European Review for Medical and Pharmacological Sciences 2017; 21 (1 Suppl): 17-22

Sildenafil-associated hepatoxicity: a review of the literature

S. GRAZIANO[1], A. MONTANA[2], S. ZAAMI[3], M.C. ROTOLO[1], A. MINUTILLO[1], F.P. BUSARDÒ[3], E. MARINELLI[3]

[1]Drug Abuse and Doping Unit, Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy
[2]Laboratory of Forensic Toxicology, Department "G.F. Ingrassia", University of Catania, Catania, Italy
[3]Unit of Forensic Toxicology (UoFT), Department of Anatomical, Histological, Forensic and Orthopedic Sciences, Sapienza University of Rome, Rome, Italy

Abstract. – Sildenafil citrate (Viagra®) is a vasoactive agent available worldwide since 1998 for the treatment of male erectile dysfunction. It is a selective phosphodiesterase type 5-enzyme inhibitor able to potentiate the downstream effects of nitric oxide on smooth muscle relaxation and vasodilation through its effects on the cyclic guanosine monophosphate (c-GMP) pathway in the erectile tissue of the penis. When sildenafil is orally administered, it is rapidly absorbed with a maximum plasma concentration achieved within 1 h and has a terminal half-life of between 3 to 6 h. The drug is extensively and rapidly metabolized by the liver, primarily by the CYP3A4 enzyme. Although the drug is well tolerated, specific adverse events have been observed, like flushing, headaches, dyspepsia, and visual disturbances. Liver toxicity related to sildenafil consumption has been considered a very rare event. However, in the last decade, some cases of sildenafil-associated hepatotoxicity have been reported. Furthermore, some hepatic intoxications have been reported after the intake of "natural" or "herbal" aphrodisiac supplements sold through Internet, sex shops, social media, and by word-of-mouth found to contain sildenafil and other phosphodiesterase type 5 (PDE-5) inhibitors. Studies investigating a possible link between sildenafil use and liver damage are limited, and the underlying mechanism responsible for hepatotoxicity is still missing. Studies in animals evidence that the hematopoietic function of the liver may have severely been affected as a result of a probable toxic effect of sildenafil. Here, the studies reporting liver toxicity by sildenafil in humans and in animals are reported and discussed.

Key Words:
Sildenafil, Hepatotoxicity, Liver toxicity.

Introduction

Sildenafil citrate (Viagra®) is a vasoactive agent, which became available worldwide in 1998 for the treatment of male erectile dysfunction. The drug acts by inhibiting the phosphodiesterase type 5 (PDE5) enzymes that specifically degrade the cyclic guanosine monophosphate (cGMP), responsible for the nitric oxide induced smooth muscle relaxation and vasodilatation[1]. PDE5 is found in particularly high concentration in the *corpus cavernosum*, the erectile tissue of the penis; it is also found in the retina and vascular endothelium. Increased cGMP concentration results in vasodilation and an increased inflow of blood in penis tissue which facilitates the generation and maintenance of an erection[2,3]. Recently, it has been found that the vasodilatory effects of sildenafil also help to reduce symptoms of pulmonary arterial hypertension and it is thus also applied for this medical indication[4-6]. Sildenafil is available as film-coated tablets, orodispersible tablets, powder for oral suspension, and in solutions for injection. Its therapeutic dosage ranges from 10 to 100 mg/day and is well tolerated[7]. Common side effects include headaches, flushing, back pain, visual disturbances, nasal congestion, and tachycardia. Sildenafil is contraindicated in patients using nitrates and, to a lesser extent, alpha-blockers since it improves the hypotensive effects of these drugs, leading to serious cardiovascular effects, like myocardial ischemia and stroke[8,9]. Sildenafil results to be completely metabolized in the liver by cytochrome P450 microsomal isozymes 3A4 (major route) and 2C9 (minor route)[10,11]. It has been shown that

Corresponding Author: Francesco Paolo Busardò, MD; e-mail: fra.busardo@libero.it

some hepatic conditions (i.e. hepatic congestion, hepatic cirrhosis, elevated hepatic pressure) can affect sildenafil clearance leading to an increased drug concentration inside the body[12]. Liver toxicity related to sildenafil consumption has been considered a very rare event. However, in the last 10 years, some cases of sildenafil-associated hepatotoxicity have been reported[13-18]. It is well known that sildenafil can also be easily purchased from illegal dealers (e.g. medicines and drugs of abuse pushers) or through Internet websites without medical prescription, mandatory for this drug. Moreover, it has been identified in counterfeit medications and/or herbal supplements sold as a "natural" aid in erectile dysfunction[19] and can be used for recreational purposes in the belief that the drug increases libido and improves sexual performance also in healthy individuals. It is possible to speculate that cases of unexpected intoxications hepatic dysfunctions due to the illicit, not declared, and/or unaware sildenafil consumption have been completely missed[20,21]. In this paper, we give an overview of the reported cases of sildenafil-associated hepatotoxicity and of the studies that have investigated the effects of sildenafil use and liver damage.

Materials and Methods

The identification of scientific articles was performed in main databases as Pubmed, Biosis Medline, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE, up to November 2016 using the following keywords: "sildenafil", "Viagra", "liver", "hepatotoxicity", "liver damage", "hepatic dysfunction", "liver harm", "liver toxicity", "liver failure", "liver injury". The main keywords "sildenafil" and "Viagra" were individually searched and then again in association to each of the others. The papers not suitable for the purpose of the review were excluded. Papers were screened independently by three co-authors and included if selected at least by two of them.

Results

Sildenafil Mechanism of Action and Metabolism

As above reported, sildenafil is a selective PDE-5 inhibitor able to potentiate the downstream effects of nitric oxide on smooth muscle relaxation and vasodilation through its effects on the cyclic guanosine monophosphate (c-GMP) pathway in the corpora cavernosa, as well as the pulmonary vasculature and the retina[22,23]. When sildenafil is orally administered to healthy volunteers, it is rapidly absorbed and metabolized, with a maximum plasma concentration achieved within 1 h and a terminal half-life of between 3 to 6 h[10,11]. Its absolute oral bioavailability is about 40%. Sildenafil is cleared almost exclusively by hepatic metabolism. The primary metabolite is the N-desmethyl sildenafil, UK-103, 320, which has a similar PDE-5 specificity profile, but with about half the potency on the parent drug. Moreover, its plasma concentrations reach about 40-50% of those of the parent drug, following oral administration.

Sildenafil-Associated Hepatotoxicity Reports

International literature concerning sildenafil-associated liver toxicity in humans is scarce: up to now only five studies exist reporting cases of hepatotoxicity secondary to sildenafil consumption.

The first case of sildenafil-associated hepatic toxicity was described in 2003 in a 65-year-old man, who assumed sildenafil (50 mg Viagra® 1-2 times/month) under medical supervision[17]. Although the subject had taken the medication for about 1 year, he had never shown any sildenafil-associated side effects, when suddenly 24 h after the intake of a Viagra pill, he presented constipation followed by epigastric pain, 38.5°C body temperature, and 2 days later brown urine. Physical examination showed an enlarged tender liver together with increased levels of serum aspartate aminotransferase and alanine aminotransferase (AST and ALT respectively), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) liver functionality enzymes. These values normalized in the following 2 (GGT) and 4 (AST, ALT, and ALP) months, respectively. According to the criteria for drug-induced liver disorders[24], a sildenafil-associated hepatotoxicity was suggested as being probably related to an ischemic mechanism, since the patient was also under medical treatment for cardiac insufficiency with a calcium antagonist. Immediately after this first case, a sildenafil-associated hepatitis was described[18] in a 56-year-old man with no liver disease risk factors, who took sildenafil (Viagra®, 25 mg) in two different occasions at 48 h of delay, between the first and the sec-

ond. After about one month, he presented dark urine, jaundice, increased levels of serum AST, ALT, GGT, ALP and total bilirubin. A liver biopsy showed anomalies associated with cholestatic hepatitis. Tests for anti-hepatitis C virus antibodies, IgM anti-hepatitis A virus, IgM and IgG anti-hepatitis E, and tests for Epstein-Barr and Cytomegalovirus, were all negative. Anti-mitochondrial, anti-nuclear, anti-reticulum endoplasmatic, and anti-smooth-muscle antibodies were also absent in serum. Doppler echocardiography showed no alterations. The patient clinically normalized within about one month after the first onset of clinical signs, except for the total bilirubin that decreased slowly falling by 50% within 180 days. It was hypothesized that the sildenafil-associated hepatitis was due to an immune-allergic mechanism, since the liver biopsy showed a high number of eosinophils. In 2005, a case of acute liver toxicity was observed in a 49-year-old man with no risk factors other than medical treatment for diabetes (glibenclamide), prescribed with Viagra® (50 mg/day) for erectile dysfunction[16]. After 4 weeks he showed a right hypochondrial pain without fever, jaundice, palpable hepatomegaly and with no signs of encephalopathy. Blood analysis was characterized by normal GGT, ALP and total bilirubin values, but with increased AST and ALT. Clinical condition and liver enzyme values returned to normality in 20 days after sildenafil withdrawal, suggesting a diagnosis of sildenafil-associated hepatotoxicity from unknown mechanisms. The antidiabetic drug (glibenclamide) was excluded from the hepatitis genesis, since the altered hepatic condition improved without withdrawing that drug. A 59-year-old healthy man was admitted to the hospital in 2008 because of jaundice, pruritus, anorexia, nausea, fatigue, weight loss and a tender, palpable liver[15]. He did not declare any medication, dietary supplement or xenobiotic administration in the previous days. Serum analysis showed increased total bilirubin, ALP, AST, and ALT values. Liver biopsy showed a severe cholestasis in the sinusoids and a large number of eosinophilic granulocytes in the portal field and sinusoids. Renal function, electrolytes, hematologic parameters, serum albumin, and prothrombin time were all normal. Serology for hepatitis A, B, and C, cytomegalovirus and Epstein-Barr virus and auto-antibodies (antinuclear, antimitochondrial, and anti smoot-muscle antibodies) were negative. Confronted with the analytical findings, the patient finally admitted he used sildenafil (50 mg, tablets) a few times in the previous three months. Clinical conditions and hepatic functions were found to be normal within 3 months of the admission. On the basis of the liver enzyme and histological patterns, the case was classified as a hepatocanalicular injury, linked to a probable immune-mediated mechanism. Another case of liver damage was described in 2009, involving a healthy 58-year-old man with jaundice, pruritus, and malaise[14]. The laboratory values showed increased levels of liver enzymes and the laparoscopic examination revealed a green, enlarged liver, with a smooth surface without nodularity. Liver biopsy revealed features of intrahepatic cholestasis, with marked bile stasis in canaliculi around the pericentral area and a minimal cellular necroinflammation in the portal area. All the possible causes of hepatitis, such as viral infection, metabolic diseases, and autoimmune etiology, were excluded. The patient initially declared no history of recent drug use or excessive alcohol intake. However, he finally confessed to having taken sildenafil 50 mg one month before symptom onset. The drug was obtained from a friend and used, as self-declared, for "recreational" purposes. Clinical conditions improved rapidly without any medical treatment and were found to be normal four months after symptom onset. A diagnosis of probable sildenafil-induced cholestatic hepatotoxicity was formulated, but the causal relationship between sildenafil use and liver damage remained uncertain.

Hepatotoxicity Induced By a Herbal Supplement Containing Sildenafil

In the past years, sildenafil and other phosphodiesterase Type 5 (PDE-5) inhibitors have been detected in the majority of "natural" or "herbal" aphrodisiac supplements sold through Internet, sex shops, social media, and by word-of-mouth. A Dutch study showed that more than three-quarters of herbal supplements used to enhance sexual potency contain therapeutic doses of sildenafil or its analogues[19]. However, up to now, only one report has been published about liver toxicity caused by the consumption of an adulterated "Chinese herbal" supplement, called "Tiger King" commercialized for sexual enhancement[13]. A 65-year-old male was admitted to hospital after a week of malaise and weakness. He had a history of cirrhosis and acute hepatitis, and referred occasional mild

alcohol consumption. One month before admission, he was treated for community-acquired pneumonia. He denied the use of other drugs or herbal and dietary products. Physical examination revealed chronic signs of cirrhosis and acute hepatitis. Laboratory analysis showed increased AST and ALT values, and a slight elevated level of total bilirubin. During hospitalization, the patient finally admitted the use of a "natural herbal medicine" for sexual enhancement called "Tiger King" purchased from a local dealer and taken two and half weeks before symptoms onset (half tablet/time, 2-3 times/week). Chemical analysis of the product evidenced the presence of sildenafil, and it was calculated that the patient assumed a dose of about 20-35 mg each time. Within three days after hospital admission, the patient's clinical status and liver function improved without any specific treatment. His liver function tests normalized thirty days post discharge. According to the Naranjo adverse drug reaction scale[25] and the Roussel Uclaf Causality Assessment Method (RUCAM)[26] the probability of association of hepatotoxicity with sildenafil was "possible" and "probable" respectively (Naranjo score of 4, RUCAM score of 7). Although the mechanism underlying liver toxicity remained unknown, the authors proposed that in the patient the pre-existing liver damage had led to a major susceptibility to sildenafil-associated hepatotoxicity.

Sildenafil and Liver Damage

The use of sildenafil citrate as a treatment for erectile dysfunction was approved in March 1998 by the United States Food and Drug Administration, and in September 1998 by the European Medicines Agency. The safety profile of sildenafil has been investigated in over 120 manufacturer-sponsored clinical trials and other independent studies; moreover, some comprehensive reviews have also been published[27,28]. Common sildenafil-related adverse effects include headaches, facial flushing, nasal congestion, and dyspepsia, and are mild to moderate. As previously described[10,11] sildenafil is extensively and rapidly metabolized by the liver, primarily by CYP3A4 enzymes. A recent review involving 67 double-blind placebo-controlled trials and post-marketing safety database[29] showed that in males with moderate hepatic impairment the sildenafil safety profiles are similar to those in males with erectile dysfunction and no impairment of hepatic function. Specifically, only 23% of men with hepatic impairment treated with sildenafil experienced a worsening of their alkaline phosphatase, AST, ALT, or total bilirubin values; however, none of these alterations was attributed to sildenafil. A 77 % of men with hepatic impairment experienced sildenafil-related adverse effects (mild to severe) compared with 37% of placebo patients with hepatic impairment.

A study[30] published in 2011 investigated the histological effects of sildenafil citrate on the liver of adult Wistar rats treated daily with 3 different sildenafil dose concentrations for 6 weeks. Histological results showed a dilatation of the central vein of the liver with lysed red blood cells and a cytoarchitectural distortion of the organ; increased levels of liver enzymes were also observed. The authors suggest that the hematopoietic function of the liver may have been highly affected as a result of the probable toxic effect of sildenafil. Another study by Nna et al[31] reported that chronic administration of sildenafil in adult Wistar rats could cause significant alteration in liver functions as revealed in the increased serum concentration of liver enzymes and bilirubin; moreover, following sildenafil withdrawal, only a poor reversal of hepatotoxicity was observed. Jarrar et al[32] found that subchronic exposure to sildenafil overdoses reveals significant biochemical and structural (i.e. hepatocytes nuclear alterations, necrosis, bile duct hyperplasia, inflammatory cells infiltration, hepatic vessels congestion) alterations in the hepatic tissues that might affect liver functions.

Conclusions

Although the published literature suggests a possible link between hepatotoxicity and the use of sildenafil, the mechanism underlying liver toxicity is still unknown. The few cases reported to date suggest that sildenafil-associated liver damage is a rare but not impossible event. However, it should be considered that the manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure, and so it could be possible that some sildenafil-associated hepatotoxicity cases may have been totally missed, especially when sildenafil consumption is not declared, illicit, and/or unaware (i.e. in case of counterfeit herbal products for erectile dysfunction)[20,21,33].

Authors Contributions

All the authors contributed to the manuscript and all of them performed the literature search. SG and FPB wrote the first manuscript draft. All the authors have been involved in revising it critically for important intellectual content and all of them have given final approval to the version to be published.

Acknowledgements

The authors thank Michele Sciotti for technical assistance in manuscript preparation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Turko IV, Ballard SA, Francis SH, Corbin JD. Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (Type 5) by sildenafil and related compounds. Mol Pharmacol 1999; 56: 124-130.
2) Salonia A, Rigatti P, Montorsi F. Sildenafil in erectile dysfunction: a critical review. Curr Med Res Opin 2003; 19: 241-262.
3) Jackson G, Gillies H, Osterloh I. Past, present, and future: a 7-year update of Viagra (sildenafil citrate). Int J Clin Pract 2005; 59: 680-691.
4) Wang RC, Jiang FM, Zheng QL, Li CT, Peng XY, He CY, Luo J, Liang ZA. Efficacy and safety of sildenafil treatment in pulmonary arterial hypertension: a systematic review. Respir Med 2014; 108: 531-537.
5) Chaumais MC, Perrin S, Sitbon O, Simonneau G, Humbert M, Montani D. Pharmacokinetic evaluation of sildenafil as a pulmonary hypertension treatment. Expert Opin Drug Metab Toxicol 2013; 9: 1193-1205.
6) Doganci S, Yildirim V, Yesildal F, Erol G, Kadan M, Ozkan G, Avcu F, Ozgurtas T. Comparison of angiogenic and proliferative effects of three commonly used agents for pulmonary artery hypertension (sildenafil, iloprost, bosentan): is angiogenesis always beneficial? Eur Rev Med Pharmacol Sci 2015; 19: 1900-1906.
7) Goldstein I, Tseng LJ, Creanga D, Stecher V, Kaminetsky JC. Efficacy and safety of sildenafil by age in men with erectile dysfunction. J Sex Med 2016; 13: 852-859.
8) Carson CC. Long-term use of sildenafil. Expert Opin Pharmacother 2003; 4: 397-405.
9) Carson CC. Cardiac safety in clinical trials of phosphodiesterase 5 inhibitors. Am J Cardiol 2005; 96: 37M-41M.
10) Muirhead GJ, Rance DJ, Walker DK, Wastall P. Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil. Br J Clin Pharmacol 2002; 53: 13S-20S.
11) Walker DK, Ackland MJ, James GC, Muirhead GJ, Rance DJ, Wastall P, Wright PA. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. Xenobiotica 1999; 29: 297-310.
12) Muirhead GJ, Wilner K, Colburn W, Haug-Pihale G, Rouviex B. The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. Br J Clin Pharmacol 2002; 53: 21S-30S.
13) Nissan R, Poperno A, Stein GY, Shapira B, Fuchs S, Berkovitz R, Hess Z, Arieli M. A case of hepatotoxicity induced by adulterated “Tiger King”, a Chinese herbal medicine containing sildenafil. Curr Drug Saf 2016; 11: 184-188.
14) Enomoto M, Sakaguchi H, Ominami M, Iwai S, Morikawa H, Tamori A, Kawada N. Sildenafil-induced severe cholestatic hepatotoxicity. Am J Gastroenterol 2009; 104: 254-255.
15) Wolfhagen FH, Vermeulen HG, de Man RA, Lesterhuis W. Initially obscure hepatotoxicity attributed to sildenafil. Eur J Gastroenterol Hepatol 2008; 20: 710-712.
16) Daghfous R, El Aidli S, Zaiem A, Loueslati MH, Belkahia C. Sildenafil-associated hepatotoxicity. Am J Gastroenterol 2005; 100: 1895-1896.
17) Maroy B. [Cytolytic acute hepatitis probably due to sildenafil (Viagra)]. Gastroenterol Clin Biol 2003; 27: 564-565.
18) Balian A, Touati F, Huguenin B, Prevot S, Perlemuter G, Naveau S, Chaput JC. [Probable sildenafil (Viagra) induced acute hepatitis in a patient with no other risk factors]. Gastroenterol Clin Biol 2005; 29: 89.
19) Reeuwijk NM, Venhuis BJ, de Kaste D, Hoogenboom LA, Rietjens IM, Martena MJ. Sildenafil and analogous phosphodiesterase type 5 (PDE-5) inhibitors in herbal food supplements sampled on the Dutch market. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2013; 30: 2027-2034.
20) Pellegrini M, Rotolo MC, Busardò FP, Pacifici R, Pichini S. Non-allowed pharmacologically active substances in physical and sexual performance enhancing products. Curr Neuropharmacol 2016 Oct 28. [Epub ahead of print]
21) Pichini S, Marchei E, Pacifici R, Marinelli E, Busardò FP. Chemsex intoxication involving sildenafil as an adulterant of GHB. Drug Test Anal 2016 Aug 16. [Epub ahead of print]
22) Boolell 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: 47-52.
23) Moreland RB, Goldstein II, Kim NN, Traish A. Sildenafil citrate, a selective phosphodiesterase type 5 inhibitor. Trends Endocrinol Metab 1999; 10: 97-104.

24) Danan G, Bénichou C, Begaud B, Biour M, Couzigou P, Evreux JC, Lagier G, Berthelot P, Benhamou JP. [Criteria of imputation of acute hepatitis to a drug. Results of consensus meetings]. Gastroenterol Clin Biol 1987; 11: 581-585.

25) Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domeco C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

26) Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993; 46: 1323-1330.

27) Salonia A, Rigatti P, Montorsi F. Sildenafil in erectile dysfunction: a critical review. Curr Med Res Opin 2003; 19: 241-262.

28) Padma-nathan H, Eardley I, Kloner RA, Laties AM, Montorsi F. A 4-year update on the safety of sildenafil citrate (Viagra). Urology 2002; 60: 67-90.

29) Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract 2010; 64: 240-255.

30) Eweka AO, Eweka A. The effects of sildenafil citrate on the liver and kidneys of adult wistar rats (Rattus norvegicus) – a histological study. In: Azita G, ed. sexual dysfunctions – special issues 2011; 59-65.

31) Nna VU, Akpan UP, Okon VE, Atangwho IJ. Hepatotoxicity following separate administration of two phosphodiesterase-5 inhibitors (sildenafil & tadalafil) and opioid (tramadol); evaluation of possible reversal following their withdrawal. J App Pharm Sci 2015; 5: 105-113.

32) Jarrar BM, Almansour MI. Hepatic histological alterations and biochemical changes induced by sildenafil overdoses. Pak J Pharm Sci 2015; 28: 2119-2127.

33) Giorgetti R, Tagliabracci A, Schifano F, Zaami S, Marinelli E, Busardò FP. When “chems” meet sex: a rising phenomenon called “ChemSex”. Curr Neuropharmacol 2016 Nov 17. [Epub ahead of print]