

Dermatological Side Effects of Sildenafil among a group of Iraqi Males

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Summary:

Background: Sildenafil is a drug that is used to treat erectile dysfunctions, it acts by inhibiting CGMP specific phosphodiesterase type 5, an enzyme that regulates blood flow in the penis. The most common adverse effects of sildenafil are headache, dyspepsia, nasal congestion and impaired vision which includes photophobia and blurred vision. Many dermatological side effects are present like flushing, urticaria, sweating and many others.

Patients and Methods: Fifty six males were included in this study, with ages between 37 – 60 years and a mean age of 50.1 ± 7.1 years. The study was conducted from November 2004 till May 2009 in the Department of Dermatology of Al-Kadhymia Teaching Hospital in Baghdad; all patients experienced dermatological side effects every time they use the drug. Full history and full examination including dermatological examination were done for all patients.

Results: The commonest dermatological side effect was flushing of the face which was seen in 44 (78.6%) patients followed by hyperhidrosis which was seen in 14 (25%) patients then urticaria which was seen in 12 (21.4%) patients. It is seemed that side effects were more with 100mg dose than with 50mg dose (78 side effect against 22 one) and this result was statistically significant.

Conclusion: Dermatological side effects of sildenafil are fairly common and dermatologist must be aware of these side effects especially when he searches for the cause of angioedema, urticaria, pruritis as well as erythroderma.

Keywords: Sildenafil, Dermatological, Side effects.

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Introduction:

Sildenafil citrate, sold as Viagra and under various other trade names, is a drug that is used to treat erectile dysfunctions in males. It was developed and being marketed by the pharmaceutical company Pfizer. Since 1998, sildenafil has been the prime treatment for erectile dysfunction and it is frequently called the 'blue pill'.(1) The mechanism of action of sildenafil citrate involves the release of nitric oxide (NO) in the corpus cavernosum of the penis, this NO binds to the receptors of the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (CGMP), leading to smooth muscle relaxation (vasodilatation) of the intimal cushions of the helicine arteries, resulting in an increased inflow of blood into the spongy tissue of the penis causing an erection. (2) Sildenafil is a potent and selective inhibitor of CGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of CGMP in the corpus cavernosum.(3) The molecular structure of sildenafil is similar to that of CGMP and acts as a competitive binding agent of PDE5 in the corpus cavernosum, resulting in more CGMP and better erection. (2, 3) Uses of sildenafil citrate include Sexual dysfunction; the primary indication of sildenafil is treatment of erectile dysfunctions (inability to sustain a satisfactory erection to complete intercourse). It is used now as a standard treatment for erectile

dysfunction in all settings, including diabetes.(4) People on antidepressants may experience sexual dysfunction, either as a result of their illness or as a result of their treatment and a study showed that sildenafil improved sexual function in men in this situation. (5) The same researchers found that sildenafil was able to improve the sexual function in female patients on antidepressants as well. (6, 7) Other common indications include pulmonary hypertension and altitude sickness. (8, 9) The dose of sildenafil for erectile dysfunction is 25 mg to 100 mg taken not more than once per day between 30 minutes and 4 hours prior to sexual intercourse.(10) Contraindications include those who use organic nitrites and nitrates, such as glyceryl trinitrate (nitroglycerin), sodium nitroprusside, amyl nitrite ("poppers"),(11) also men for whom sexual intercourse is inadvisable due to cardiovascular risk factors, Severe hepatic impairment (decreased liver function), Severe impairment in renal function, Hypotension (low blood pressure), Recent stroke or heart attack, Hereditary degenerative retinal disorders (including genetic disorders of retinal phosphodiesterases). The most common adverse effects of sildenafil include headache, flushing, dyspepsia, nasal congestion and impaired vision (including photophobia and blurred vision).(12) Some sildenafil users have complained of seeing everything tinted blue (cyanopsia).(13) Some complained of blurriness and loss of peripheral vision and it may lead to vision impairment in rare cases,(14)

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and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy.(15, 16) Rare but serious adverse effects found through post marketing surveillance include priapism, severe hypotension, myocardial infarction, ventricular arrhythmias, stroke, increased intraocular pressure and sudden hearing loss. (12) As a result, the FDA announced that the labeling for all PDE5 inhibitors, including sildenafil, required a more prominent warning of the potential risk of sudden hearing loss. (17) Dermatological side effects include rash which was reported in at least 2% of patients and other side effects include urticaria, herpes simplex, pruritis, sweating, skin ulcer, contact dermatitis and exfoliative dermatitis. (18) Interactions Care should be exercised by patients who are also taking protease inhibitors which inhibit the metabolism of sildenafil, effectively multiplying the plasma levels of sildenafil, increasing the incidence and severity of side-effects. It is recommended that patients using protease inhibitors limit their use of sildenafil to no more than one 25 mg dose every 48 hours. Concomitant use of sildenafil and an alpha blocker may lead to low blood pressure, but this effect does not occur if they are taken at least four hours apart. (19) This study was designed to determine the dermatological side effects of Sildenafil among a group of Iraqi males.

Patients and Methods:

Fifty six Iraqi males were included in this study, with ages between 37 & 60 years and a mean age of 50.1 ± 7.1 years. The study was conducted between November 2004 & May 2009 in the Department of Dermatology of Al-Kadhymia teaching hospital in Baghdad. Every one of the patients experienced dermatological side effect every time he took the drug and this side effect was documented after excluding other causes of every one of the side effects. Full history including age, occupation, the dose (and the manufacture)of the drug when taken, the duration between the ingestion of the drug and the appearance of the dermatological side effect, history of other drugs in take, history of systemic and other illnesses, also full examination including dermatological examination were done for all patients by the same dermatologist. The drug was prescribed by different doctors from inside and outside the hospital including the researcher himself (as the drug is usually prescribed by many different medical branches) and the drug was obtained from different pharmacies including the hospital pharmacy. All patients attended the dermatology department due to the appearance of the same rash every time they took the drug and no one of them discovered accidentally. Those 56 males took either 50 or 100 mg tablets and some of them took 50 mg and if he had no benefit then took a 100 mg tablet. The drug manufactures were multiple as some of those men took the standard Pfizer tablets others took tablets made by other manufactures as Indian Ranbaxy co. and even

some Arabic manufactures. Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as percentages. Descriptive characteristics of patients were compared using χ^2 tests with Yate's correction for continuity. All database management and statistical analyses were performed with SPSS software (10th version). The level of significance was set at (P-value < 0.05).All probability values were two-sided.(20)

Results:

Fifty six Iraqi males were included in this study, with ages between 37 & 60 years and a mean age of 50.1 ± 7.1 years. Thirty eight (67.9%) of these patients were diabetics and the other 18 (32.1%) took the drug for different other causes including psychological problems. All patients had the same side effects every time they took the drug, and the minimal number of attacks at time of examination was three and some of those patients experienced the side effects many times monthly (at each time they took the drug), the attacks appeared between few hours and 10 days from the time of taking the drug depending on the type of the dermatological side effect, the earliest side effects to be appear were flushing and urticaria which appeared within few hours after taking the drug and the latest was maculo-papular rash which appeared after up to 10 days in many occasions. Some patients had more than one side effect and it is seemed that side effects were more with 100mg dose than with 50mg dose (78 side effects appeared with 100mg dose against 22 side effects appeared with 50 mg) and this result was statistically significant (P value ≤ 0.0001 & Chi square = 60.5). The commonest side effect was flushing of the face which was seen in 44 (78.6%) patients followed by hyperhydrosis which was seen in 14 (25%) patients then urticaria which was seen in 12 (21.4%) patients (Table 1). Some of the side effects were sever and considered as emergencies like angioedema and erythroderma. The patients used sildenafil tablets from different manufactures and experienced side effects from all of these including the original Pfizer manufacture and so the side effects are due to the drug itself not to the manufacture.

Table 1: Dermatological side effects of sildenafil

Side effect	Number (No.=56)	%
Flushing	44	78.6
Hyperhydrosis	14	25
Urticaria	12	21.4
Pruritis	10	17.9
Maculopapular rash	8	14.3
Dermatitis	5	8.9
Angioedema	5	8.9
Erythroderma	1	1.8
Skin ulcer	1	1.8

Discussion:

Dermatological side effects were not mentioned in details previously in any study but seem to be fairly common among Iraqi males, side effects other than the dermatological ones were fully determined but unfortunately they are still few in number and so our study considered as the first one to be done in Iraq and may be the first one in the other different parts of the world regarding this aspect, however, it was previously mentioned that skin rash may appeared in 2% of patients who took sildenafil (18) and this point needs volunteers studies in Iraq similar to what occurred abroad. Dundar et al showed that flushing of the face was shown in 75% of the men that took sildenafil and this result is nearly similar to what's appear in our study which showed that flushing appeared in 78.6% of Iraqi males and flushing was the only dermatological manifestation that commonly mentioned in the literature⁽²¹⁾, however, it was mentioned in other studies that flushing appeared in 10% of the patients only and this difference from our study may be due to the difference in patient's number, the difference in the used dose of the drug or due to the little concentration on the dermatological side effects in the literature. (18)

This study showed the appearance of dermatological side effects that did not mentioned in the literature as diffuse dermatitis and angioedema that may be severely affects the patients also other cutaneous side effect may be life threatening like erythroderma and even urticaria.

This study also showed that the higher the dose of the drug, the more the side effects will appear (78 side effects appeared with 100 mg dose and only 22 with 50 mg dose) and the result was statistically significant, this point was also not mentioned in the literature. It shown in this study that the drug itself and not the manufacture seems to be the cause of the side effects as drug from all known manufactures caused these side effects.

Conclusions:

Dermatological side effects of sildenafil are fairly common and a dermatologist must be aware of them especially when he searches for the cause of angioedema, urticaria, pruritis as well as erythroderma and some of these side effects are serious and life threatening.

The higher the dose of the drug the higher the incidence of the side effects will be seen. The drug itself and not the manufacture seems to be the cause of the side effects as drug from all known manufactures caused these side effects.

References:

1. Aubetawe Bro Morgannwg University NHS Trust (4-7-2008). "Research at ABM". <http://www.abm.university-trust.wales.nhs.uk/>

[page.cfm?orgId=743&pid=29457](http://www.cfm?orgId=743&pid=29457). Retrieved 6-8-2008.

2. Bolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, Osterloh IH, Gingell C. "Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction". *Int J Impot Res* 1996; 8 (2): 47-52.

3. Terrett NK et al. Sildenafil (Viagra), a potent and selective inhibitor of Type 5 CGMP phosphodiesterase with utility for the treatment of male erectile dysfunction". *Bioorg Med Chem Lett* 1996; 6: 1819-1824.

4. Vardi M, Nini A. "Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus". *Cochrane Database Syst Rev* 2007; (1): CD002187.

5. Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil: A randomized controlled trial. *JAMA* 2003 Jan; 289 (1): 56-64.

6. Nurnberg HG, Hensley PL, Lauriello J, Parker LM, Keith SJ (). Sildenafil for women patients with antidepressant-induced sexual dysfunction. *Psychiatr Serv* 1999 Aug; 50 (8): 1076-8.

7. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction. *JAMA* 2008; 300 (4): 395-404.

8. Richalet JP, Grataudour P, Robach P et al. Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension". *Am. J. Respir. Crit. Care Med.* 2005; 171 (3): 275-81.

9. Fagenholz PJ, Gutman JA, Murray AF, Harris NS. Treatment of high altitude pulmonary edema at 4240 m in Nepal. *High Alt. Med. Biol.* 2007; 8 (2): 139-46.

10. Oh SS, Zou P, Low MY, Koh HL. Detection of sildenafil analogues in herbal products for erectile dysfunction. *Journal of Toxicology and Environmental Health Part A.* 2006 Nov; 69(21): 1951-8.

11. Venhuis BJ, Blok-Tip L, de Kaste D. Designer drugs in herbal aphrodisiacs. *Forensic Science International.* 20 May 2008; 177(2-3): e25-7.

12. "Pill Identifier". *Drugs.com.* http://www.drugs.com/pill_identification.html. Retrieved 10-2-2009.

13. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, Zusman RM. Use of sildenafil (Viagra) in patients with cardiovascular disease. *Journal of the American College of Cardiology* 1999; 33 (1): 273-82.

14. "VIAGRA Prescribing Information" (PDF). Pfizer. October 2007. http://www.pfizer.com/files/products/uspi_viagra.pdf. Retrieved 21-8-2008.

15. Pomeranz; Pomeranz HD and Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (viagra): a report of seven new cases. *J Neuroophthalmol* 2005; 25 (1): 9-13.

16. Egan; Egan R and Pomeranz H. Sildenafil (Viagra) associated anterior ischemic optic neuropathy. *Arch Ophthalmol* 2000; 118 (2): 291–2.
17. Boshier A, Pambakian N, Shakir SA. A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; 40 (9): 422–3.
18. <http://www.drugs.com/sfx/viagra-side-effects.html>
19. Akash R, Hrishikesh D, Amith P, Sabah S. Case report: association of combined nonarteritic anterior ischemic optic neuropathy (NAION) and obstruction of cilioretinal artery with overdose of Viagra. *J Ocul Pharmacol Ther* (2005); 24 (4): 315–7.
20. Duncan RC, Knapp RG, Miller MC (Eds). *Introductory biostatistics for the health sciences*, 1977, Wiley & Sons Inc.; PP: 79-85.
21. Dündar M, Koçak I, Dündar SO, Erol H. Evaluation of side effects of sildenafil in group of young healthy volunteers. *J Int Urol and Nephrol* 2001 Dec; 32(4):705-708.