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The Effect of Sex Enhancing Drugs on Different Organs in Male Swiss Albino Mice: Values of Safety

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Abstract

Erectile dysfunction (ED) and tde-drug (Sildenafil Citrate) are commonly known, in public as Viagra or Revatio causes serious histopathological side effects at overdosed or misused. This study concluded that there is was an increasing risk for male reproductive function, which can be disrupted by exposure to sex enhancing drug that can exogenously mimic and increase or disturb the testis, at overdoses of erectile drugs. One possible consequence of exposure for these xenobiotics is disruption of spematogenesis and the Sertoli cells, along with sever effects on different other organs.

Keywords: Tde-drugs; Sildenafil; Spermatogenesis; Hepatic cells; Nephrocytes; Eye retina; Smooth muscle fibers; Pituitary gland

Abbreviations: MU: Mucosa; BC: Bowman's Capsule; N: Nucleus; BV: Blood Vessel; OC: Oxyntic Cell; CONL: Choroid Outer Nuclear Layer; CT: Connective Tissue; OPL: Outer Plexiform Layer; CU: Collecting Tubule; PC: Peptic Cell; CV: Central Vein; PE: Peritonial Epithelium; DC: Defected Cell; PP: Pigmented Epithelium; GC: Gland Cell; RAC: Rods and Cones; TGC: Tumour of Gland Cell; SE: Spermiogenesis; GL: Ganglion Cell SG: Spermatogenesis; GM: Glomerulus; SM: Submucosa; HG: Hepatic Granuloma; SR: Sarcomeres; HL: Hepatic Lobule; UT: Uriniferous Tubule; IC: Interstitial cell; INL: Inner Nuclear Layer

Introduction

Tadalafil, Levitra (Vardenafil), Sex enhancing drugs such as Alprostadil (Caverject, Muse, Edex)Viagra (Sildenafil), Cialis or yohimine (Yocon, Yodoxin) have become some of the most "prescribed" and abused pharmaceuticals [1]. Indeed, it is reasonable to believe that recreational use of erectile drugs may exceed medical use. The erectile drugs are rapidly absorbed into the blood with maximum observed plasma concentrations reached within 30 to 120 minutes. The world's largest pharmaceutical company, Pfizer concluded that Viagra, with a trade name of tde, (also known by tde chend), a tiny sex lettered word has created a revolution in our world. The term Viagra never existed in any language on this earth. But then how did Brand Viagra evolve? Pfizer [2] chose this name because it was not used in English or in any other foreign language and hence it did not convey a particular meaning. Researchers wanted a name which was safe to avoid causing any humiliation or misunderstanding to anybody. It was by a chance that they discovered its ability as a therapeutic medicine of erectile dysfunction, having developed it principally to treat angina. They decided to target the action of the new medicine onto the enzyme PDE (Phosphodiesterase).

It is very important for impotent men to go through the entire list of side effects before seeking impotence treatment. Problems with impotence medications like Viagra, Levitra and Cialis can include minor side effects like headaches (opens up arteries in the brain's lining and causes excess pressure) and major side effects like heart attacks. Another major problem comes for people who are taking drugs like nitroglycerin for angina. Nitroglycerin works by increasing nitric oxide, and it helps with angina by opening up the arteries that supply the heart with oxygen. Taking nitroglycerin and impotence medication together, the increased nitric oxide plus the blocking of PDE5 can aggravate problems. The combination of impotence medications with any types of nitrate medications could result in a severe drop in blood pressure and lead to extreme dizziness, fainting or even a heart attack. All these three medications may in rarest event cause a condition called Priapism. All these medicines may cause dizziness and may affect the ability to drive or operate machinery safely.

There are hardly any drugs which work perfectly, and anti-impotence medications are no exception [3,4]. But the basic question remains-why side effects occur?. Every medicine which is intended to work in a particular part of the body to make positive changes may affect other parts of the body unintentionally [5,6]. This happens because when a medicine is taken, it flows throughout the entire body and may affect a part of body where it should not. For example, aspirin is a drug that relieves pain, but this same drug can also erode the stomach lining and thin the blood. Recently, it was mentioned that Viagra may cause a sudden hearing loss as a potential side effect [7]. The FDA (Washington CNN) said manufacturers of enhancing sex drugs such as Viagra, Levitra or Cialis must change the labels 'to display more prominently the potential risk of sudden hearing loss' according to the agency's web site (written by Falco [8] and Emotional Health Agency, and Sophia Keenan, 2007 enews). A new study in Britain concluded that Viagra pills killed 109 British citizens and wounded others. The study issued by the Regulatory Agency and health care products and medicines. The results are published in the "Sun Newspaper". 44 British victims of Viagra have died of a heart attack and 29 others died directly. The Emotional Health Agency said seven British victims claimed that they were blinded by taking Viagra tablets, and two complained of injuries in hearing. PDE6 is used in the cone cells in the retina, so Viagra affects colour vision. Many people who take Viagra notice a change in the way they perceive green and blue colours, or they see their surroundings with a bluish tinge for several hours.

In three key articles in the Journal of the American Medical

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Association over fifty years ago [9-11], it was recorded that testosterone treatment on its own can restore potency in the majority of andropausal men. Testosterone can increase the amount of red blood cells and the pigment haemoglobin, however it is common to find that men with low levels of testosterone have low levels red cells and haemoglobin before treatment is started; in fact some are clearly anaemic. In such cases Testosterone Replacement Therapy (TPT) merely normalizes their blood picture. Recently there has been great interest about the benefits of testosterone on the cardiovascular system. It has been reported that men with abnormally low levels of testosterone may be at greater risk of cardiovascular disease. Such men with heart disease when given TRT to normalize their testosterone levels gain cardiovascular benefit and one study has shown that blood flow in the coronary arteries is improved. Other studies have shown that men with low levels of testosterone have an adverse cholesterol, blood sugar and blood clotting factor profile and therefore may be at greater risk of cardiac problems. Testosterone replacement therapy reverses these adverse profiles when they are present. It has also been shown that men with abnormally low levels of testosterone are at greater risk of osteoporosis and fracture of the hip and that replacement may benefit the bones.

The present study was undertaken to study the histopathological effects of chronic use of Sildenafil citrate on the testis, liver, kidney, pituitary gland, the eye retina, smooth muscle fibers and the heart muscle. To the best of our knowledge, there are inadequate reports on the histopathological changes in the seminiferous tubules, hepatocytes, nephrocytes, cardiac muscles, smooth muscle fibers and eye vasculature following chronic Sildenafil use.

Materials and Methods

Study design

The study was performed in the department of Zoology at the University of Alexandria, Egypt.

Twenty-five adult male mice (age: 12-14 weeks), weighing 30-38 g, were used in the experiments. The animals were housed under standard laboratory conditions maintained at 22-27°C with a 12-hour light-dark cycle and fed a standard laboratory mice diet. They were divided into five groups, each comprising 5 individuals. Each group was housed in separate polypropylene cages (450 x 270 x 150 mm) provided with sawdust. This sawdust substratum is changed every other day. All groups were treated as follows:

Group I: Untreated controls;

Group II: Oral administration 25 mg Sildenafil /kg! on the alternate day;

Group III: Oral administration 50 mg/kg Sildenafil I on the alternate day;

Group IV: Oral administration 75 mg/kg Sildenafil / on the alternate day;

Group V: Oral administration 100 mg/kg Sildenafil / on the alternate day;

The dose of Sildenafil citrate was orally administrated on alternate days (three days in a week) for 4 weeks. In each cage a number of female mice were placed. The animals were sacrificed after 4 weeks of treatment. The testis, liver, pituitary gland, kidney, parts of stomach smooth muscle fibers , the eye and the heart muscle were dissected out and fixed in 10% neutral formalin solution or Bouin fixative following washing in distilled water for 24 hr, treatment in 95% ethanol for 24 hr and then in chloroform for 5 hr. The tissues were embedded in paraffin wax and 5 tm serial sections were taken. Random sections were selected and stained with haematoxylin and eosin (Sigma, USA) according to the recommended routine protocol. The slides were mounted using Canada balsam and covered with glass covers prior to viewing under the Olympus BX-40 light microscope. Photomicrographs were taken with a digital microscope camera and commented.

Observations

Testis and vas deferens histology and histopathology

Proliferation activity of the tubules diminishes and disfiguring of cells increases with the increased quantity of the dose. However, the number of disfigured sperm in 30 tubules in 3 mice for each group was calculated and the mean was found out. These calculations were then analyzed using ANOVA test.

Observations of defected sperm have been carried out using oil immersion magnification (Table 1). The vas deferens showed different degrees of malignant malformations in the treated groups.

The liver histology and histopathology

Eventually, damage of hepatic cells becomes so extensive that the normal structure of the liver was distorted, scarring of the liver, fibrosis and nodules formation (Figure 1 and 2). One of the most important factors indicative of liver damage is bilirubin, a red-yellow pigment that is normally metabolized in the liver and then excreted in the bile. In treated mice in groups 4 and 5, the liver cannot process bilirubin. The blood of treated mice in groups 4 and 5 did not clot compared with the control and groups 1 and 2. It was also observed that the spleen dilated. Constriction of the small blood vessels and bile ducts in the liver has observed. Constriction of blood vessels in other organs, including the kidney has observed. Abnormally twisted and swollen

Dose of Sildenafil in mg/kg	Balloon shaped head sperm	Hookless sperm	Folded sperm	Double head/ tailed sperm	Total
Control	0.07 ± 0.014	0.05 ± 0.021	0.04 ± 0.014	0.02 ± 0.01	0.22 ± 0.05
25 mg	0.92 ± 0.014***	0.55 ± 0.015***	0.37 ± 0.03***	0.23 ± 0.0.2***	1.07 ± 0.04***
50 mg	1.19 ± 0.01*	0.70 ± 0.03**	0.37 ± 0.04***	0.27 ± 0.025**	2.24 ± 0.06***
75 mg	2.18 ± 0.01***	0.90 ± 0.04***	0.28 ± 0.06***	0.35 ± 0.047***	3.34 ± 0.014***
100 mg	2.18 ± 0.01***	1.97 ± 0.014***	0.37 ± 0.014***	0.53 ± 0.074***	5.07 ± 0.014***

Table 1: Observations of defected sperm using oil immersion.

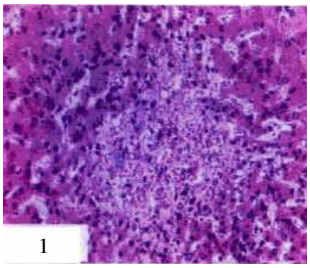

Figure 1: Photomicrograph of a transverse section of a part of the liver of a mouse of group 5.

Note: Abnormal appearance of hepatocytes is indicated by an arrow. X 250

veins were observed in the stomach and lower part of the oesophagus. Dark- coloured urine were observed in living mice of groups 4 and 5.

Cardiac and smooth muscles histology and histopathology

The cardiac muscle is a type of involuntary striated muscle found in the walls of the heart, specifically the myocardium. Cardiac muscle cells are known as cardiac myocytes (Figure 3). The cardiac muscle exhibits cross striations formed by alternating segments of thick and thin protein filaments, which are anchored by segments called T-lines. Like skeletal muscle, the primary structural proteins of cardiac muscle are actin and myosin. It was observed that the cardiac muscle fibers were thick and viability active in all the treated mice (Figure 4). This study found out that Sildenafil causes vasidilation. This observation can be interpreted that the cadiac muscle fibers are supplied with more oxygenated blood than that of the control. It was observed that the treated mice - specially groups 4 and 5 suffer from fatigue and weakness. The normal picture of the smooth muscle fibers is seen in (Figure 5). Congestion of these smooth muscle fibers takes place with the high dose of Sildenafil in group 5 (Figure 6).

The pituitary gland, or hypophysis histology and histopathology

The pituitary gland is a pea shaped and located at the base of the brain. It is a protrusion off the bottom of the hypothalamus at the base of the brain, and rests in a small, bony cavity covered with a dural fold. It is composed of two lobes: the adenohypophysis and neurohypophysis. The adenohypophysis, also referred to as the anterior pituitary is divided into anatomical regions known as the pars tuberalis, pars intermedia, and pars distalis. The neurohypophysis, is also referred to as the posterior pituitary. The pituitary is linked to the hypothalamus by the pituitary stalk. The pituitary gland is known as the master endocrine gland. Figures 7 and 8 show the histological overview of the anterior and posterior lobes respectively. Pituitary tumours were observed in the different parts of the gland in groups 4 and 5 (Figures 7-9). These tumours were variable with regard to staining. Some tumours took up the stains hematoxylin and eosin and others were negatively stained. As large pituitary spots of tumour grew upwards, the tumour can elevate and compress the optic chiasma. A progressive loss of the outer peripheral vision occurred or loss of visual acuity (blurry vision). In other cases, the tumor can outgrow its blood supply, leading to swelling of the dead tissue.

The kidney histology and histopathology

The kidney or metanephros is bean shaped, with the indent being called the hilum. The hilum is the region of the kidney where the renal artery and nerves enter and the ureter and renal vein exit. The

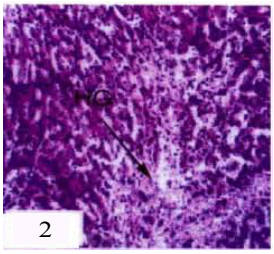

Figure 2: Photomicrograph of a transverse section of a part of the liver of a mouse of group 5.

Note: Distortion and necrosis of hepatocytes. X 250

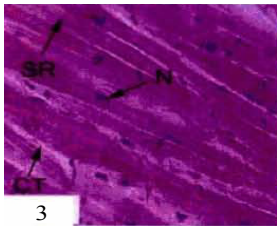

Figure 3: Photomicrograph of a transverse section of a part of the cardiac muscle of a mouse of the control group. X 250.

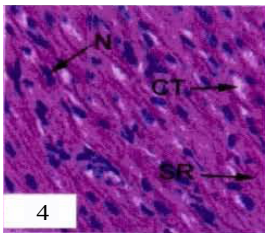

Figure 4: Photornicrograph of a transverse section of a part of the cardiac muscle of a mouse of group 5.

Note: Thickening of muscle fibers and aggregation of blood vessels. X 250

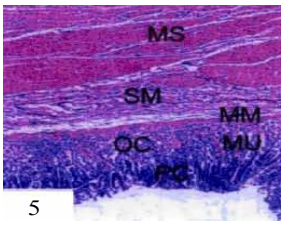

Figure 5: Photomicrograph of a transverse section of a part of the stomach of a mouse of the control group showing smooth muscle fibers . X 250.

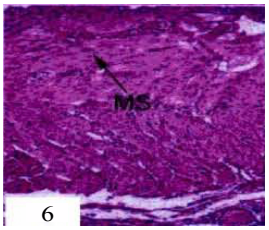

Figure 6: Photomicrograph of a transverse section of a part of the stomach of a mouse of group 5.

Note: Abnormal appearance of smooth muscle fibers . X 250

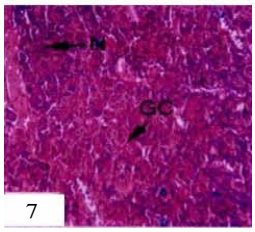

Figure 7: Photomicrograph of a transverse section of a part of the anterior pituitary of a mouse of the control group. X 250.

periphery of the kidney is surrounded by a connective tissue capsule. It is composed of an external cortical and an internal medullary substance. The cortex or cortical substance is soft and granulated. It is the region where the renal corpuscles (glomeruli plus Bowman's capsules) and most of the nephric tubule is located. The medulla or medullary substance is a pyramid-shaped mass of tubules. It does not have any renal corpuscles, but is composed of nephric tubules, collecting ducts and numerous capillaries. The glomerulus, lying in the cortex, consists of a tuft of capillaries. This tuft is surrounded by the glomerular capsule, which is a cuplike dilation of the end of the renal tubule. This combination is called Malpighian corpuscle (Figures 10-12). The renal tubule begins with the Malpighian corpuscle, takes multiple turns, forming the proximal convoluted tubule, extends towards the hilum in the medullary portion to form the descending loop of Henle, doubles back on itself as the ascending loop of Henle, and goes through several more turns as the distal convoluted tubule. The structural and functional unit of the kidney is called a nephron. Several of the nephrons terminate in one collecting tubule. Several collecting tubules unite to form a renal pyramid, which drains the urine into a branch (calyx) of the renal pelvis. The suprarenal gland lies on top of each kidney, medially, below diaphragm. The cortex is divided into three zones (starting from the capsule): the zona g1omewlbsa the zona fasciculata, and the zona reticular is. It is pyramid shaped on the right side and semilunar shaped on the left side and has a fibrous capsule. Several irritation spots in the different portion of the kidney were clearly observed and increase in amount with the increase of dose concentration (Figure 12).

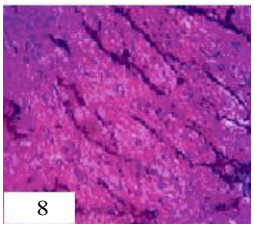

Figure 8: Photomicrograph of a transverse section of a part of the posterior pituitary of a mouse of the control group. X250.

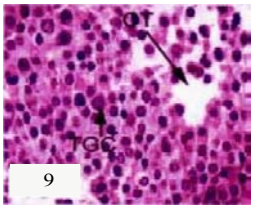

Figure 9: Photomicrograph of a transverse section of a part of the anterior pituitary of a mouse of group 5.

Note: Pituitary tumours were observed in the different parts of the gland X 250

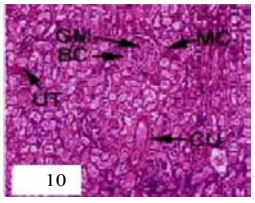

Figure 10: Photomicrograph of a transverse section of a part of the kidney of mouse of the control group. X 250.

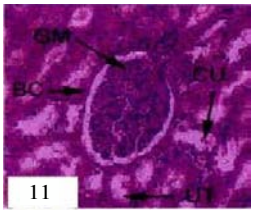

Figure 11: Photomicrograph of a transverse section of a part of the kidney of a mouse of the control group. showing Malpighian corpuscle. X 400.

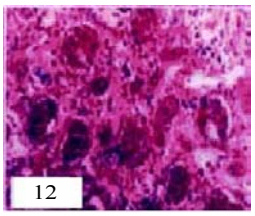

Figure 12: Photomicrograph of a transverse section of a part of the kidney of a mouse of group 5.

Note: Abnormal appearance of Malpighian corpuscle. X 250

Eye histology and histopathology

The results of the present study demonstrated that Sildenafil citrate can cause dilatation of the choriodal capillaries in mice of groups 4 and 5, although the retina was not seen to be affected histopathologically. Thus, the Sildenafil has its major effect on the choroidal circulation in male mice, suggesting the potential involvement of Sildenafil in circulatory defects of the choroids. Choroidal dilatation was found and it may cause choroidal dysfunction. Sildenafil may alter the vascular flow or choroidal volume because of its systemic effects on vascular smooth muscle. The results show that there is a dilatation of the choroidal vessels after Sildenafil treatment and this may lead to congestive effects within the eye (Figure13-16). An increase in choroidal vessels volume affects retina and retinal pigment epithelial functions and, if severe, could predispose to retinal detachment. The results of the present study demonstrate that chronic use of Sildenafil citrate causes complications in the choroid of mice. These visual effects need to be investigated in humans.

Discussion

Pfizer [2] stated that the side effects of Sildenafil are mostly mild to moderate. They usually go away after a few hours. Some of these are more likely to happen with higher doses. headache, feeling flushed, upset stomach, trouble telling blue and green apart or seeing a blue tinge on things, eyes being more sensitive to light , blurred vision and having an erection that lasts more than 4 hours. If the erection is not treated right away, long-term loss of potency could occur, sudden decrease or loss of sight in one or both eyes. Hemophilia Ontario Spring [12] stated that everyone has no doubt heard about the new "wonder drug" for impotency. Taken an hour before anticipated sexual activity it has a 43 to 70% success rate. Taken with organic nitrates, Viagra can seriously endanger or take a life. Nitrates taken with Viagrcan significantly lower the blood pressure. Pfizer [2], producer of Viagris currently investigating at least six deaths that occurred while these men were using their product.

To our knowledge, there have been no reports of the histopathological side effects of Sildenafil into the testis, liver, kidney, smooth muscle fibers and Central Nervous System (CNS). Therefore,

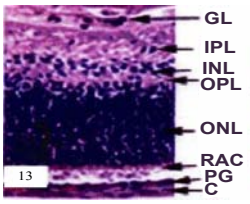

Figure 13: Photomicrograph of a transverse section of a part of the retina of a mouse of the control group. X 250.

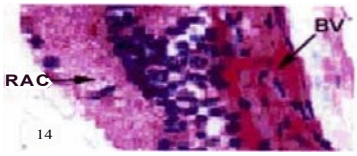

Figure 14: Photomicrograph of a transverse section of a part of the retina of a mouse of group 5.

Note: Distortion of cones and rods and aggregation of blood vessels. X 250

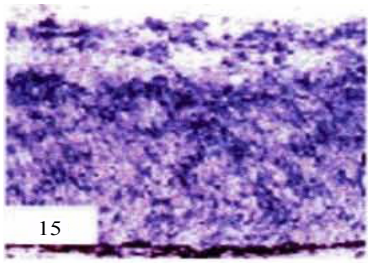

Figure 15: Photomicrograph of a transverse section of a part of the retina of a mouse of group 5.

Note: Distortion of cones and rods and aggregation of blood vessels. X 400

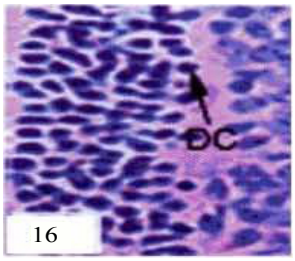

Figure 16: Photomicrograph of a transverse section of a part of the retina of a mouse of group 5.

this study aims to evaluate the effects of Sildenafil citrate. A number of doctors warned of the spread of fake medicines for the treatment of Erectile Dysfunction (ED), to be replicated and smuggled to Egypt, pointing out the danger to the health of people and their diseases. These doctors added that purchasing of medicines through pharmacies are not so great deceit of counterfeit products which are difficult to detect. This came in conjunction with the campaign launched by the Arab Society for Sexual Health in collaboration with Bayer Schering's drugs campaign, under the rubric of "restoring the health of men", to encourage men to consult a doctor and find solutions to them when faced with a similar problem. This collaboration showed a recent study conducted by Bayer - Schering drugs to the habits and sexual behaviors among both men and women, that 50% of Egyptian men over the age of 40 years are infected with sexual vulnerability, and 18% over the age of twenty are infected as well. As the study was 62% of Saudis to the problems of nationality and 60% of Turks and 61% of the UAE. The study estimated the size of men with impaired sexual level of the world's 152 million men. It is expected that the prevalence of ED in the world to 322 million men by 2025.

The research confirmed the existence of a relationship between depression and sexual impotence, for the patient, may lead to a loss of self-esteem, and distorted the idea of self-taken, and the severance of relations between persons. The study confirmed that despite the many ways available for the treatment of ED that only a small percentage of men who suffer from this situation are the ones who have access to treatment, which indicates a need for greater awareness of the means of treatment in this area and open up more channels for dialogue between the patients and doctors.

This study found out that the increased dose of Sildenafil citrate influences the process of spermatogenesis and spermeogenesis. Moreover, increasind dose caused abnormalities in the general morphology of the sperm including double head sperm, coiled tail, etc.

Gümüş et al. [13] also found out abnormalities in the testis of rat due to increased dose of Sildenâfil. They studied the histopathological effects of Sildenafil citrate on rat corpus cavemosum through light and electron microscopies. They concluded that the corpus cavernosum was elongated and the number of blood vessels was increased. The amount of connective tissue in the penis was increased and dense collagen and smooth muscle fibers were observed in treated rats. Electron microscopical analysis showed that stromal structures of the corpus cavernosum were increased in treated rats. Fibroblasts showed signs of activation and the number of other stromal cells was increased. Immature newly synthesized collagen fibers penetrated the endothelial basement membranes. In addition, endothelial cells in treated rats also showed signs of activation such as cytoplasmic granules, whereas the surface area of blood vessels was increased and the basement membranes were thickened. The decrease in the cauda epididymidal sperm counts is clear indications that Sildenafil can affect one or more aspects of spermatogenesis as well as spermiogenesis. Though a direct effect of Sildenafil on the cellular mechanisms of spermatogenesis can not be exonerated; it is likely that the impairment of the hormonal mechanisms concerned with the regulation of spermatogenesis may as well be the underlying cause. The sperm acquire the capacity to nibtility during their epididymal transit, and in the normal course all cauda epididymidal sperm are motile. The contributory factors to the initiation of spermatozoal motility, mainly in the form of proteins and small molecular weight substances, emanate from the epididymal epithelial cells.

The impairment of motility of the cauda epididymidal sperm of Sildenafil-treated mice, thus, is a reflection of the effect of Sildenafil on the physiology of epididymis. The various other sperm abnormalities, including retention of CD, are also indications that epididymis is also a target to Sildenafil toxicity. Again, these effects may be attributed to the impairment of hormonal mechanisms. However, some of the abnormalities like coiled tail, lasso-like sperm, fusion of tails, etc., suggest a direct toxic effect of Sildenafil at the level of epididymis.

The altered sperm morphology, in the coiling of tail around an apparently malformed head, could be attributed to both testicular and epididymal effects of Sildenafil. Coiling of the sperm tail is usually the product of abnormal axoneme and / or the outer dense fibrils, and may also suggest alterations in the sperm surface proteins. The outcome of the study affirms the male reproductive toxic effects of Sildenafil when

applied as a therapeutic against ED. Since male reproductive toxicology and male contraception are two sides of the same coin, the negative consequences of Sildenafil on the sperm may be taken to advantage for further study.

In this study it was found that high dose of Sildenafil citrate in groups 3 and 4 showed damage of hepatic cells. These cells become so extensive that the normal structure of the liver is distorted. Scarring of the liver, hepatic fibrosis and formation of nodules increase with the increased quantity of dose. The abdomen was swollen. One of the most important factors indicative of liver damage is bilirubin, a red-yellow pigment that is normally metabolized in the liver and then excreted in the bile. In treated mice in groups 4 and 5, the liver cannot process bilirubin. It is well observed as the treated animals with swollen abdomen scarified and blood was sucked. The blood vessels of the cardiac muscle were dilated. This observation can be interpreted that the cadiac muscle fibers are supplied with more oxygenated blood than that of the control. It was observed that the treated mice specially groups 4 and 5 suffer from fatigue and weakness. Several irritation spots in the different portion of the kidney were clearly observed and increase in amount with the increase of dose concentration. An increase in choroidal vessels volume affects retina and retinal pigment epithelial functions and, if severe, could predispose to retinal detachment. The results of the present study demonstrate that chronic use of Sildenafil citrate causes complications in the choroid of mice. These results have been previously observed in rats [14,15]. The European Public Assessment Report (EPAR) [16] and Muñiz and Holstege [17] stated that Patients with liver problems or severe kidney problems should start treatment with the 25-mg dose. Viagra should not be taken with nitrates (medicines used to treat angina). Because Viagra has not been studied in patients with severe liver disease, hypotension (low blood pressure), recent stroke or myocardial infarction (heart attack), or a hereditary eye disease, such as retinitis pigmentosa, these patients should not use it. Sildenafil citrate is rapidly absorbed, reaching maximum plasma concentrations within one hour after oral usage, and its mean terminal half- life is 3 to 5 hours [18]. Arancio et al. [19] and Fazan et al. [20] showed minimal reductions in systemic and pulmonary artery pressure without any serious cardiovascular effects after Sildenafil usage. Baratti and Boccia [21] reported that Sildenafll had no significant effect on aortic and superior mesenteric artery blood flow in ED patients. In a recent study performed on dogs, significant increases were observed for the Vmax and RI of the aorta as well as decreases in the right carotid and left segmental renal arteries Vmax [22]. PDE type 5 is present in vascular smooth muscle and platelets. A recent animal study showed that PDE5 is present in the brain tissue, cerebellum and hippocampus [23]. In this study, PDE inhibitors caused cerebral artery dilatation, whereas Ambriz-Tututi et al. [24] found that Sildenafil usage had no significant effects on cerebral blood flow and the diameter of cerebral and extracerebral arteries.

In this study it was observed that pituitary tumours were observed in the different parts of the gland in groups 4 and 5. These tumours were variable with regard to staining. Some tumours took up the stains hematoxylin and eosin and others were negatively stained. As large pituitary spots of tumour grew upwards, the tumour can elevate and compress the optic chiasma. A progressive loss of the outer peripheral vision, blurry vision or loss of visual acuity occurred. In other cases, the tumour can outgrow its blood supply, leading to swelling of the dead tissue. Ayta et al. [18] investigated the effects of Sildenafil citrate on the middle cerebral arteries. As in the previous studies, the researchers observed no significant effects; rather they found an insignificant decreasing trend in blood flow rates.

Argoff et al. [25] investigated the effect of Sildenafil on the pulmonary artery in primary pulmonary hypertension. They showed vasodilatation in the pulmonary artery and a decrease in pulmonary vascular resistance. They claimed that this drug may represent the first line of therapy in asthmatic patients. In another report, milrinone, a PDE3 inhibitor, improved clinical outcome in patients with subarachnoidal hemorrhage by a mechanism of reverse vasospasm [26]. In a recent animal study, administration of Sildenafil to rats with embolic stroke enhanced angiogenesis and selectively increased cerebral blood flow in the ischemic boundary, improved the neurological functional recovery compared to the control group [27]. In another study, Blokland et al. (2006) analysed the effects of Sildenafil citrate on the cerebral vasospasm. The vasodilatoiy effect of Sildenafil citrate was observed to be significant on normal cerebral vessels and following subarachnoid hemorrhage induced vasospasm. According to these results, Sildenafil citrate may useful in the treatment of cerebrovascular diseases. Harris et al. [28] concluded that Sildenafil appears to significantly increase the blood flow velocity and choroidal circulation. Most studies suggest an increase in choroidal blood flow, with a lesser effect on the retinal vasculature. Lundberg et al. [29], described the histological picture of the brain and identified the abnormalities in the stucture of pituitary gland.

In discussing the different results and observations of this work, it was found that the high dose or misuse of Sildenafil can lead to serious histopathologicalmalformations. The results and observations of this work agree with those of EPAR [16] and Fazan et al. [20], Harris et al. [28], Argoff et al. [25], Ambriz-Tututi et al. [24], Bender and Beavo [22], Gümüş et al. [13], Vatansever et al. [15], Laties and Zrenner [14], Muñiz and Holstege [17] and Arancio et al. [19]. Whereas, the results and observations of this work disagree with Levinson et al. [30], Mittleman et al. [30], Becher et al. [32], Glina et al. [33], Lewis et al. [34], and Cheitlin et al. [35].

Lubbock [36] concluded that a slice of cool, fresh watermelon has effects similar to Viagra. Watermelons contain an ingredient called citrulline that can trigger production of a compound that helps relax the body's blood vessels, similar to what happens when a man takes Viagra. Citrulline is found in all colours of watermelon and is highest in the yellow-fleshed types, said Penelope Perkins-Veazie [37]. One would need to eat about six cups of watermelon to get enough citrulline to boost the body's arginine level.

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