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Phosphodiesterase Type 5 (PDE5) Inhibitors

Updated: August 2, 2017.

OVERVIEW

The phosphodiesterase type 5 (PDE5) inhibitors cause vasodilation in the penis and lung by blocking the breakdown of cyclic guanosine monophosphate (cGMP) which results in prolongation of the action of mediators of vasodilation including nitric oxide (NO). The type-5 phosphodiesterases are isoforms of this enzyme that are found primarily in the corpus cavernosum of penis and vasculature of the lung. For these reasons, the two major actions of the PDE5 inhibitors are to prolong penile erection and decrease pulmonary vascular pressure. They have little effect on the systemic vasculature.

Four PDE5 inhibitors are currently approved and in use for treatment of erectile dysfunction including sildenafil (Viagra: 1998), tadalafil (Cialis: 2003), vardenafil (Levitra: 2003) and avanafil (Stendra: 2012), all of which are recommended to be taken orally one-half to 4 hours before sexual intercourse. Typically, no more than once daily use is recommended. The PDE5 inhibitors are not approved for use in women. Sildenafil is approved for use in pulmonary hypertension where two to three times daily chronic dosing is used. Its safety and efficacy are still under experimental evaluation, particularly in patients with end stage liver disease (hepato-pulmonary syndrome) and in patients with sickle cell anemia with pulmonary hypertension.

Rare single case reports of acute liver injury have been reported with use of PDE5 inhibitors, mostly with sildenafil, most likely becausethe others have been available for a shorter time and are less commonly used. The four agents share a similar mechanism of action, but have structural differences, and it is not clear whether liver injury is a class effect or specific to sildenafil. Chronic sildenafil use has not been associated with serum aminotransferase elevations.

The following links are to individual drug records. References to hepatotoxicity and safety of the PDE5 inhibitors are given together after this Overview section.

- Avanafil
- Sildenafil
- Tadalafil
- Vardenafil

ANNOTATED BIBLIOGRAPHY

References updated: 02 August 2017

Abbreviations: PDE5, phosphodiesterase type 5

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, p. 717.

(Textbook of hepatotoxicity published in 1999, before the availability of PDE5 inhibitors).

Michel T, Hoffman BB. Therapy of myocardial ischemia and hypertension. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 745-88.

(Textbook of pharmacology and therapeutics; use of PDE5 inhibitors with nitrates can cause severe hypotension; PDE5 inhibitors in current use are metabolized by CYP3A4 and drug-drug interactions may also complicate their use).

Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338: 1397-404. PubMed PMID: 9580646.

(Randomized controlled trial of sildenafil vs placebo in 532 men for 24 weeks; "Laboratory test results indicated no evidence of sildenafil-induced abnormalities").

Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA 1999; 281: 421-6. PubMed PMID: 9952201.

(Randomized controlled trial of sildenafil vs placebo in 268 men; side effects included headache, dyspepsia, flushing, rhinitis and visual disturbance; "There were no laboratory test abnormalities attributable to sildenafil use").

Christiansen E, Guirguis WR, Cox D, Osterloh IH; Sildenafil Multicentre Study Group. Long-term efficacy and safety of oral Viagra (sildenafil citrate) in men with erectile dysfunction and the effect of randomised treatment withdrawal. Int J Impot Res 2000; 12: 177-82. PubMed PMID: 11045912.

(Study of 233 men treated with sildenafil for 16 weeks, followed by 8 weeks withdrawal and then open label study; flushing in 7%, headache 6%, dyspepsia 5%; no reports of jaundice or hepatitis, but no ALT monitoring).

Chen KK, Hsieh JT, Huang ST, Jiaan DB, Lin JS, Wang CJ; ASSESS-3 Study Group. ASSESS-3: a randomised, double-blind, flexible-dose clinical trial of the efficacy and safety of oral sildenafil in the treatment of men with erectile dysfunction in Taiwan. Int J Impot Res 2001; 13: 221-9. PubMed PMID: 11494079.

(Randomized controlled trial of sildenafil vs placebo in 236 patients; no mention of ALT elevations or liver injury).

Brock GB, McMahon CG, Chen KK, Costigan T, Shen W, Watkins V, Anglin G, Whitaker S. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002; 168 (4 Pt 1): 1332-6. PubMed PMID: 12352386.

(1112 men given tadalafil or placebo for 12 weeks, headache in 14% and dyspepsia in 10%, but no "clinically relevant differences in the incidence of abnormal laboratory changes" between placebo and tadalafil).

Maroy B. [Cytolytic acute hepatitis probably due to sildenafil (Viagra)]. Gastroenterol Clin Biol 2003; 27: 564-5. French. PubMed PMID: 12843928.

(65 year old man developed malaise within 24 hours of starting sildenafil followed by dark urine [bilirubin not given, ALT 114 times ULN, Alk P 5 times ULN], with rapid recovery; no recurrence on restarting sildenafil suggesting that episode was due to ischemic hepatitis caused by hypotension in the setting of underlying cardiac disease).

Carson CC. Long-term use of sildenafil. Expert Opin Pharmacother 2003; 4: 397-405. PubMed PMID: 12614192.

(Review of pharmacology, use, efficacy and safety of sildenafil; currently used by more than 12 million men; no mention of hepatic side effects).

Michelakis ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D, Wang SH, Modry D, Archer SL. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. Circulation 2003; 108: 2066-9. PubMed PMID: 14568893.

(Five patients given sildenafil at 50 mg thrice daily for 3 months had improvement in functional capacity and decreases in pulmonary artery pressure: "Liver enzymes … remained unchanged").

Masson P, Lambert SM, Brown M, Shabsigh R. PDE-5 inhibitors: current status and future trends. Urol Clin North Am 2005; 32: 511-25. PubMed PMID: 16291042.

(Review of PDE5 inhibitors including mechanisms of action, pharmacology, efficacy and safety in therapy of erectile dysfunction; no mention of hepatic toxicity or ALT elevations on therapy).

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. French. PubMed PMID: 15738907.

(56 year old man developed jaundice 3 weeks after taking 2 doses of sildenafil [bilirubin 8 times ULN, ALT 8 times ULN, Alk P 2 times ULN], resolving 1 month later).

Daghfous R, El Aidli S, Zaiem A, Loueslati MH, Belkahia C. Sildenafil-associated hepatotoxicity. Am J Gastroenterol 2005; 100: 1895-6. PubMed PMID: 16086731.

(49 year old man developed right upper quadrant pain 4 weeks after starting sildenafil for erectile dysfunction [bilirubin and Alk P normal, ALT 1.2 times ULN], with rapid resolution with stopping, but not appearing on rechallenge; more likely gastrointestinal intolerance rather than frank hepatotoxicity).

van Ahlen H, Zumbé J, Stauch K, Landen H. The real-life safety and efficacy of vardenafil: an international post-marketing surveillance study—results from 29,358 German patients. J Int Med Res 2005; 33: 337-48. PubMed PMID: 15938595.

(Postmarketing use and safety report covering ~30,000 patients; adverse reactions in 1.3%, but no report or mention of liver injury).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to a PDE5 inhibitor).

Wolfhagen FH, Vermeulen HG, de Man RA, Lesterhuis W. Initially obscure hepatotoxicity attributed to sildenafil. Eur J Gastroenterol Hepatol 2008; 20: 710-2. PubMed PMID: 18679077.

(59 year old man developed jaundice and pruritus after using sildenafil intermittently for 3 months [bilirubin 5.2 rising to 19 mg/dL, ALT 1665 U/L, Alk P 173 U/L], resolving within 3 months of stopping [Sildenafil: Case 1]).

Enomoto M, Sakaguchi H, Ominami M, Iwai S, Morikawa H, Tamori A, Kawada N. Sildenafil-induced severe cholestatic hepatotoxicity. Am J Gastroenterol 2009; 104: 254-5. PubMed PMID: 19098889.

(58 year old man developed jaundice and pruritus one month after starting sildenafil [bilirubin 8.5 mg/dL, ALT 64 U/L, Alk P 476 U/L] without rash, fever, eosinophilia or autoantibodies, biospy showing intrahepatic cholestasis, resolved over ensuing 4 months).

Essaid A, Timraz A. [Cholestatic acute hepatitis induced by tadalafil (Cialis)]. Gastroenterol Clin Biol 2010; 34(4-5): e1-2. French. PubMed PMID: 20171032.

(38 year old man developed fatigue followed by jaundice 5 days after starting tadalafil [bilirubin 2.5 mg/dL, ALT 4 times ULN, Alk P 4 times ULN], resolving within 2 months of stopping).

Eriksson C, Gustavsson A, Kronvall T, Tysk C. Hepatotoxicity by bosentan in a patient with portopulmonary hypertension: a case-report and review of the literature. J Gastrointestin Liver Dis 2011; 20: 77-80. (29 year old woman with pulmonary hypertension developed jaundice 18 months after starting long term bosentan [bilirubin 10 mg/dL, ALT 600 U/L, Alk P 480 U/L, INR 1.8], resolving within 8 weeks on prednisone and not recurring when switched to sildenafil and ambrisenatan). PubMed PMID: 21451802.

Arif SA, Poon H. Tadalafil: a long-acting phosphodiesterase-5 inhibitor for the treatment of pulmonary arterial hypertension. Clin Ther 2011; 33: 993-1004. PubMed PMID: 21762988.

(Review of pharmacology, efficacy and safety of tadalafil in pulmonary hypertension states that minor side effects are common, but does not mention hepatotoxicity or ALT levels).

Jing ZC, Yu ZX, Shen JY, Wu BX, Xu KF, Zhu XY, Pan L, et al.; Efficacy and Safety of Vardenafil in the Treatment of Pulmonary Arterial Hypertension (EVALUATION) Study Group. Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 2011; 183: 1723-9. PubMed PMID: 21471085.

(Controlled trial of vardenafil vs placebo in 66 patients with pulmonary hypertension reported that adverse events were "generally mild and transient", not mentioning hepatotoxicity or ALT levels).

Goldstein I, McCullough AR, Jones LA, Hellstrom WJ, Bowden CH, Didonato K, Trask B, Day WW. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. J Sex Med 2012; 9: 1122-33. PubMed PMID: 22248153.

(Controlled trial of 3 doses of avanafil vs placebo for 12 weeks in 646 men with erectile dysfunction; adverse events included headache, flushing, back pain, nasal congestion and bronchitis; no mention of ALT levels or hepatotoxicity).

Lowe G, Costabile RA. 10-Year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors. J Sex Med 2012; 9: 265-70. PubMed PMID: 22023666.

(Among 26,451 spontaneous reports [2,181 deaths] submitted to the FDA over 10 years, adverse events included cardiovascular events, deafness, amnesia, flushing, rash, tinnitus, headahce and excessive masturbation; ALT elevations and liver injury were not mentioned).

Burke RM, Evans JD. Avanafil for treatment of erectile dysfunction: review of its potential. Vasc Health Risk Manag 2012; 8: 517-23. PubMed PMID: 22973106.

(Review of pharmacology, mechanism of action, clinical efficacy and safety of avanafil based upon three premarketing studies; discussion of safety makes no mention of blood chemistry results, ALT levels or hepatotoxicity).

Kedia GT, Uckert S, Assadi-Pour F, Kuczyk MA, Albrecht K. Avanafil for the treatment of erectile dysfunction: initial data and clinical key properties. Ther Adv Urol 2013; 5: 35-41. PubMed PMID: 23372609.

(Review of the clinical trials of avanafil in erectile dysfunction mentions that severe adverse events were rare, but no specific discussion of side effects or mention of ALT elevations or hepatotoxicity).

Avanafil (Stendra) - another PDE5 inhibitor for erectile dysfunction. Med Lett Drugs Ther 2014; 56 (1442): 37-8. PubMed PMID: 24818838.

(Concise review of the mechanism of action, efficacy and safety of avanafil shortly after its approval in the US; no mention of ALT elevations or hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, Presentation and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to sildenafil or other PDE5 inhibitors).

Lasaponara F, Sedigh O, Pasquale G, Bosio A, Rolle L, Ceruti C, Timpano M, et al. Phosphodiesterase type 5 inhibitor treatment for erectile dysfunction in patients with end-stage renal disease receiving dialysis or after renal transplantation. J Sex Med 2013; 10: 2798-814. PubMed PMID: 23346948.

(Review of published reports on use of PDE5 inhibitors to treat erectile dysfunction in patients on hemodialysis and patients with renal transplants, found similar efficacy and safety as reported in healthy persons; no mention of ALT elevations or hepatotoxicity).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, but none were attributed to sildenafil or other PDE5 inhibitors).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to sildenafil or other PDE5 inhibitors).

Nissan R, Poperno A, Stein GY, Shapira B, Fuchs S, Berkovitz R, Hess Z, et al. A case of hepatotoxicity induced by adulterated "Tiger King", a Chinese herbal medicine containing sildenafil. Curr Drug Saf 2016; 11: 184-8. PubMed Citation (65 year old man developed acute liver injury 2 weeks after taking a product for erectile dysfunction called "Tiger King" that was later found to be adulterated with sildenafil [bilirubin 1.8 mg/dL, ALT 984 U/L, Alk P 326 U/L, INR 1.37], recovering within 1 month with supportive care only).

Graziano S, Montana A, Zaami S, Rotolo MC, Minutillo A, Busardò FP, Marinelli E. Sildenafil-associated hepatoxicity: a review of the literature. Eur Rev Med Pharmacol Sci 2017; 21 (1 Suppl): 17-22. PubMed Citation (Review of the literature on sildenafil hepatotoxicity with clinical descriptions of the five published cases).