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ORIGINAL PAPER

A survey on the experience of 136 Italian urologists in the treatment of erectile dysfunction with PDE5 inhibitors and recommendations for the use of Avanafil in the clinical practice

Vincenzo Mirone [1], Ferdinando Fusco [1], Fabio Parazzini [2], Alessandro Zucchi [3]

[1] Dipartimento Ostetricia, Ginecologia, Urologia - Clinica Urologica Università di Napoli Federico II, Italy;
[2] I Clinica Ginecologica, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università di Milano, Italy;
[3] Clinica Urologica ed Andrologica, Università di Perugia, Italy.

Summary

Introduction: PDE5 inhibitors are the first-line treatment for erectile dysfunction. Although all these drugs share the same mechanism of action, each agent could have different characteristics in terms of selectivity, pharmacokinetics and tolerability profile.
Materials and Methods: This manuscript illustrates a project, undertaken by the Italian Society of Urology in order to obtain a "snapshot" of the experience of Italian urologists with the use of PDE5 inhibitors in the clinical practice. This project included a survey, targeting a sample of 136 Italian urologists experienced in the treatment of ED, and the organization of a conference of experts who, based on the findings of the survey, the scientific literature and the clinical experience, would define some recommendations for the use of PDE5 inhibitors in clinical practice with a particular focus on Avanafil, the most recent drug in this class.
Results: The following recommendations on the use of Avanafil were issued: 1) In patients who are candidates for the use of Avanafil, it is advisable to use the 200-mg dose from the first administration; 2) When used at the highest dose (200 mg), Avanafil shows a favourable tolerability profile with an efficacy similar to that of other agents; 3) The patient should be instructed to take Avanafil on an empty stomach, i.e., 30-45 minutes before or 2 hours after a meal; 4) The efficacy window of Avanafil is between 30 minutes and 6 hours after dosing, which qualifies this molecule as a new drug with an intermediate duration of action; 5) Avanafil at a dose of 50-100 mg/day may be a therapeutic option in chronic rehabilitation.
Conclusions: Among PDE5 inhibitors, Avanafil is a new agent with an intermediate duration of action, characterized by high efficacy and good tolerability even at the highest dose (200 mg).

KEY WORDS: *Erectile dysfunction; PDE5 inhibitors; Avanafil; Italian survey; Recommendations; Dosage.*

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INTRODUCTION

Erectile dysfunction (ED), defined as the consistent or recurrent inability to attain and maintain an erection sufficient for satisfactory sexual performance, is a condition with a high prevalence worldwide; it has been estimated that 5-20% of men are affected by moderate-to-severe ED at some time during their sexual life (1).
The introduction in the clinical practice of phosphodiesterase type 5 inhibitors (PDE5is), in the early 1990s, represented a milestone in the treatment of ED.
Penile erection is a complex neurovascular event that occurs due to relaxation of cavernosal helicine arteries and smooth muscle of corpora cavernosa in combination with a coincident veno-occlusion, leading to blood distension of the corporal sinusoid and resultant penile rigidity (2). The primary mediator of this process is the nitric oxide (NO)/cyclic guanosin-monophosphate (cGMP) pathway. Phosphodiesterase type 5 (PDE5), the enzyme which breakdowns cGMP in the corpus cavernosum, regulates the NO-mediated relaxation of smooth muscle cells. The mechanism of action of PDE5is consists precisely in the inhibition of PDE5, which results in increased cGMP concentrations with continued activation of the NO/cGMP pathway and subsequent increase in blood flow into the corpora cavernosa (3).
The efficacy of PDE5 inhibitors is independent of patient age, etiology of ED (organic, psychogenic, mixed), and baseline severity of the condition (4).
Four PDE5is (*Sildenafil, Tadalafil, Vardenafil,* and *Avanafil*) have so far been approved for clinical use in Italy.
Avanafil, the most recently marketed molecule, differs pharmacologically from the other agents of the same class due to its higher selectivity for the PDE5 isoenzyme. Indeed, PDE5 inhibitors have different selectivities for this isoenzyme, as they may exert inhibitory effects on other PDE isoforms resulting in potential side effects, sometimes serious enough to require treatment discontinuation. On the other end, the greater the selectivity for the PDE5 isoenzyme, the less likely is the occurrence of adverse events potentially related to the inhibition of other PDE isoforms (5). Experimental studies have shown that *Avanafil* has higher selectivity for PDE5 than for other isoenzymes. It is generally believed that the high selectivity of *Avanafil* results in better tolerability compared with other less selective agents (5, 6).

No conflict of interest declared.

The efficacy of *Avanafil* in the treatment of ED is confirmed by a number of double-blind, placebo-controlled, randomized clinical trials, conducted both in the general population (7) and in "*difficult*" patient subgroups, such as those with diabetes mellitus (8) or those who have undergone nerve-sparing radical prostatectomy (9). In these clinical trials, *Avanafil* demonstrated a rapid onset of action, often as early as 15 minutes after dosing, a prolonged therapeutic effect (in some cases up to 6 hours after administration), and a good tolerability (10). After approximately two years from the *Avanafil* launch in Italy, urologists have now developed a specific clinical experience with the use of this drug. However, there are still some "*uncertainties*" about the best use of *Avanafil*, particularly with regard to dosage, efficacy, and safety profile compared with older PDE5is.

In order to obtain a "*snapshot*" of the use of *Avanafil* in the clinical practice, and to make recommendations for its "*best*" use, the Italian Society of Urology (*SIU, Società Italiana di Urologia*) started a project involving:

1) a survey, targeting a sample of Italian urologists experienced in the treatment of ED, with a particular focus on their clinical experience with the use of *Avanafil*; and
2) the organization of a conference of experts who, based on the findings of the survey and the scientific literature, would define some recommendations for the use of *Avanafil* in clinical practice.

This paper describes, in its first part, the preliminary results of the survey, and subsequently presents the recommendations made by the conference of experts.

Material and methods

This research was conducted from February to April 2016 through an online survey. SIU members were invited to answer anonymously a number of questions included in a questionnaire. In particular, SIU local chairpersons and physicians experienced in the treatment of ED were invited to participate.

The questionnaire investigated the number of ED patients treated over the past 12 months, and the proportion of them treated with *Avanafil*. Physicians were also asked to indicate, based on their clinical experience, the characteristics of the patients (expressed in percentage) who had been treated with *Avanafil* 100 mg and 200 mg. The aim of this survey was to collect information on physicians' experience in this context; therefore, detailed information on individual patients was not collected.

A total of 136 urologists responded to the survey (88.2% male; mean age 47 years, range 26-71 years; 48.5% of the respondents stated they worked mainly in a hospital setting).

Overall, urologists who participated in this survey stated that they had treated 17.856 patients during the 12 months prior to the completion of the questionnaire. Of these, 13% were treated with *Avanafil* 100 mg, and 26% with *Avanafil* 200 mg (the same patient could have been treated, at different times, with both doses of *Avanafil*).

Table 1 shows the characteristics of the patients treated with *Avanafil* 100 mg and 200 mg, the patient satisfaction, and the frequency of side effects.

Patients treated with *Avanafil* 200 mg were on average older and were more likely to report comorbid diabetes mellitus. The use of *Avanafil* 100 mg was more common in treatment-naïve patients. Patient satisfaction was greater in those treated with *Avanafil* 200 mg. Likewise, the frequency of side effects was slightly higher in individuals treated with the higher dose of *Avanafil*: overall, the observed difference in the frequency of side effects was essentially due to a higher frequency of headaches.

The methodology chosen for the production of recommendations was that of the "*consensus conference*", which involves the drafting of recommendations by a "*jury*" at the end of a presentation and consultation of experts summa-

Table 1.
Characteristics of patients receiving Avanafil 100 mg and 200 mg as reported by physicians participating in the SIU survey.

Patient characteristics	Patients treated with Avanafil 100 mg (%)	Patients treated with Avanafil 200 mg (%)
Age (years) > 50/< 50	61.6/38.4	65.7/34.3
Organic-based ED	56.6	51.1
Comorbid diabetes mellitus	28.6	36.2
First treatment (treatment-naïve pts)	45.7	40.4
On-demand use	65.4	63
Patient satisfaction (yes/no)	54.2/45.8	58.4/41.6
Frequency of side effects		
Any side effects	15.9	22.4
Headache*	12.6	16.5
Hot flushes	5.5	4.1
Back ache	2.5	1.1
Rash/itching	2.6	2

* *Only the side effects reported in more than 2% of the patients in at least one of the two groups are listed.*
The percentages shown are mean percentages, weighted by the number of patients treated by each physician.

rizing scientific knowledge on a given topic. The critical analysis of the literature enables the "*jury*" to compare the available evidence with expert opinions or reports.
This method implies the following steps:
1. the definition of the themes of the recommendations;
2. the search for relevant literature;
3. the preparation of the first draft of the consensus statement by a drafting group;
4. the discussion by a "jury" of experts, and the preparation of the final document.

In March 2016, the drafting group identified the themes of the recommendations, searched PubMed using the key words "*avanafil, erectile dysfunction, treatment*", and then prepared a first draft of the recommendations.
The experts invited to take part in the production of the recommendations participated in a workshop that was held on April 21-22, 2016. During this workshop, the results of the literature review and the findings of the SIU survey, reported in the introduction of this paper, were presented.
Subsequently, the recommendations prepared by the drafting group were also presented.
The expert panel was composed of 16 SIU local chairpersons and 32 experts (2 per local area) in the treatment of ED, identified among the SIU members by the local chairpersons of the association.

Results

All the experts discussed, amended, and approved in plenary session the recommendations that are presented herein, with comments illustrating their rationale and relevance for the clinical practice.

1. In patients who are candidates for the use of Avanafil, it is advisable to use the 200-mg dose from the first administration.

The data of this survey indicate that the 200-mg dose of *Avanafil* is the most commonly used in clinical practice. This practice is supported at least partly by scientific literature. *Corona et al.* (11) have recently published a systematic review of the literature on randomized controlled trials (RCTs), evaluating *Avanafil versus* placebo in the treatment of erectile dysfunction. This systematic review included five placebo-controlled RCTs, showing that *Avanafil* was superior to placebo in improving vaginal penetration and achieving a successful sexual intercourse. This review of the literature concluded that both the 100- and 200-mg doses of *Avanafil* were effective and well tolerated. Actually, the single most commonly reported adverse effect with *Avanafil* 200 mg was an increased frequency of headache compared to *Avanafil* 100 mg, although this difference was not statistically significant (this finding has also been reported in the present survey on the clinical practice in Italy). No differences were observed between the two groups in the rate of treatment continuation.
With regard to efficacy, the analysis of published studies indicates a greater efficacy (although not statistically significant) of the treatment with the 200-mg dose. The effect of *Avanafil* 100 mg was also lower in elderly subjects, while no differences were observed with *Avanafil* 200 mg.
The observation that the 200-mg dose of *Avanafil* shows greater efficacy in all patient categories, while having a substantially similar tolerability profile, clearly supports the recommendations of our working group.

2. When used at the highest dose (200 mg), Avanafil shows a favourable tolerability profile with an efficacy similar to that of other agents.

Chen et al. (12) have recently published a "*network meta-analysis*" that included RCTs evaluating the efficacy of *Sildenafil, Tadalafil, Vardenafil,* and *Avanafil*, usually in comparison with placebo. Overall, the authors included 82 RCTs (for a total of 47626 patients) for the efficacy analysis, and 72 RCTs (20325 patients) for the tolerability analysis.
The authors concluded that there were no significant differences between *Avanafil*, *Sildenafil, Tadalafil*, and *Vardenafil*, when the maximum recommended doses of these drugs (200, 100, 20 and 20 mg, respectively) were administered. With regard to tolerability, *Avanafil* was significantly associated with a lower incidence of adverse effects when drugs were given at the maximum recommended dosage patients were treated with the maximum recommended doses of these drugs (200, 100, 20, and 20 mg, respectively).

3. The patient should be instructed to take Avanafil on an empty stomach, i.e., 30-45 minutes before or 2 hours after a meal.

It is important to adequately educate the patient about the fact that *Avanafil* should be taken on an empty stomach. In fact, the median Time to Maximum Plasma Concentration (T_{max}) is obtained within 30-45 minutes after dosing, and the concomitant intake with food causes a delay in median T_{max} of 1 hour and 25 minutes , as reported in the Summary of Product Characteristics (SPC) of *Avanafil* (13).

4. The efficacy window of Avanafil is between 30 minutes and 6 hours after dosing, which qualifies this molecule as a new drug with an intermediate duration of action.

Table 2 shows the median Tmax and the plasma half-life (in hours) of the four PDE5 inhibitors available today in Italy for the treatment of ED (13-17). With regard to *Avanafil*, discordant data about half-life have been presented in the literature. Its terminal half-life is 6-17 h, as reported in the SPC, while the apparent T1/2 is 1.20 to

Table 2.
T_{max} and plasmatic half-life of PDE5-inhibitors (13-17).

Parameter	Avanafil	Sildenafil	Vardenafil	Tadalafil
T_{max} (median)	30-45 min	1 h	1 h	2 h
Plasmatic half-life	1.20-5 h	3–5 h	4–5 h	17.5 h (mean)

5 hours (17), in line with the duration of the therapeutic effect observed in clinical trials.
It is quite clear from above that *Avanafil* can be qualified as a new agent with an intermediate duration of action, as compared with other active substances.

5. Avanafil at a dose of 50-100 mg/day may be a therapeutic option in chronic rehabilitation.
There is scientific evidence supporting the use of PDE5 inhibitors as on-demand or chronic (daily) treatment for penile rehabilitation following radical prostatectomy. The fibrosis of cavernous bodies has been associated with reduced penile length: experimental studies have demonstrated that, following bilateral cavernous nerve injury, there is a significant reduction in the cavernosal smooth muscle/collagen ratio. Chronic use of PDE5is has been specifically studied with the aim to improve this clinical problem. *Avanafil* has been shown to be effective in the treatment of patients with ED following radical prostatectomy. When prescribed for chronic use, these agents are usually given at the lowest dose available (18), and increasing their dose does not seem to improve their efficacy (19).

Discussion

As emphasized by the recent guidelines of the European Association of Urology (EAU), PDE5is are the first-line therapeutic option for most men with ED. Currently available PDE5is (*Sildenafil, Tadalafil, Vardenafil, and Avanafil*) have the same mechanism of action; therefore, their efficacy is substantially similar at comparable doses. There are, however, relevant differences in the pharmacokinetic profile and degree of selectivity between different agents, and this should be taken in account in the therapeutic decision-making process.
The high selectivity of *Avanafil*, in particular, gives this agent a very satisfactory tolerability profile, as pointed out also by one of the recommendations in this paper, which suggests that good tolerability is one of the main "strengths" of *Avanafil* compared to other molecules.
The prevailing opinion among the participants in this survey is that, in patients who are candidates for the use of *Avanafil*, the 200-mg dose should be used from the start of the treatment; in fact, this dose provides an appropriate balance between the efficacy and tolerability of PDE5is, in combination with satisfactory response and compliance rates. According to the findings of this survey, there seem to be no significant differences in terms of efficacy between *Avanafil, Sildenafil, Tadalafil,* and *Vardenafil* when the maximum recommended doses of these drugs are used (200, 100, 20, and 20 mg, respectively); moreover, *Avanafil* shows a favourable tolerability profile when used at the highest dose (200 mg), with an efficacy similar to that of other agents.
A crucial point for the successful treatment of ED with PDE5is is the effectiveness of Doctor-Patient communication in relation to the proper administration of prescribed medications and the outcomes to be expected, both in terms of efficacy and response times. In fact, if these issues are not adequately explained to the patients, they may mistakenly believe that the treatment prescribed is ineffective and/or may inappropriately stop or change their medications on their own initiative.
In particular, the patient should be instructed to take *Avanafil* on an empty stomach, i.e., 30-45 minutes before or 2 hours after a meal, in order to obtain an optimal therapeutic effect; it is also necessary to explain that the efficacy window of *Avanafil* is between 30 minutes and 6 hours after dosing, which qualifies this new PDE5i as an agent with intermediate duration of action.
Finally, a topic of great interest that has emerged from this survey is that *Avanafil*, used at a dose of 50-100 mg/day, can be a therapeutic option for long-term penile rehabilitation, confirming the literature data that support the use of PDE5-inhibitors as on-demand or chronic treatment for penile rehabilitation after radical prostatectomy (20).

Conclusions

Avanafil, a highly selective PDE5 inhibitor, characterized by rapid onset of action and prolonged therapeutic effect, is an effective and well tolerated option for the treatment of ED. The present survey, conducted by SIU among Italian urologists, largely confirms the clinical efficacy and tolerability of *Avanafil* in a real-life setting, even at the highest dose (200 mg), in line with the results of previous international clinical trials conducted to evaluate this PDE5 inhibitor.

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Correspondence

Vincenzo Mirone, MD
mirone@unina.it

Ferdinando Fusco, MD (Corresponding Author)
ferdinando-fusco@libero.it

Dipartimento Ostetricia, Ginecologia, Urologia
Clinica Urologica Università di Napoli Federico II, Italy

Fabio Parazzini, MD
fabio.parazzini@unimi.it

I Clinica Ginecologica, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università di Milano, Italy

Alessandro Zucchi, MD
zucchi.urologia@gmail.com

Clinica Urologica ed Andrologica, Università di Perugia, Italy