EFFECT OF SILDENAFIL IN CAVERNOUS ARTERIES OF PATIENTS WITH ERECTILE DYSFUNCTION

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ABSTRACT

Introduction: Sildenafil citrate is a type 5 phosphodiesterase inhibitor, which has demonstrated excellent results in the treatment of erectile dysfunction. The effect of sildenafil citrate in the cavernous arteries of patients with erectile dysfunction has not been established yet. The objective of this study was to assess the effect of sildenafil citrate in the cavernous arteries of patients with erectile dysfunction, following an intracavernous injection of alprostadil.

Materials and Methods: 29 male patients, with mean age of 53.8 years (32 to 75 years), were prospectively evaluated. The mean time with complaint of erectile dysfunction was 50.5 months (6 to 168 months). Each patient was his own control. Patients underwent a measurement of peak systolic velocity before and after use of sildenafil citrate associated with 5 micrograms of alprostadil, through ultrasonic velocitometry Knoll/MIDUS® system. In the interval between measurements, approximately 15 days, patients used 3 tablets of sildenafil at home with their partners.

Results: Using only 5 mcg of alprostadil, average peak systolic velocity was 23.9 cm/s, and when associated to 50 mg of sildenafil it was 24.8 cm/s. Despite the increase in the flow rate caused by sildenafil, the difference was not statistically significant, $Z_{calculated} = -0.695$ NS (Wilcoxon test). Twenty one of the 29 patients (72.4%) showed global improvement in sexual performance with the use of sildenafil citrate at home. There was not a statistically significant correlation between the global response to sildenafil citrate and the increase in the peak systolic velocity.

Conclusion: We concluded that, even though the use of 50 mg of sildenafil citrate associated with 5 mcg of alprostadil provides an increase in the peak systolic velocity of the cavernous arteries, there was no statistic difference in relation to alprostadil alone. There was no correlation between the global response to sildenafil and the increase in the peak systolic velocity.

Key words: penis; arteries; penile erection; corpus cavernosum; phosphodiesterases inhibitors
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INTRODUCTION

Erectile dysfunction is the persistent inability to reach or maintain an erection that is sufficient for a satisfactory sexual intercourse (1,2). In Brazil, some degree of erectile dysfunction was found in 39.8% of the studied population (3).

Until 1996, treatments recommended for erectile dysfunction were the vacuum devices, the therapy with injectable vasoactive drugs and penile prosthesis (4), when the first clinical results with the use of sildenafil citrate were published (5,6). The response according to dosage was 60, 84 and 100%, respectively with doses of 25, 50 and 100 mg of sildenafil, compared with a response of 5% from those who received placebo (7). A significant improvement of erections following the use of sildenafil citrate was demonstrated in several trials, reaching a success rate of 70 to 90% (6-10).

Objectively, the action of sildenafil citrate was confirmed by penile plethysmography, with a mean dura-

tion of rigidity above 60% in relation to placebo (11). The effect of sildenafil citrate in the cavernous arteries' flow was confirmed in men without complaints of erectile dysfunction (12), through an increase in the peak systolic velocity with the use of sildenafil citrate that was similar to that obtained with papaverine (13,14).

The objective of this study was to assess the effect of sildenafil citrate in the cavernous arteries of patients with erectile dysfunction, following an intracavernous injection of alprostadil.

MATERIALS AND METHODS

A prospective, comparative, clinical trial was performed, in which the patient was his own control, in 29 male patients, with ages ranging from 32 to 75 years (mean 53.8 years) and with complaints of erectile dysfunction.

The time since settlement of the erectile dysfunction picture ranged from 6 to 168 months (mean 50.5 month). Laboratory analysis consisted of dosage of serum total testosterone, prolactin and fasting glycemia.

After the patient had fulfilled the inclusion criteria, we started the study. The first visit aimed the baseline assessment of cavernous arteries. The patient was conducted to a special, isolated and comfortable room. After some minutes for adapting to the environment, 5 mcg of alprostadil were applied by intracavernous route with a 30-gauge needle. The patient remained resting in this room and with material containing visual erotic stimulation available. Following a 15-minute period, we started the examination. Patients who did not present a satisfactory erection following the drug application were excluded from the study and referred to other type of treatment.

We used ultrasonic velocitometry by the Knoll/MIDUS system (Urometrics, St Paul, Minnesota) for measurement of the peak systolic velocity. The system is comprised by 2 ultrasonic fixed angle transducers (60°). The frequency of each transducer is 8 MHz and it has a measurement capability of blood flow in amplitude from 1 to 200 cm/s. The transducer has a focal distance of 1.2 cm (15).

Measurements were obtained in a standardized way in all patients. With the patient in supine position, the transducers were positioned in the base of the penis and moved laterally until a consistent signal was captured by the earphone and viewed in the computer screen. Data from left and right cavernous arteries were obtained separately. Signals were recorded in high-speed charts in function of time.

Upon completion of the examination, the patient received a box containing 4 tablets of sildenafil citrate 50 mg. The patient was instructed to use 3 tablets at home, with his partner in a period of 15 days, always one hour before the sexual intercourse. The fourth tablet should be taken one hour before the next visit, when a new assessment would be done. The use of sildenafil at home aimed to assess each patient's response to the medication and to compare it with the results obtained in the second assessment.

Before the patient was released, he was instructed about the possibility of priapism, and to come back to the hospital if the erection lasted for 4 hours or more. In the second assessment, in average 15 days after the first one, patients initially answered to the following question: the use of the medication improved your sexual performance in this period? Yes or no? Regardless the answer, a new assessment was performed. Approximately 1 hour after administrating 50 mg of sildenafil citrate, the patient received 5 mcg of alprostadil by intracavernous route in the private room and once more used visual erotic stimulation for 15 minutes, and then was submitted to the measurement of peak systolic velocity, following the same steps of the initial assessment.

All data were classified in tables and submitted to statistical analysis.

In order to study potential differences between the peak systolic velocity of right and left cavernous arteries, both for periods pre- and post-administration of sildenafil citrate, as well as the average for the pre-period in relation to the average for the post-period, we used Wilcoxon non-parametric test for 2 non-independent samples. In order to study potential associations between the peak systolic velocity and the patient's global response to sildenafil citrate, we used the qui-square test (χ^2) for association tables following the Cochran's restrictions and when

present, we used Fisher's exact test. In all cases, the rejection level for the null hypothesis was always fixed in a value below or equal to 0.05 (5%). When the calculated statistic presented significance, we used an asterisk (*) to characterize it, otherwise, we used non-significant (NS).

RESULTS

The tests were performed with total cooperation by the patients, who followed the instructions made. All patients used visual erotic stimulation for performing the examinations. No patient was excluded due to side effects or interruption in the follow-up. Patients returned within the established period of 15 days, with few exceptions, which did not compromise the study's final result.

The measurement of peak systolic velocity was performed separately for right and left cavernous arteries. We used the simple mean between them for comparative analysis, after we had compared the 2 sides that were statistically similar (Figure-1).

Mean values increased from 23.9 cm/s to 24.8 cm/s following the use of sildenafil citrate, however it was not statistically significant in our sampling. The statistical analysis of data obtained is expressed in Table-1.

The response to use of sildenafil citrate at home with the partner was positive in 72.4% of patients. When the groups are divided by age range, the response is enhanced for the group < 50 years, presenting 86.67% of yes answers ($p = 0.086$), Figure-2.

Comparative analyses between the several variables are presented in Tables-2 and 3.

Adverse events reported by patients were mild headache in 4 patients (13.8%), gastrointestinal upset in 2 (6.9%) and facial rush in 6 (20.7%). One patient (3.4%) presented priapism lasting for 6 hours after the second assessment, when alprostadil was used in combination with sildenafil citrate. The outcome was favorable, requiring only puncture and irrigation of the corpora cavernosa with saline solution, with complete detumescence (Figure-3).

DISCUSSION

The introduction of sildenafil citrate as an option for treating the erectile dysfunction changed urologists' daily practice. The diagnostic arsenal used for investigating the patient was gradually replaced, and many times on request of the patient himself, by a simple test of drug use at home with his partner.
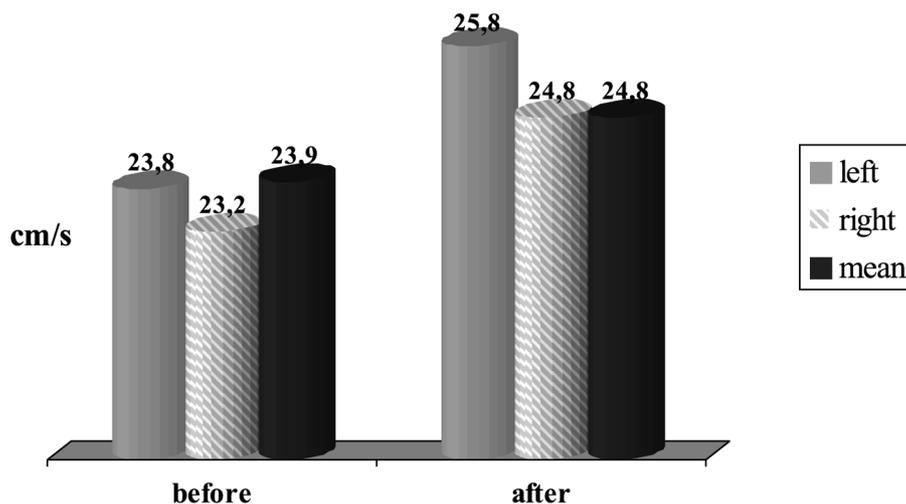

Figure 1 – Mean values of peak systolic velocity of the cavernous arteries before and after administration of sildenafil citrate.

Table 1 – *Statistical analysis of differences between the mean peak systolic velocity of cavernous arteries before and after use of sildenafil citrate.*

	N	Mean cm/s	Minimal Value	MaximalValue	Wilcoxon Test
Before	29	23.9	13	39	
After	29	24.8	12	46.5	Z= -0.695 NS

NS – non significant

The mechanism of action of sildenafil citrate was already well established at a cellular level, but there is little information about the effect of the drug on the cavernous arteries' flow during the erection (12-14).

Our sample intended to maximally represent the outpatient profile for erectile dysfunction. Patients' mean age was 53.9 years with a mean time with complaint of 4.2 years. The methodology for obtaining the erection used the routine diagnostic methods for patients with erectile dysfunction. The drug-induced erection test was the choice method for baseline assessment of the cavernous arteries' flow, and at the same time, it selected the patients who could continue in the study.

During the interval period between assessments, patients used sildenafil citrate at home for evaluating their global response to the drug. In this way, we tried to eliminate the stress of an examination room inside a hospital, and also to allow the pa-

tient to use the drug in the natural environment where we intended that the medication would act. The assessment of results of the study's domiciliary phase was done with a simple question about improvement and global satisfaction of sexual performance, which in our opinion is the patient's goal. Seventy-two percent of patients reported improvement of erections and stated that they were satisfied with the use of the drug at home. On the second assessment of the cavernous arteries velocitometry, now using sildenafil citrate, we performed once more the drug-induced erection test with 5 mg of alprostadil so that the potential advantage obtained with the sildenafil citrate could be assessed in a reliable way. The use of visual erotic stimulation was warranted by the very mechanism of action of the drug in question. Visual erotic stimulation can reduce the stress factors inherent to the examination and thus to improve the erectile response (16).

Our data were initially analyzed by comparing the peak systolic velocity of the left and right cav-
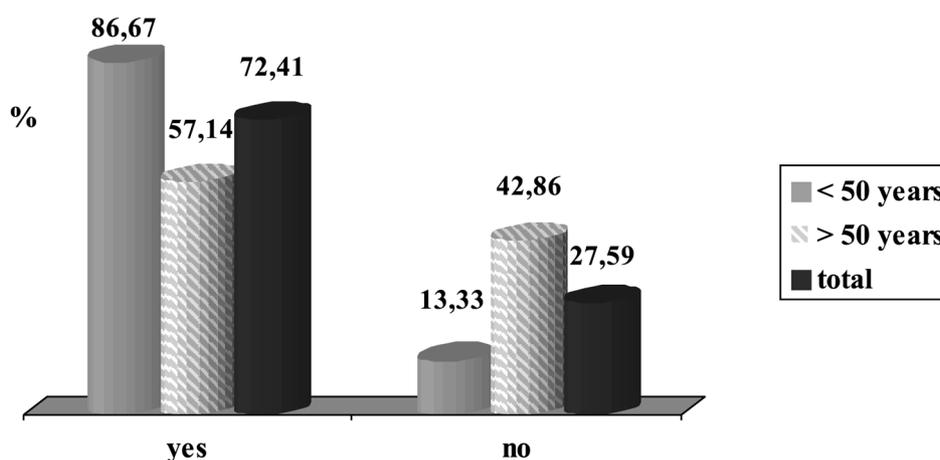

Figure 2 – *Global response to sildenafil citrate according to age.*

Table 2 – Individuals with peak systolic velocity values = 23 cm/s, according to age and global response.

Global Response	< 50 Years	> 50 Years	Total
No	0	6	6
Yes	4	7	11
Total	4	13	17

Fisher's exact test, p = 0.1387 or 13.87%, non-significant.

Table 3 – Individuals with peak systolic velocity values > 23 cm/s, according to age and global response, with statistical results.

Global Response	< 50 Years	> 50 Years	Total
No	1	1	2
Yes	5	5	10
Total	6	6	12

Fisher's exact test, p = 0.7727 or 77.27%, non-significant.

ernous arteries on the baseline assessment and on the assessment following the use of sildenafil citrate. On the baseline assessment, the mean peak systolic velocity was 23.8 cm/s and 23.2 cm/s for the left and right sides respectively, $Z_{calculated} = -0.313$ NS (Wilcoxon test) and on the period following the use of sildenafil citrate, the mean peak systolic velocity was 25.8 cm/s and 24.8 cm/s for the left and right sides respectively, $Z_{calculated} = -0.397$ NS (Wilcoxon test).

Since there was no statistically significant difference between right and left sides, we used the average between both sides for assessment of changes obtained with the use of sildenafil citrate. The mean peak systolic velocity on the baseline assessment was 23.9 cm/s and 24.8 cm/s following the use of sildenafil citrate. Despite the increase observed, the difference was not statistically significant, $Z_{calculated} = -0.695$ NS

(Wilcoxon test), probably due to the small number of patients studied in this sample.

Of the 21 patients who showed improvement of sexual performance, 11 (52.4%) presented a mean peak systolic velocity lower or equal to the median (23 cm/s) and 10 (47.6%) higher than 23 cm/s (p = 0.25 NS, Fisher's exact test), demonstrating that there was no relation between the patient's clinical improvement and the peak systolic velocity.

We analyzed separately those patients with a mean peak systolic velocity following sildenafil citrate above the median (23 cm/s) as for age and global response. The result between the groups was identical. Ten patients responded to sildenafil citrate and 2 did not. Among those who responded, 5 (50%) were from the group of patients with age under 50 years and 5 (50%) above or equal to 50 years, and one from
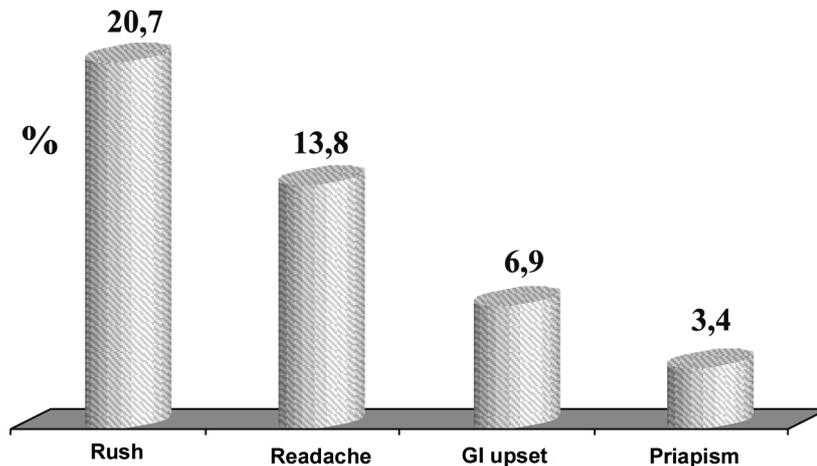

Figure 3 – Adverse events.

each group did not respond. There was no difference between age ranges.

In the groups of individuals aged under 50 years, 9 patients responded to sildenafil citrate, with 4 and 5 patients presenting respectively a peak systolic velocity lower or equal and higher than 23 cm/s ($p = 0.6$ NS, Fisher's exact test).

This study analyzed the change in the cavernous arteries flow with the use of sildenafil citrate and its correlation with the patient's clinical response to the medication. We did not try to present an objective confirmation of the drug's pharmacodynamic efficacy, also because the characteristics of the study and the size of the sample did not allow that.

A recent study has assessed the efficacy of sildenafil citrate in 433 men with the diagnosis of erectile dysfunction. Among the several parameters that were studied, the better response to sildenafil citrate in patients with a diagnosis of veno-occlusive dysfunction in relation to the intracavernous injection (17) attracts our attention. The performance of a cavernosometry could give us some additional data in order to fundament the role of the sildenafil citrate in the cavernous veno-occlusive mechanism, and should be used in future studies.

CONCLUSION

The use of 50 mg of sildenafil citrate does not provide an additional increase in relation to that obtained with the use of 5 mcg of alprostadil, of the peak systolic velocity of the cavernous arteries in patients with erectile dysfunction, as measured by ultrasonic velocitometry. There is no correlation between the patient's clinical response to 50 mg of sildenafil citrate and the changes in the peak systolic velocity of the cavernous arteries in patients with erectile dysfunction.

REFERENCES

1. NIH Consensus Statement. Impotence. 1992; 10: 1-31.
2. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, Mckinlay JB: Impotence and its medical and psy-chosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994; 151: 54-61.
3. Moreira JR ED, Lobo CFL, Glasser D: A population-based survey to determine the prevalence of erectile dysfunction and its correlates in the state of Bahia. Braz J Urol. 1999; 25 (suppl.): T-1012, 254.
4. Montague DK, Barada JH, Belker AM, Levine LA, Nadig PW, Roehrborn CG, et al.: Clinical Guidelines Panel on Erectile Dysfunction Summary Report on the Treatment of Organic Erectile Dysfunction. J Urol. 1996; 156: 2007-11.
5. Sharlip ID: 100 days with Viagra: The medical and social impact in the United States of America. Urol. Contemp. 1998; 4: 151-5 [in Portuguese].
6. Boolell M, Gepi-Attee S, Gingell CJ, Allen MJ: Sildenafil, a novel effective oral therapy for male erectile dysfunction. Br J Urol. 1996; 78: 257-61.
7. Goldstein I, Lue T, Padma-Nathan H, Rosen R, Sterrs W, Wicker PA: Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med. 1998; 338: 1397-404.
8. Padma-Nathan H, Steers WD, Wicker PA: Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Int J Clin Pract. 1998; 52: 375-9.
9. Morales A, Gingell C, Collins M, Wicker PA, Osterloch IH: Clinical safety of oral sildenafil citrate (Viagra™) in the treatment of erectile dysfunction. Int J Impot Res. 1998; 10: 69-74.
10. Glina S, Bertero E, Claro JFA, Damião R, Faria G, Fregonesi A, et al.: Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in Latin America. Braz J Urol. 2001; 27: 148-54.
11. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, et al.: Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res. 1996; 8: 47-52.
12. Aversa A, Mazzilli F, Rossi T, Delfino M, Isidori AM, Fabbri A: Effects of sildenafil (Viagra™) administration on seminal parameters and post-ejaculatory time in normal males. Hum Reprod. 2000; 15: 131-4.
13. Arslan D, Esen AA, Secil M, Aslan G, Celebi I, Dicle O: A new method for the evaluation of erectile dysfunction: sildenafil plus Doppler ultrasonography. J Urol. 2001; 166: 181-4.
14. Casabé A, Bechara A, Roletto L, Cheliz G, Fredotovich N: Evaluación arterial peneana com ecodoppler dinâmico bajo acción de drogas vasoactivas intracavernosas y con sildenafil: estudio comparativo. Rev Argent Urol. 2000; 65: 48-52.

15. Knoll LD, Abrams JH: Evaluation of penile ultrasonic velocitometry versus penile duplex ultrasonography to assess penile arterial hemodynamics. Urology 1998; 51: 89-93.
16. Morales A, Harris C, Condra M, Heaton JP: Validation of visual sexual stimulation in the etiological diagnosis of impotence. Int J Impot Res. 1990; 2 (suppl. 2): 109.
17. McMahon CG, Samali R, Johnson H: Efficacy, safety and patient acceptance of sildenafil citrate as treatment for erectile dysfunction. J Urol. 2000; 164: 1192-6.

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