Effect of vardenafil on semen parameters in infertile men: A pilot study evaluating short-term treatment

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ABSTRACT. Background: Several in vivo and in vitro studies have been carried out in order to evaluate the efficacy of long-term treatment with phosphodiesterase type-5 (PDE5) inhibitors (PDE5i) on spermatogenesis, but the results are still controversial. Aim: To evaluate the effects of vardenafil on seminal parameters of infertile men after a short-term treatment. Materials/subjects and methods: A total of 205 male subjects were randomized to receive a single dose of vardenafil 10 mg (73 men, group B), a single dose of vardenafil 10 mg every other day for 15 days (67 men, group C), and no treatment (65 men, group A). Semen parameters were evaluated before and after the end of the treatment in each of group A, B, and C, respectively. Additionally, an IIEF-5 questionnaire was administered to all patients with erectile dysfunction (ED) before and after each treatment period. Results: The semen parameters in groups B and C has shown a significant increase in percentage forward motility after vardenafil administration as compared with baseline (p<0.001). In group C, we observed an increase in the mean semen volume and an improvement in the mean total sperm concentration (p<0.001) as compared with baseline. Conclusions: We showed the efficacy of vardenafil in the treatment of ED and, on a large series of infertile patients, the positive effect on sperm motility after a single-dose administration. It also showed that after 15 days of treatment on alternate days is also achieved an improvement in sperm concentration. (J. Endocrinol. Invest. 35: 897-900, 2012)

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INTRODUCTION

Infertility affects up to 15% of reproductive-aged couples worldwide (1). The male has a reduced reproductive capacity in about 50% of cases, resulting in some men having a reduced self-esteem. Moreover, the scheduling of sexual intercourse, semen collection techniques, and long periods of diagnostic and treatment procedures may lead to some sexual dysfunction with a psychogenic basis, like erectile dysfunction (ED) and premature ejaculation (2, 3). Further psychological stress induced by ED could be added to a real difficulty in conceiving, causing a progressive decrease in the frequency of sexual intercourse and, thus, an additional obstacle to pregnancy. In the past decade, the management of ED by means of phosphodiesterase type-5 (PDE5) inhibitors (PDE5i) has been studied in infertile couples with the goal of improving erections and facilitating sexual relations. The human genome contains 21 genes encoding for 11 different PDE protein families: families 4, 7, and 8 being specific for the hydrolysis of cAMP, families 5, 6, and 9 for cGMP and the remaining (PDE1, 2, 3, 10, and 11) having a mixed specificity (4). In the human testis many PDE are expressed: the cAMP-specific isoforms 4A, 4C, 7B, and 8A, the cGMP-specific isoform 5A and the nucleotide-aspecific isoforms 1A, 1C, 10A, and 11A (4). The cGMP-specific PDEs, in particular, is found in Leydig and peritubular myoid cells of rat testis (5), and a weak mRNA expression has been spotted also in human spermatozoa (6). Among the several molecules that selectively inhibit PDE5, only three, namely sildenafil, tadalafil, and vardenafil, received marketing authorization and were introduced as an effective treatment for ED (7). Such molecules can also be used to facilitate semen collection in patients undergoing assisted reproductive technologies (ART) (8, 9). This, therefore, has stimulated interest in the potential effects of PDE5 inhibition and the consequent raise in intracellular cGMP on sperm parameters and fertilizing capacity (10, 11) since traces of these molecules can be found in the ejaculate (12). Several in vivo and in vitro studies have been carried out in order to evaluate the efficacy of long-term treatment with PDE5-i on spermatogenesis, but the results are still controversial (10-12). The aim of our study was to determine whether the use of vardenafil in men from infertile couples could have an effect on semen parameters and if this effect could occur even after a short-term treatment.

MATERIALS AND METHODS

Study design and subjects

The study was approved by our Institutional Ethics Committee. This was a randomized, open label, parallel group study designed to evaluate the effects of vardenafil on seminal parameters of men from infertile couples. Eight hundred and forty-one male subjects undergoing clinical evaluation for infertility at our center, from May 2008 to May 2010, were screened to be enrolled by an andrologist. The patients were submitted to physical examination, sexual habits, hormonal reproductive profile, and serum chemistry for metabolic diseases, ultrasound doppler scan testicular, seminal, and immunological analysis performed in our laboratory. The antisperm antibodies were assessed by direct immunobead test...
Results

As shown in Table 1 and 2, the groups did not differ for age, serum hormone levels or seminal parameters at T0. Effects of treatment with vardenafil on seminal parameters are showed in Table 2. A significant increase in the percentage of spermatozoa with forward motility was observed between the two time points in both groups B and C. Forward motility was significantly increased also when compared with the mean value of group A at T1.

In group C, a significant increase in the mean semen volume and in the mean total sperm concentration was observed. These differences were maintained when compared to group A at the same time point. No difference among the groups was observed for the percentage of morphologically abnormal spermatozoa.

Vardenafil had no effect on the hormonal plasma levels: only in group C a slight increase in total serum testosterone was observed, but it did not reach statistical significance (data not shown). In the population subgroup presenting ED, patients form groups B and C reported an improvement in sexual performance, as assessed by the IIEF-5 questionnaire (Table 3). Three subjects in group B reported headache as side effect of the treatment. No side effects were reported in group C.

Discussion

The efficacy and safety of PDE5i in the treatment of ED has been widely demonstrated (16-19). Moreover, their efficacy in modulating a variety of other pathologies, has been shown in the past decade (20). Vardenafil is considered to be effective in improving the quality of the relationship in both the partners of a couple (21). Many men report experiences of temporary ED during programmed sexual intercourses or treatments involving assisted reproductive technologies. For these reasons, PDE5i are frequently used in the management of male infertility (9, 22). In addition, several in vitro and in vivo studies have been carried out in order to assess the effects of PDE5i on spermatogenesis. Some authors have shown that sildenafil and tadalafil have a concentration-dependent stimulatory effect on sperm motility in vitro (8, 23-25). Nevertheless, extrapolations to the in vivo setting must be carefully considered, because the effects of these molecules might be influenced by some modulating factors in the human body, and the concentrations tested in vitro are hardly reached following oral administration.

To date, the influence of PDE5i on sperm is still a matter of debate (10). In fact, many authors did not detect any effect of a PDE5i on seminal parameters after both acute (12, 26) and chronic administration (27, 28). On the other hand, in vivo several studies conducted on very few patients treated with PDE5i on a daily basis demonstrated a significant effect on the motility of spermatozoa (22, 29, 30). Grammeniatis et al. (31) reported that the daily intake of vardenafil 10 mg for 45 days improved both the quality and the quantity of sperm from infertile men. This led the authors to suggest a stimulation of prostatic se-