European Society for Sexual Medicine

Issue 38 – January 2018

ESSMToday

ESSM NEWSLETTER

www.essm.org

HIGHLIGHTS FROM THE EDITION

CONTACT
ESSM Secretariat
Via Ripamonti 129 – 20141 Milan, Italy
Phone: +39–02–56 601 625
Fax: +39–02–70 048 577
Email: admin@essm.org

IMPRINT
Publisher: ESSM
Editor-in-Chief: Ferdinando Fusco, Italy
Layout: CPO HANSER SERVICE

Effects of PDE5 inhibitors on the male reproductive potential: A dinner conversation

by Fotios Dimitriadis, Athanasios Zachariou, Nikolaos Sofikitis

Fotios Dimitriadis (FD)
X-Assisted Professor, Department of Urology, Tottori University School of Medicine, Yonago, Japan

helabio@yahoo.gr

Athanasios Zachariou (AZ)
University Scholar, Department of Urology, Ioannina University School of Medicine, Ioannina, Greece

zahariou@otenet.gr

Nikolaos Sofikitis (NS)
Professor and Chair, Department of Urology, Ioannina University School of Medicine, Ioannina, Greece

v.sofikitis@hotmail.com

AZ: Gentlemen, the restaurant is great, please relax, and let's have a nice dinner.

NS: Fotios, I see that your face looks skeptical and confused. Why? You do not like the wine?

FD: I have just finished the outpatient clinic. One of my idiopathic infertile patients asked me a difficult question which I receive several times every week: Are there any effective pharmaceutical agents for the therapeutical alleviation of oligoasthenoteratozoospermia?

NS: To the best of my knowledge there are fewer than five randomized, placebo-controlled trials evaluating the effects of pharmaceutical agents on the reproductive potential of infertile men.

FD: After 2009, the number of publications on the effects of PDE5 inhibitors on quantitative and qualitative sperm parameters has been dramatically increasing, isn't it interesting?

AZ: It is interesting but not unexplainable. Let us remember that several members of the families of phosphodiesterases are present both in the testis and in the epididymis.

FD: Do you mean that specific cellular subpopulations within either the testis or the epididymis are positive for distinct members of the phosphodiesterases' families?

NS: To the best of my knowledge, peritubular myoid cells are positive for PDE5 expression. Leidyg cells are positive for PDE11A, PDE4B, PDE5, PDE8A and PDE11. Sertoli cells are known to be positive for PDE1, PDE3 and PDE4 expression. Human epididymis is known to be positive for PDE3 and PDE5 expression. Vascular monocytes within the testis are positive for PDE11 and PDE5. Vas deferens is positive for PDE5. Prostate is positive for PDE5a, PDE11A4 and PDE11A1. It is logical to hypothesize that administration of inhibitors of PDE5 may affect testicular endocrine and exocrine function, epididymal function, prostatic secretory function and prostatic physiology. However it should be emphasized that PDE5 inhibitors may additionally inhibit to a smaller degree other phosphodiesterase families within the testis. For instance, PDE5 inhibitors additionally inhibit to a smaller degree PDE11, PDE4, PDE8, and PDE3. Therefore administration of PDE5 inhibitors may affect several cellular subpopulations within the male reproductive tract.

AZ: What about the subpopulations of haploid male gametes?

FD: Spermatids are positive for PDDE11, PDE4A, PDE4D, PDE1A, and PDE1C. Spermatozoa are positive for PDE1A, PDE3A, PDE4, PDE5, PDE6, and PDE10A.

AZ: And what about the subpopulations of diploid male gamete?

FD: Spermatogonia are positive for PDE11A, PDE1, and PDE2. Primary spermatocytes are positive for PDE11, PDE3, PDE4, and PDE1C.

NS: The above localization of selected PDE5-families explains the enhanced Leydig cellular secretory function and the increased Sertoli cellular secretory function after administration of either sildenafil or vardenafil. In fact, the increased Leydig cellular secretory function post-sildenafil administration has been proven by the increased INSL3 production by human Leydig cells after sildenafil administration. On the other hand, the increased Sertoli cellular secretory function post-vardenafil administration has been proven by the increased androgen-binding activity/content produced by human Sertoli cells after vardenafil administration. Increased peripheral serum testosterone concentration has been demonstrated post-avanafil administration, as well.

AZ: Do the above alterations in the secretory function of Leydig or Sertoli cells affect any of the standard parameters of the semen analysis?

FD: The enhanced Leydig or Sertoli cell secretory function after sildenafil or vardenafil administration may result in increased intraepididymal lumen concentrations of testosterone or androgen binding protein allowing optimal epididymal sperm maturation process. The final result may be an increase in sperm motility after administration of either sildenafil or vardenafil. An alternative mechanism to explain the beneficial effects of sildenafil on sperm motility may be the enhanced prostatic secretory function established after administration of sildenafil. In fact post-sildenafil administration increased concentrations of markers of prostatic secretory function have been demonstrated. Therefore a second

Effects of PDE5 inhibitors on the male reproductive potential: A dinner conversation

attractive hypothesis may be that administration of sildenafil, acting on prostatic PDE5, increases prostatic secretory function with an overall result a positive effect on sperm motility. Such a positive effect of sildenafil, vardenafil, or avanafil on sperm motility has been demonstrated very vividly in our laboratory and in other independent laboratories. In a previous study the beneficial effects of avanafil on sperm motility were attributed to the longer length of sperm midpiece post-avanafil administration. It is well known that the sperm midpiece is the "battery" of the spermatozoon and therefore positive effects of avanafil on the sperm cytoskeleton affecting the sperm motility have been demonstrated in the above study. On the other hand, other groups did not demonstrate a positive effect of sildenafil on the standard parameters of semen analysis.

AZ: What kind of patient subpopulations were employed in the above studies?

FD: In all of the above studies, one at least of the standard parameters of the semen analysis was abnormal (sperm concentration, or sperm motility, or sperm morphology) in all the participants. One meta-analysis and systematic review in 2017 has demonstrated that oral PDE5 inhibitor treatment could modestly increase the sperm motility and morphology in infertile men.

AZ.: I understand that sildenafil or vardenafil have been proven in several studies effective to improve sperm motility in oligoasthenospermic infertile men. Do the above substances affect reproductive hormones?

FD: It appears that the above pharmaceutical agents do not affect serum reproductive hormonal levels. On the other hand, a recent report has indicated that avanafil administration increases the peripheral serum testosterone levels.

AZ: What about the effects of tadalafil on sperm qualitative and quantitative parameters?

NS: Tadalafil is known to inhibit to a certain degree the PDE11. PDE11 is highly expressed in the testis, prostate, and developing spermatozoa. PDE11 knockout mice display reduced sperm concentration, rate of forward progression, and percentage of live spermatozoa. Pre- ejaculated sperm from the above mice display increased premature/spontaneous capacitance. In the above study from UK the authors emphasize that agents, like tadalafil, that inhibit PDE11 may have the potential to disrupt regulation of spermatozoa cAMP, and as a result may have detrimental effects on sperm physiology. A study from Andria, Italy, has demonstrated that once-a-day tadalafil administration improves the spermogram parameters in fertile patients. However the above study has been criticized because the respective results refer to fertile patients. It would be a more clinically significant study, a clinical trial evaluating the effects of tadalafil on the reproductive potential of infertile patients since a small impairment in sperm qualitative and quantitative parameters may not be clinically important in fertile patients, however, an impairment in sperm qualitative and quantitative parameters may have more serious consequences in infertile patients (especially if they do not want to participate in assisted reproductive technology programs). In another communication from New Orleans, LA, USA, it has been proven that there are not deleterious effects of nine months of daily tadalafil 20 mg on spermatogenesis or hormones related to testicular function in men elder than 45 years old. In a similar fashion, the above study cannot be unequivocally interpreted as a clinical trial establishing a safety profile for tadalafil due to the barrier that the latter study has employed men with relatively high (or normal) sperm concentration, normal sperm motility, and normal sperm morphology. In another different study from New Orleans, LA, USA, it has been demonstrated that chronic daily administration of tadalafil at doses of 10 and 20 mg for six months has no adverse effects on spermatogenesis on reproductive hormones in men older than 45 years. However, for subjects to be enrolled in the latter study, semen samples had to have certain minimum normal values based on WHO criteria. Thus the latter study has similar, as above stated, limitations due to the fact that men with male factor infertility and at least one abnormal parameter of the semen analysis had not been included. In an in vitro study from Cairo, Egypt, it has been shown that semen samples recovered from asthenozoospermic men and subsequently treated with tadalafil concentration equal to 1 mg/ml demonstrate significant increase in sperm progressive motility, whereas, specimens treated with 4 mg/ml tadalafil concentration demonstrate a significant decrease in sperm motility. Scientists suggested that the effect of tadalafil on sperm motility in vitro can be explained by a stimulation of the cAMP-protein kinase A pathway, whereas the inhibitory effect of this substance on PDE11 may also contribute to the effect of tadalafil on sperm motility. All the above studies should be coupled with the reports that tadalafil has been shown to inhibit human recombinant PDE11A1 activity at therapeutic concentrations, which is highly expressed in the testis and prostate, and its important function in spermatogenesis has been documented. On the other hand, several studies have indicated that sildenafil and vardenafil are one-two orders of magnitude more selective for PDE5 than PDE11 compared with tadalafil. The later studies offer a safety profile for sildenafil and vardenafil for sperm physiology, in contrast to the existing concerns on the influence of tadalafil on sperm parameters in men with abnormal values in semen parameters.

AZ: Dear friends, what about azoospermic men? Is it safe to recommend the administration of any PDE5 inhibitor in non-obstructed azoospermic men prior to the performance of testicular biopsy?

DF: The international literature supports that administration of vardenafil in men with non-obstructive azoospermia does not alter the sperm

Effects of PDE5 inhibitors on the male reproductive potential: A dinner conversation

recovery rate after testicular biopsy procedures. Thus non-obstructed azoospermic men with erectile dysfunction may use vardenafil without any consideration for the outcome of a subsequent testicular biopsy procedure.

AZ: Gentlemen, let me remind you that the positive effects of PDE5 inhibitors on erectile function may assist a subpopulation of men who attempt to produce a semen sample at the day of oocyte pick-up (in assisted reproductive trials), to reduce their stress and produce a semen sample of better quality. In these cases the production of a semen sample with higher quantitative or qualitative sperm parameters may be due to the reduction of the stress during the ejaculation process and the subsequent achievement of higher sexual satisfaction. Several studies from Yonago, Japan, have indicated that the higher the sexual satisfaction is, the higher the semen quality is. In addition, in the above studies, it has been shown that semen samples selected via sexual intercourse are of higher quality than semen samples collected via masturbation. Thus administration of vardenafil, or sildenafil, or avanafil may be indicated in men attempting to produce a semen sample during the day of the female partner-oocyte pick-up.

FD: What about the effects of udenafil on male reproductive capacity?

AZ: No adverse reproductive effects of udenafil have been observed in experimental animals in dose under 70 mg/kg.

FD: Dear friends, let me remind you that PDE5 is present in the vas deferens. Are there any effects of PDE-5 inhibitors on the vas deferens?

AZ: It has been shown that in patients with premature ejaculation, sildenafil plus paroxetine has a significantly higher therapeutic success rate that paroxetine alone. The inhibitory effect of sildenafil on PDE5 increases the level of cGMP in the vas deferens muscular fibers achieving the relaxation of the smooth muscle cells in vas deferens. This may prolong the time necessary for the achievement of ejaculation. Furthermore sildenafil may induce reduction in adrenergic neurotransmission in the smooth muscular fibers of the vas deferens and subsequently may reduce its pattern of contraction.

FD: Let me add that PDE5 is additionally expressed in epididymis. It has been demonstrated that no alterations occur in the epididymal secretory function by administering vardenafil. Additionally, it has been observed that in oligozoospermic infertile men treated with sildenafil, no increase in semen levels of α-glucosidase (a marker of epididymal function) is found. Furthermore, the effect of sildenafil on epididymal semen parameters has been evaluated in Sprague-Dawley rats. It has been demonstrated a significant increase in epididymal sperm motility and concentration compared to the control group.

NS: Since you are speaking for the male accessory genital glands, let us remember that PDE5 is expressed in the seminal vesicles, as well. The outcome of different studies of PDE5 inhibitors on the seminal vesicular physiology is controversial. The effect of sildenafil on the seminal vesicles in oligozoospermic men has been evaluated. Comparing semen samples before and after sildenafil treatment, no significant difference in seminal fructose levels, which is a marker of seminal vesicular function, has been observed. In an interesting study, the ultrasound alterations of seminal vesicle in infertile diabetic patients treated with tadalafil for three months have been studied. Compared to placebo, a significant reduction in seminal fundus/body ratio, a

Effects of PDE5 inhibitors on the male reproductive potential: A dinner conversation

higher pre- and post-ejaculation anteroposterior diameter, and a significant increase in seminal ejection have been observed.

AZ: We have discussed a lot for the effects of PDE5 inhibitors on sperm motility. Furthermore, some studies tend to suggest that vardenafil or sildenafil increase the total sperm count and the sperm morphology. However, are there any studies evaluating the effects of PDE5 inhibitors on sperm functional assays? It is well known that the standard parameters of semen analysis cannot predict accurately the male reproductive potential. Thus we need to employ sperm functional assays in order to appreciate the effects of PDE5 inhibitors on the male reproductive potential.

FD: The potential effect of sildenafil on spermatozoal ability to undergo capacitation process has been investigated. The investigators demonstrated that several concentrations of sildenafil may activate the capacitation process of washed spermatozoa. In another study, the impact of sildenafil on sperm acrosomal reaction has been evaluated. Spermatozoa were exposed to different doses of sildenafil. The investigators demonstrated that sildenafil affected the sperm acrosomal reaction with enhanced percentage of acrosomally reacted spermatozoa in comparison with the control specimens. It has been demonstrated that cGMP directly opens cyclic nucleotide-gated channels for calcium entry into the spermatozoa initiating the acrosome reaction.

FD: Let us go to the DNA structure. Do PDE5 inhibitors affect the spermatozoa DNA integrity?

AZ: There is a study that has been awarded a Ph.D. title from Greece indicating that spermatozoa treated with tadalafil in vitro demonstrated an increased DNA fragmentation. In that study it has been hypothesized that elevation of the second messenger cGMP level due to inhibition of PDE5 by tadalafil activates a nuclear cGMP-dependent protein kinase PKG with an overall detrimental effect on sperm chromatin structure. In addition tadalafil upregulating spermatozoal NOS expression subsequently increases intracellular sperm nitric oxide profiles which may diffuse in the sperm nucleus. Thus the intranuclear NO increased levels may exert their effect on nuclear transcriptional factors and chromatin remodeling enzymes. Alternatively it may hypothesized that the effect of tadalafil on sperm DNA is due to the formation of hydrogen bonds between the C=O groups of the molecule of tadalafil and the NH2 group in the guanine moiety of the DNA. The latter hypothesis is strongly supported by previous research efforts indicating a similar mechanism responsible for the interaction between sildenafil with salmon sperm DNA.

FD: So, which is the conclusion of our previous discussion? Is it appropriate to recommend the usage of PDE5 inhibitors as an adjunct tool for the therapeutic management of male infertility?

NS: We may suggest that administration of sildenafil, vardenafil, or avanafil may be recommended for semen production during assisted reproductive technology trials when the stress of the male is a great barrier for the production of a semen sample. Considering that randomized controlled trials provide positive results for the influence of sildenafil, or vardenafil, or avanafil on sperm motility, it may be suggested that the above pharmaceutical agents may have a beneficial role in the alleviation of asthenospermia in idiopathic infertile men. Definitely, additional research efforts are justified to further investigate the influence of PDE5 inhibitors on sperm qualitative, quantitative, and functional parameters and on semen physiology. Furthermore it appears to be of great clinical importance to further investigate the role of PDE11 in spermatogenesis process, epididymal sperm maturation process, and the overall sperm fertilizing capacity taking into serious consideration a) that PDE11 is highly expressed in spermatogonia, spermatocytes and spermatids in addition to its expression in Leydig cells, and b) that studies from Kent, U.K., have suggested that agents that inhibit PDE11 level have the potential to disrupt regulation of spermatozoal cAMP, and as a final result may have detrimental effects on sperm physiology and may lead to a reduced fertilization ability according to the investigators opinion.

AZ: The steaks and the hamburgers have just arrived, the red wine smells and tastes good, and let us enjoy our dinner.

REFERENCES

1. Alp H, Cirit U, Tas M, Rifaioglu MM, Hatipoglu NK, Aytekin I, Yucel M, Firat U, Ozmen MF, Seker U, Eren LB: **Effects of sildenafil citrate, isoniazid, and streptomycin on testicular tissue and epididymal semen quality in rats**. Urology; 80: 953 e9-14. 2012.
2. Chen J, Mabjeesh NJ, Matzkin H, Greenstein A: **Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation.** Urology; 61:197-200.2003.
3. Chung MK, Kim JC, Kim WB, Kang KK, Han SS: **Fertility study of the new pyrazolopyrimidinone derivative DA-8159 for erectile dysfunction in rats.** Arzneimittelforschung; 54:179-86. 2004.
4. Corvasce A, Albino G, Leonetti T, Filomena B A, Marucco E C: **Once-a-day Tadalafil administration improves the spermogram parameters in fertile patients.**Archivio Italiano di Urologia e Andrologia; 87:210-213. 2015.

Effects of PDE5 inhibitors on the male reproductive potential: A dinner conversation

5. Cuadra DL, Chan PJ, Patton WC, Stewart SC, King A: **Type 5 phosphodiesterase regulation of human sperm motility.** Am J Obstet Gynecol.;182:1013-5. 2000.

6. Dimitriadis F, Giannakis D, Pardalidis N, Zikopoulos K, Paraskevaidis E, Giotitsas N, Kalaboki V, Tsounapi P, Baltogiannis D, Georgiou I, Saito M, Watanabe T, Miyagawa I, Sofikitis N: **Effects of phosphodiesterase 5 inhibitors on sperm parameters and fertilizing capacity.** Asian J Androl; 10: 115–133, 2008.

7. Dimitriadis F, Tsampalas S, Tsounapi P, Giannakis D, Chaliasos N, Baltogiannis D Miyagawa I, Saito M, Takenaka A, Sofikitis N: **Effects of phosphodiesterase-5 inhibitor vardenafil on testicular androgen-binding protein secretion, the maintenance of foci of advanced spermatogenesis and the sperm fertilising capacity in azoospermic men**; Andrologia 44: 144–153, 2012.

8. Dimitriadis F, Tsounapi P, Saito M, Watanabe T, Sylakos A, Tsabalas S, Miyagawa I, Sofikitis N: **Is there a role for PDE5 inhibitors in the management of male infertility due to defects in testicular or epididymal function?** Current Pharmaceutical Design; 15: 000-000, 2009.

9. Dimitriadis F, Tsambalas S, Tsounapi P, Kawamura H, Vlachopoulou E, Haliasos N, Gratsias S, Watanabe T, Saito M, Miyagawa I, Sofikitis N: **Effects of phosphodiesterase-5 inhibitors on Leydig cell secretory function in oligoasthenospermic infertile men: a randomized trial.** BJU international; 106: 1181–1185, 2010.

10. Gur S, Sikka SC, Pankey EA, Lasker GF, Chandra S, Kadowitz PJ, Hellstrom WJG: **Effect of avanafil on rat and human corpus cavernosum.** Andrologia; 47: 897–903.2015.

11. Hellstrom WJG, Gittelman M, Jarow J, Steidle C, McMurray J, Talley D, Watts S, Mitchell CL, McGill JM: **An evaluation of semen characteristics in men 45 years of age or older after daily dosing with tadalafil 20 mg: results of a multicenter, randomized, double-blind, placebo-controlled, 9-month study**. European urology; 53: 1058–1065, 2008.

12. Hellstrom WJG, Overstreet JW , Yu A, Saikali K, Shen W, Beasley CM Jr, Watkins VS: **Tadalafil has no detrimental effect on human spermatogenesis or reproductive hormones.** The Journal Of Urology; 170: 887–891, 2003.

13. Koyuncu H, Serefoglu EC, Ozdemir AT and Hellstrom WJG: **Deleterious effects of selective serotonin reuptake inhibitor treatment on semen parameters in patients with lifelong premature ejaculation.** International Journal of Impotence Research; 24: 171 – 173.2012.

14. La Vignera S, Condorelli RA, Vicari E, Lotti F, Favilla V, Morgia G, Maggi M, Calogero AE: **Seminal vesicles and diabetic neuropathy: Ultrasound evaluation after prolonged treatment with a selective phosphodiesterase-5 inhibitor.** Andrology;1:245-50.2013.

15. Lefièvre L, De Lamirande E, Gagnon C: **The cyclic GMP-specific phosphodiesterase inhibitor, sildenafil, stimulates human sperm motility and capacitation but not acrosome reaction.** J Androl.; 21:929-37. 2000.

16. Mirone V, Debruyne F, Dohle G, Salonia A, Sofikitis N, Verze P, Fode M, Chapple C, on behalf of the URO-TRAM working group: **European association of urology position statement on the role of the urologist in the management of male hypogonadism and testosterone therapy.** European Urology; 72: 164–167, 2017.

17. Mostafa T: **Tadalafil as an in vitro sperm motility stimulant.** Andrologia; 39: 12–15.2007.

18. Sofikitis N, Dimitriadis F, Skouros S, Stavrou S, Seminis G, Giannakis I, Tsounapi P, Lantin P, Chaliasos N, Takenaka A: **P-01-065 Effects of Avanafil on semen quality and sperm cytoskeleton in oligoasthenospermic infertile men: A randomized controlled trial.** Presented in 18th congress of the European Society for Sexual Medicine, February 4 – 6, 2016, Madrid, Spain.

19. Sofikitis NV, Miyagawa I: **Endocrinological, biophysical, and biochemical parameters of semen collected via masturbation versus sexual intercourse.** J Androl.;14:366-73.1993.

20. Tan P, Liu L, Wei S, Tang Z, Yang L, Wei Q: **The effect of oral phosphodiesterase-5 inhibitors on sperm parameters: A meta-analysis and systematic review.** Urology; 105:54-61. 2017.

21. Vlachopoulou E, Gratsias S, Lazaridis A, Ovrenovits M, Giannakis D, Baltogiannis D, Vartholomatos G, Lazaros L, Georgiou I, Sofikitis N: **Effects of PDE5 inhibitors on sperm motility, sperm membrane permeability, and sperm DNA structure.** Presented in 38th Annual American Society of Andrology, April 10 –16, 2013, San Antonio, Texas.

22. Wayman C, Phillips S, Lunny C, Webb T, Fawcett L, Baxendale R and Burgess G: **Phosphodiesterase 11 (PDE11) regulation of spermatozoa physiology.** Int J Impot Res.; 17: 216-23, 2005.

23. Yamamoto Y, Sofikitis N, Mio Y, Miyagawa I: **Influence of sexual stimulation on sperm parameters in semen samples collected via masturbation from normozoospermic men or cryptozoospermic men participating in an assisted reproduction programme.** Andrologia; 32:131-8.2000.