Official title: Evaluation of the clinical and molecular efficacy of daily avanafil in Egyptian males with erectile and endothelial dysfunction (Randomized Placebo-Controlled study)

NCT number: NCT04374994

Document date: 20-9-2018

INTRODUCTION

Penile erection is a neurovascular process that occurs in response to the activation of pro-erectile autonomic pathways and is controlled by numerous tightly regulated events. Pathologic alteration in the endothelium of penile vasculature and/or erectile tissue and/or impairment of neurovascular processes can result in erectile dysfunction (ED). [1]

Erectile dysfunction, the persistent inability to achieve or maintain an erection for satisfactory sexual performance, is a highly prevalent disorder associated with a significant burden of illness. The prevalence and incidence of ED are strongly age-related, affecting more than half of men >60 years. [2-4]

Erectile dysfunction is an early symptom or alert of cardiovascular disease, due to the common risk factors and pathophysiology mediated through endothelial dysfunction that may explain the association between ED and other vascular disease e.g., DM, CVD, and atherosclerosis. [4]

The vascular endothelium is involved in numerous physiologic functions and its dysfunction leads to impaired vasodilatation. This is attributed to decreased bioavailability of nitric oxide (NO) which is a molecule with a key role in vascular tone regulation and thus impaired NO bioactivity is a major pathogenic mechanism of ED. [5,6]

Endothelin-1 (ET-1) is a 31-amino-acid peptide with potent and prolonged vasoconstrictor activity. It exerts its biological effect through the activation of specific endothelin receptors. Endothelin receptors have been found in human corporal smooth muscle membranes. ED was suggested to be

the result of impaired endothelium-dependent smooth muscle relaxation due to increased release of ET-1. [7,8]

Oral phosphodiesterase type 5 (PDE5) inhibitors are recommended as first-line therapy for ED of varying aetiology and severity. [9,10]

However, many patients are dissatisfied with available therapies due to high cost, adverse events and perceived lack of efficacy. Therefore, the development of novel PDE5 inhibitors with enhanced selectivity, faster onset of action, increased potency and improved tolerability is desirable. [11,12]

Recently, a new PDE5ì, avanafil, has become available worldwide. The evaluation of safety profile suggests that avanafil is associated with a lower incidence of side effects and approved for the treatment of ED by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in April 2012 and in June 2013, respectively.[13-15]

The most important characteristic of avanafil, in comparison to the first-generation PDE5is, is its high selectivity for PDE5, particularly in relation to PDE6, PDE1, and PDE11. Avanafil has selectivity for PDE5 over PDE1 and PDE6 similar to tadalafil, but, unlike tadalafil, has negligible affinity for PDE11. [14,15]

AIM OF THE WORK

The aim of the work is to investigate the impact of daily avanafil on the function and levels of some soluble molecular markers of penile endothelium in men with erectile dysfunction.

PATIENTS

The study will be conducted on 140 adult males complaining of ED associated with diseases that may affect endothelial function such as diabetes mellitus, hypertension and/or dyslipidemia from outpatient clinic of Dermatology, Venereology and Andrology Department of the Alexandria main University Hospital.

They will be randomized into two groups:

Intervention group: will include seventy adult males and will receive daily avanafil for four weeks.

Control group: will include seventy adult males and will receive a placebo instead.

- An informed consent will be taken from all subjects prior to the onset of the study.
- Approval of the medical ethics committee of Alexandria Faculty of Medicine will be obtained.

Exclusion criteria:

1. Patients aged < 18 years.
2. Patients with contraindications to treatment by PDE inhibitors.
3. Patients with diseases that increase the risk of priapism (eg, leukemia and multiple myeloma).

METHODS

ALL studied groups will be subjected to:

1. Full history taking with complete general and genital examination.
2. Diagnosis and severity of ED was determined according to IIEF-5 questionnaire. Erectile dysfunction will be defined as a score of < 22 in the self reported International Index of Erectile Function-5 questionnaire (IIEF-5). [16]

The International Index of Erectile Function (IIEF-5) Questionnaire

Over the past 6 months:					
1. How do you rate your **confidence** that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
3. During sexual intercourse, **how often** were you able	Almost never/never 1	A few times (much	Sometimes (about half the time) 3	Most times (much	Almost always/always 5

The International Index of Erectile Function (IIEF-5) Questionnaire

to maintain your erection after you had penetrated (entered) your partner?		less than half the time) 2		more than half the time)4	
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/always 5
IIEF-5 scoring: The IIEF-5 score is the sum of the ordinal responses to the 5 items. 22-25: No erectile dysfunction 17-21: Mild erectile dysfunction					

The International Index of Erectile Function (IIEF-5) Questionnaire

12-16: Mild to moderate erectile dysfunction
8-11: Moderate erectile dysfunction
5-7: Severe erectile dysfunction

3. The patients in the intervention group will receive avanafil 50 mg orally for 4 weeks. They will be instructed to take their medication on an empty stomach every evening. A total of 28 pills will be prescribed at study entry and patients will be asked to count and report any unused medication at the end-of-study visit.
4. The patients in the control group will receive placebo tablets for 4 weeks.
5. Markers of endothelial function will be measured in plasma at baseline and end of treatment using standard methods and commercially available kits (Human Endothelin 1(ET-1) ELISA Kit, Nitric oxide (NO) ELISA Kit and Human Cyclic guanosine monophosphate(cGMP) ELISA Kit).[17-19]
6. The primary outcome will be the percentage of change of NO, cGMP and ET1 serum levels from baseline to 4 weeks posttreatment with avanafil.
7. The secondary outcome will be comparing avanafil with placebo group regarding posttreatment NO, cGMP and ET1 serum levels and percentage of change from baseline.

ETHICS OF RESEARCH

Research on human or human products:

☐ Prospective study: informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.

☐ Retrospective study: confidentiality of records will be considered.

☐ DNA/genomic material: informed consent for DNA / genomic test and for research will be taken from patients. No further test will be carried out except with further approval of committee and patients. If the samples will travel outside Egypt the researcher will be responsible for transportation and security approval.

☐ All drugs used in the research are approved by the Egyptian Ministry of Health.

Research on animal:

☐ The animal species are appropriate for the test.

☐ After test, if animal will suffer, it will be euthanized and properly disposed.

☐ After operation, it will have a proper postoperative care.

RESULTS

The data will be recorded, tabulated, statistically analyzed and represented in appropriate figures and diagrams to fulfill the aim of the work.

DISCUSSION

The findings will be discussed in view of achievement of the aim. The results of other related studies will be compared to those of the current one.

REFERENCES

1. Giuliano F. New horizons in erectile and endothelial dysfunction research and therapies. Int J Impot Res 2008; 20:2-8.

2. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafi l in the treatment of erectile dysfunction. Sildenafi l Study Group. N Engl J Med 1998; 338:1397-404.

3. McKinlay JB. The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000; 12(l4):6-11.

4. Jackson G, Rosen R, Kloner R, Kostis J. The Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk: New Guidelines for Sexual Medicine. J Sexual Medicine 2006; 3(1):28-36.

5. Chong AY, Blann AD, Lip GY. Assessment of endothelial damage and dysfunction: observations in relation to heart failure. QJM 2003; 96(4): 253-67.

6. Lue TF. Erectile dysfunction. N Engl J Med 2000; 342(24):1802-13.

7. Rossi P, Menchini FF, Fiorini I, Palego P, Simi S, Rossi B, et al. Comparison between plasma concentrations of testosterone, nitric oxide and endothelin 1–2 in penile and brachial venous blood: preliminary results in men with psychogenic impotence. Biomed Pharmacother 1998; 52:308-10.

8. Francavilla S, Properzi G, Bellini C, Marino G, Ferri C, Santucci A. Endothelin-1 in diabetic and nondiabetic men with erectile dysfunction. J Urol 1997; 158:1770-4.

9. Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. Chapter 1: the management of erectile dysfunction: an AUA update. J Urol 2005; 174:230-9.

10. 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.

11. Madduri SD. After two years, did Viagra live up to its expectations? Mo Med 2001; 98:243-5.

12. Limin M, Johnsen N, Hellstrom WJ. Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. Expert OpinInvestig Drugs 2010; 19:1427-37.

13. Chen L, Staubli SE, Schneider MP, Kessels AG, Ivic S, Bachmann LM, et al. Phosphodiesterase 5 Inhibitors for the Treatment of Erectile Dysfunction: A Trade-off Network Meta-analysis. EurUrol 2015; 68:674-80.

14. Smith WB, McCaslin IR, Gokce A, Mandava SH, Trost L, Hellstrom WJ.PDE5 inhibitors: considerations for preference and long-term adherence. Int J Clin Pract 2013; 67:768-80.

15. Kyle JA, Brown DA, Hill JK. Avanafil for erectile dysfunction. Ann Pharmacother 2013; 47:1312-20.

16. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999; 11(6):319-26.

17. Bouallegue A, Daou GB, Srivastava AK. Endothelin-1-induced signaling pathways in vascular smooth muscle cells. Curr Vasc Pharmacol 2007; 5:45-52.

18. El Melegy NT, Ali ME, Awad EM. Plasma levels of endothelin-1, angiotensin II, nitric oxide and prostaglandin E in the venous and cavernosal blood of patients with erectile dysfunction. BJU Int 2005; 96 (7):1079-86.

19. Pradelles P, Grassi J, Chabardes D, Guiso N. Enzyme immunoassays of adenosine cyclic 3′,5′-monophosphate and guanosine cyclic 3′,5′-monophosphate using acetylcholinesterase. Anal Chem 1989; 61:447-53.