatitis was accomplished using ultrasound Dopplerography and pharmacological testing by phosphodiesterase inhibitors of 5th type (PDEI-5). The positive impact of PDEI-5 (such as Sildenafil, Vardenafil, Udenafil and Tadalafil) on organs' blood supply was revealed. The changes of USDG parameters were found comparable and, at the same time, individual. For patient-specific choosing the medicinal agent it is advisable to perform the pharmacological tests for each patient. The choice of the medicine for treating erectile dysfunction and chronic prostatitis should be made on the basis of the results of ultrasound Dopplerography and pharmacological testing for each selected and tested medicine. For this purpose it is preferably to choose the medicine, which improves the blood flow in penis and, at the same time, in prostate gland and in testes.

KEYWORDS — ultrasound Dopplerography, pharmacological testing, penis, prostate gland, testes, Sildenafil, Vardenafil, Udenafil, Tadalafil, erectile dysfunction, chronic prostatitis, phosphodiesterase inhibitor selection.

INTRODUCTION

Appearance on the market several 5th type phosphodiesterase inhibitors (PDEI-5), such as Sildenafil, Vardenafil, Udenafil and Tadalafil, has raised a point about their preferable choice [1–5]. The clinicians are based on subjective patient's impression of intake one or another medicine (International Index of Erectile Function questionnaire) and try minimizing adverse reaction and adverse events (AE) [6–11]. Objectification of the response to medicine intake with relation to evidential medicine is of current importance and thus was the ***objective*** of our study [12–14]. We proposed the method of pharmacological testing [15, 16], which allows in some measure to clear up this point.

MATERIAL

30 patients aged from 30 to 68 years with chronic prostatitis (CP) of III A, B category associated with erectile dysfunction (ED) were observed. Erectile dysfunction duration constituted from 1 till 5 years. All patients had various concomitant diseases — systemic atherosclerosis, metabolic syndrome, adenoma of prostate gland of I stage. Exclusion criteria were: severe intercurrent background.

METHODS

Ultrasound Dopplerography of male organs vessels, namely deep and dorsal arteries of penis [17], intra-prostatic and paraurethral arteries [18], as well as testicular arteries [19]. The values of peak blood flow velocity (Vmax in cm/sec) in these vessels were measured with calculation of average accumulative values of these parameters in above-noted vessels of male genital system. Then the patient took one of tested medicines, namely: Sildenafil 50 mg, Vardenafil 10 mg, Tadalafil 20 mg, Udenafil 100 mg and was reinvestigated in 1 hour. The pharmacological test was performed using each of medicines at 4–7 days interval. Similar measurements, calculation and comparison of obtained values percentage wise were made.

RESULTS

All obtained parameters, their changes and statistical treatment are shown in Table 1.

Table 1. *Vmax changes in vessels of penis, prostate and testes (cm/sec)*

	sildenafil			vardenafil			tadalafil			udenafil		
n = 30	penis	prostata	testis	penis	prostata	testis	penis	prostata	testis	penis	prostata	testis
M_1	8,38	8,83	9,6	8,71	10,46	9,17	9,42	10,28	8,57	10,04	11,73	9,29
m_1	0,83	1,2	0,63	0,67	0,62	0,26	0,83	0,47	0,87	0,73	0,76	0,49
M_2	12,3	11,78	9,55	14,25	13,01	10,88	14,17	13,51	11	13,73	14,14	11,5
m_2	2,35	0,91	1,04	0,75	0,71	0,46	1,54	0,73	0,69	0,85	0,73	0,52
p=	≤0,02	≤0,05	≥	≤0,001	≤0,02	≤0,002	≤0,02	≤0,001	≤0,05	≤0,002	≤0,03	≤0,005
K	1,61	1,33	0,99	1,64	1,24	1,19	1,5	1,31	1,28	1,37	1,21	1,24

Vmax — peak blood flow velocity
M_1 — arithmetic mean in background (before pharmacological test)
M_2 — arithmetic mean after pharmacological test
m_1 — mean error of arithmetic mean in background (before pharmacological test)
m_2 — mean error of arithmetic mean after pharmacological test
K — aspect ratio M_2/M_1
Statistical treatment with method of comparison arithmetic means using Student's test Significant difference — $p \leq 0.05$

The detailed results are presented below.

TEST WITH SILDENAFIL

Mean Vmax (M±m) in deep arteries of left and right cavernous bodies of penis before testing was 8.4±0.8 cm/sec. In 1 hour after oral administration of Sildenafil 50 mg, Vmax in the same penis vessels was 12.3±2.4 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 61 %. Mean Vmax in three regions of prostate blood supply (left, right lobes, periurethral zone) before testing was 8.8±1.2 cm/sec, and after testing = 11.8±0.9 cm/sec. That is peak blood flow velocity in three regions of prostate had increased on average by 33%. Blood flow velocity did not change reliably in funiculus vessels as a result of Sildenafil intake. The weighted mean of Vmax increase in male genital organs was +31%. Only the tendency to increase the index of resistance (IR) and systolic-diastolic index S/D was noted in penis vessels and the tendency to decrease of peripheral resistance parameters (IR, PI, S/D) was observed in prostate vessels.

TEST WITH VARDENAFIL

Mean Vmax (M±m) in deep arteries of both cavernous bodies of penis before testing was 8.7±0.7 cm/sec. In 1 hour after oral administration of Vardenafil 10 mg, mean Vmax in the same penis vessels was 14.2±0.7 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 64%. Mean Vmax in threecorresponding regions of prostate before testing was 10.5±0.6 cm/sec, and after testing = 13.0±0.7 cm/sec. That is averaged peak blood flow velocity in prostate vessels had increased on average by 24%. Blood flow velocity after Vardenafil intake in funiculus vessels increased from 9.2±0.3 cm/sec to 10.9±0.5 cm/sec that is on average by 19%. The weighted mean of Vmax increase in male genital organs was +36%. Slight tendency to increase of all parameters in penis, prostate and testes (statistically not significant) was noted on the part of peripheral vascular resistance (Fig. 1).

TEST WITH UDENAFIL

Mean Vmax in deep arteries of penis before testing was 10.0±0.7 cm/sec. In 1 hour after Udenafil intake 100 mg, mean Vmax in the same penis vessels achieved 13.7±0.8 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 37%. Mean Vmax in threeabove mentioned regions of prostate before testing was 11.7±0.8 cm/sec, and after testing constituted 14.1±0.7 cm/sec. That is averaged peak blood flow velocity in prostate vessels had increased on average by 21%. Average blood flow velocity (Vmax) after Udenafil intake in both funiculus vessels (left and right) increased from 9.3±0.5 cm/sec to 11.5±0.5 cm/sec that is on average by 24%. The weighted mean of Vmax increase in male genital organs was +27%. Slight tendency to increase of peripheral vascular resistance parameters in penis and prostate (statistically not significant) was noted. Peripheral vascular resistance parameters in funiculus vessels did not change (or had slight tendency to decrease).

TEST WITH TADALAFIL

Mean Vmax (M±m) in deep arteries of both cavernous bodies of penis before testing was 9.4±0.8 cm/sec. In 1 hour after intake Tadalafil 20 mg, mean Vmax in the same penis vessels was 14.2±1.5 cm/sec that is peak blood flow velocity in penis vessels after performing the test had increased on average by 50 %. Mean

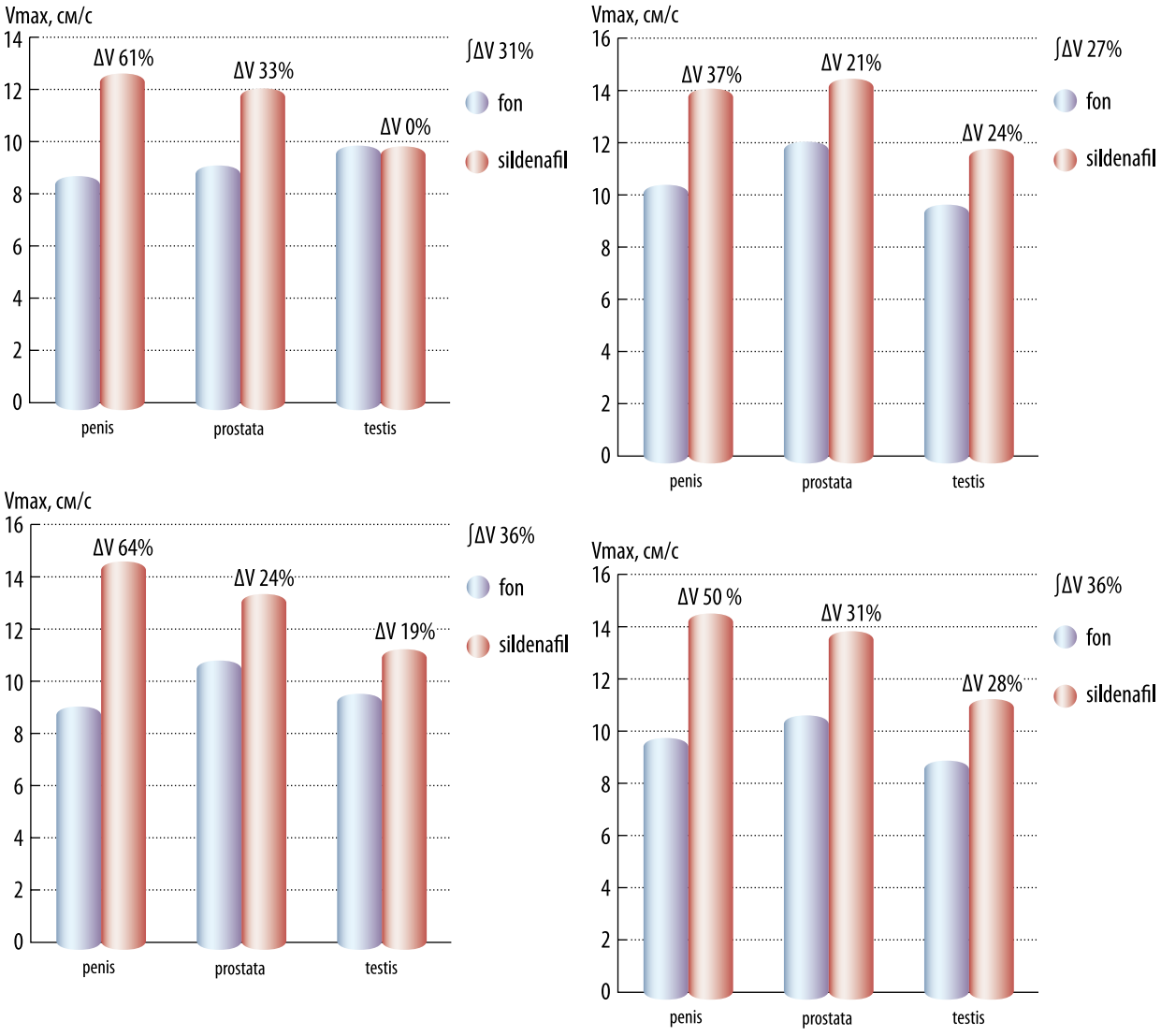
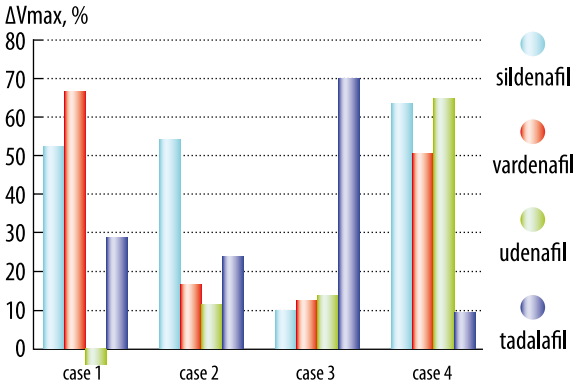


Fig. 1 a–d. *Vmax changes in vessels of penis, prostate and testes in 1 hour after intake Sildenafil (a), Vardenafil (b), Udenafil (c), Tadalafil (d).*
ΔV% — index of blood flow increase in vessels of penis, prostate and testes after pharmacological test in percentage terms
∫ΔV% — index of integral blood flow increase in vessels of male genital organs after pharmacological test in percentage terms

Vmax in threeregions of prostate before testing was 10.3±0.5 cm/sec, and after testing = 13.5±0.7 cm/sec. That is averaged peak blood flow velocity increase in prostate vessels amounted 31%. Averaged peak blood flow velocity after Tadalafil intake in both funiculus vessels increased from 8.6±0.9 cm/sec to 11.0±0.7 cm/sec that is on average by 28%. The weighted mean of Vmax increase in male genital organs was +36%. Parameters of peripheral vascular resistance in penis, prostate and testes after Tadalafil intake had statistically not significant tendency to increase (Fig. 2).

The following is a case example.



Pic. 2. *Indices of integral blood flow changes Vmax (in percentage terms) in vessels of male genital organs after pharmacological test with various PDEI-5 inhibitors in presented cases.*

Case 1. Patient S., 57 years. Diagnosis: erectile dysfunction, chronic prostatitis IIIA. The score according to IIEF-5 questionnaire was equal 19. The

investigation of PDEI-5 choosing was performed. The tested medicines were: Sildenafil 50 mg, Vardenafil 10 mg, Tadalafil 25 mg, Udenafil 100 mg. Intervals between tests were 5 days. The results — see Table 2, Fig. 1a.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Sildenafil (Viagra) 50 mg (+54.3%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became equal to 24 points.

Case 2. Patient I., 65 years. Diagnosis: erectile dysfunction, chronic prostatopathy, age-related androgens deficiency. The treatment by empirically chosen medicines had no effect. The score according to IIEF-5 questionnaire is equal = 14 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 4 days. The results — see Table 3, Fig. 1b. The percent of average blood flow velocity increase in male genital organs vessels after performing the test are shown on axis of the ordinates (Table 3).

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Vardenafil (Levitra) 10 mg. Average blood flow velocity increase in male genital system organs constituted 66.7%. This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire achieved 19 points.

Table 2. *Blood flow velocity parameters in male genital organs of patient S., 57 years*

	Vmax (cm/sec)			Vmax
	penis	prostate	testes	mean
background	9	10	10	9.7
Sildenafil	21	13	10	14.7
Vmax, %	133	30	0	54.3
background	15	9	12	12.0
Vardenafil	17	11	14	14.0
Vmax, %	13	22	16	17.0
background	10.6	9.5	7.7	9.3
Tadalafil	8.9	11.4	10.1	10.1
Vmax, %	-16	20	31	11.7
background	13	10	13	12.0
Udenafil	15	14	15	14.7
Vmax, %	16	40	16	24.0

Table 3. *Blood flow velocity parameters in male genital organs of patient I., 65 years*

	Vmax (cm/sec)			Vmax
	penis	prostate	testes	mean
background	10	11	13	11.3
Sildenafil	9.1	27.5	11.8	16.1
Vmax, %	-9	175	-9	52.3
background	6	14	13	11.0
Vardenafil	18	14	13	15.0
Vmax, %	200	0	0	66.7
background	7	12	13	10.7
Tadalafil	7	12	11	10.0
Vmax, %	0	-15	0	-5.0
background	11	13	7	10.3
Udenafil	16	11	11	12.7
Vmax, %	45	-15	57	29.0

Case 3. Patient K., 59 years. Diagnosis: erectile dysfunction, chronic prostatitis IIIB. The score according to IIEF-5 questionnaire is equal 18 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 6 days. The results — see Table 4, Fig. 1c.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Udenafil (Zydena) 100 mg (+70%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became 24 points.

Table 4. *Blood flow velocity parameters in male genital organs of patient K., 59 years.*

	Vmax(cm/sec)			Vmax
	penis	prostate	testes	mean
background	7	13	9	9.7
Sildenafil	9	16	7	10.7
Vmax, %	29	23	-22	10.0
background	9	21	11	13.7
Vardenafil	13	16	13	14.0
Vmax, %	44	-24	18	12.7
background	4	13	10	9.0
Tadalafil	6	8	13	9.0
Vmax, %	50	-38	30	14.0
background	14	9	8	10.3
Udenafil	24	17	12	17.7
Vmax, %	71	89	50	70

Table 5. Blood flow velocity parameters in male genital organs of patient O., 42 years

	Vmax(cm/sec)			Vmax
	penis	prostate	testes	mean
background	8.3	8	6.6	7.6
Sildenafil	24	9.7	5.3	13.0
Vmax, %	189	21	-20	63.3
background	7	7	10	8.0
Vardenafil	12	12	11	11.7
Vmax, %	71	71	10	50.7
background	8	7	6	7.0
Tadalafil	9	15	16	13.3
Vmax, %	13	14	167	64.7
background	9	11.1	8.9	9.7
Udenafil	9.7	11.3	10.7	10.6
Vmax, %	7	2	20	9.7

Case 4. Patient O., 42 years. Diagnosis: erectile dysfunction, chronic prostatitis II. The score according to IIEF-5 questionnaire was equal 20 points. The investigation of PDEI-5 choosing was performed. The tested medicines and doses were the same. Intervals between tests were 7 days. The results — see table 5, Fig. 1d.

Maximum difference of average blood flow velocity parameters of genital system organs before and after testing was observed at performing the test with medicine Tadalafil (Cialis) 20 mg (+64.7%). This medicine was chosen as optimal for erectile dysfunction treatment in this patient. As a result of that choice the sum according to IIEF-5 questionnaire became 24 points.

DISCUSSION

Our study showed that the efficiency of various PDEI-5 and their potential ability to increase blood supply of male genital organs is comparable. Patients' responses are individual, therefore it is necessary to personify the testing.

Blood flow velocity increase along penis vessels is not an erection, but only readiness to erection appearance and maintenance in the presence (appearance) of sexual stimulant — the NO source. This is essential for vasculogenic erectile dysfunction. The response is less marked at not-vasculogenic erectile dysfunction, and sometimes even paradoxical, that may help in differential diagnosis of erectile dysfunction origin [20]. Essential feature of PDEI-5 action is their effect on prostate blood flow [21–25]. Anatomical evidence is that penis and prostate have unified feed from the basin of internal iliac artery branches. Histological evidence is that 5thphosphodiesterase receptors present in prostate gland [26]. Pathogenetic evidence is that vasculogenic form of erectile dysfunction is combined with ischemic prostatopathy, i.e. chronic prostatitis IIIB, at which blood supply of the prostate is decreased by 2 times against norm [27–29]. The effect on blood flow is less marked in funiculus, since testicular artery deviates from aorta and is defined by the condition of central hemodynamics. Blood flow increase in the vessels takes place, usually, with the participation of rising the tone of appropriate vascular walls of responsive nature. These changes are not significant statistically, and generally are evident as a slight tendency. Therefore for clinical purposes one might use only peak blood flow velocity parameters, both averaged and integral.

Our study was of clinical applied nature, thereby we could not examine these patients for several hours in due course. Therefore the issue about blood flow parameters in male genital organs after administration 5thphosphodiesterase inhibitors in further hours remains to some extent open. In this study we also aimed to get information about the efficiency and the presence of known adverse events after intake medicine in test doses using subjective estimation scale IIEF-5.

The possibilities to choose not only specific medicine, but also to accomplish functional diagnostics of male genital organs hemodynamic disorders arise as a result of testing. Thus, for example, disorders' reversibility degree is more at chronic prostatitis IIIA and it is less at chronic prostatitis IIIB of atherosclerotic origin [30, 31].

CONCLUSION

The obtained results show very positive hemodynamic effects of studied PDEI-5 which are comparable and very individual at the same time. Integral increment percent of blood flow velocity when applying phosphodiesterase inhibitors constituted, on average roughly, 30–40% in male genital system organs (40–60% in penis, 25–40% in prostate, 15–30% in testes). So it is advisable to perform first the described pharmacological test with Dopplerography control according to developed algorithm and only after that to choose the medicine and to prescribe it to the patienton an individual basis.

While choosing the medicine for treatment erectile dysfunction and chronic prostatitis we suggest to rely on specific hemodynamic testing results of selected medicinal agents. In addition it is preferably to choose the medicine, which improves blood flow both in prostate and testes that is having the greatest integral percent of blood flow velocity increment in male genital system organs. It is essential also to consider subjective data about tolerance of the medicine and the presence of adverse events as well as patient's compliance to intake of one or another phosphodiesterase inhibitor.

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