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Fesoterodine

Updated: July 12, 2023.

OVERVIEW

Introduction

Fesoterodine is an anticholinergic and antispasmotic agent used to treat urinary incontinence and overactive bladder syndrome. Fesoterodine has not been implicated in causing liver enzyme elevations or clinically apparent acute liver injury.

Background

Fesoterodine (fes" oh ter' oh deen) is an anticholinergic agent which blocks the muscarinic acetylcholine receptors, particularly those found in the smooth muscle of the bladder. Fesoterodine increases bladder capacity and decreases bladder contractions and the urgency of urination. Fesoterodine is formulated in an extended release formulation and has a quarternary ammonium group that makes it less likely to cross the blood brain barrier. Fesoterodine was approved for use in the United States in 2008, and indications include urinary urge incontinence and overactive bladder syndrome. Fesoterodine is available in extended-release tablets of 4 and 8 mg generically and under the brand name Toviaz. The recommended adult oral dose is 4 to 8 mg once daily. Common side effects are those of parasympathetic stimulation and include dryness of the mouth and eyes, decreased sweating, headache, visual blurring, constipation, and urinary retention. Because of its structure, fesoterodine is believed to be less likely than other anticholinergic agents to cause central nervous system effects such as restlessness, confusion and hallucinations. Rare but potentially severe adverse reactions include acute narrow angle glaucoma, acute urinary retention, and severe hypersensitivity reactions.

Hepatotoxicity

Like most anticholinergic agents, fesoterodine has not been linked to episodes of liver enzyme elevations or clinically apparent liver injury. In prospective, randomized, placebo-controlled trials of fesoterodine in overactive bladder syndrome, serum aminotransferase elevations were rare, arising in less than 1% of recipients, rates similar to those in placebo recipients. Since its approval, there have been no published case reports of clinically apparent liver injury attributed to fesoterodine.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Fesoterodine has not been linked to liver injury. It is metabolized in the liver by microsomal P450 enzymes, predominantly CYP 3A4 and 2D6. Despite this, drug-drug interactions are uncommon. A major reason for its safety may relate to the low daily dose.

Drug Class: Anticholinergic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Fesoterodine – Generic, Toviaz®

DRUG CLASS

Anticholinergic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Fesoterodine	286930-02-7	C26-H37-N-O3	SID:

ANNOTATED BIBLIOGRAPHY

References updated: 12 July 2023

Abbreviations: ER, extended release.

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

(Expert review of hepatotoxicity published in 1999 before the availability of darifenacin and other therapies of overactive bladder syndrome).

Brown JH, Brandl K, Wess J. Therapeutic uses of muscarinic receptor antagonists: Muscarinic receptor agonists and antagonists. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 156-9.

(Textbook of pharmacology and therapeutics).

Chapple C, Van Kerrebroeck P, Tubaro A, Haag-Molkenteller C, Forst HT, Massow U, Wang J, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol. 2007;52:1204-12. PubMed PMID: 17651893.

(Among 1059 adults with symptomatic overactive bladder syndrome treated with fesoterodine [4 or 8 mg], tolterodine [4 mg], or placebo once daily for 12 weeks, both treatments resulted in significant decreases in number of micturitions daily [-1.8, -1.9, and -1.7 vs -1.0], but with higher adverse event rates [50%, 58%, and 50% vs 38%] and ALT elevations [<1%, 2.8% and 0 vs <1%], although "there were no clinically relevant changes in…laboratory parameters").

Nitti VW, Dmochowski R, Sand PK, Forst HT, Haag-Molkenteller C, Massow U, Wang J, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J Urol. 2007;178:2488-94. PubMed PMID: 17937959.

(Among 836 adults with overactive bladder syndrome treated with fesoterodine [4 or 8 mg] or placebo once daily for 12 weeks, improvements in numbers of micturitions, urgency episodes and incontinence were greater with

fesoterodine and adverse events were mostly mild-to-moderate, most frequently dry mouth [16% and 36% vs 7% on placebo], ALT elevations in <1% [1 of 561 on fesoterodine] and there were no treatment related serious adverse events or deaths).

Novara G, Galfano A, Secco S, D'Elia C, Cavalleri S, Ficarra V, Artibani W. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol 2008; 54: 740-63. PubMed PMID: 18632201.

(Systematic review of efficacy and safety of drugs for overactive bladder including tolterodine, propiverine, solifenacin, darifenacin, fesoterodine and oxybutynin; common side effects included dry mouth and constipation; hepatotoxicity and ALT elevations were not mentioned).

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 anticholinergics or drugs for overactive bladder).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to anticholinergics or drugs for overactive bladder syndrome).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(Among 624,673 adverse event reports in children between 2000 and 2006 in the WHO VigiBase, 1% were hepatic, but no anticholinergic was listed among the 41 most frequently implicated agents).

Van Kerrebroeck PE, Heesakkers J, Berriman S, Padmanabhan Aiyer L, Carlsson M, Guan Z. Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. Int J Clin Pract. 2010;64:584-93. PubMed PMID: 20201992.

(Among 417 adults with overactive bladder syndrome who participated in the 12 week controlled trial of fesoterodine [Chapple 2007] and were enrolled in a subsequent open-label extension study of 4 or 8 mg of fesoterodine daily for up to 32 months], 76% had at least one adverse event, most commonly dry mouth [34%], constipation [7%] and urinary tract infection [15%], which led to discontinuations in 12% of patients including 4 with acute urinary retention; no mention of ALT elevations, but "no apparent trends in … blood chemistry… were noted).

Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women: a systematic review. Ann Intern Med 2012; 156: 861-74. PubMed PMID: 22711079.

(Systematic review of the safety and efficacy of drugs used for urinary incontinence including fesoterodine, tolterodine, oxybutynin, solifenacin and trospium; most had modest effectiveness; hepatotoxicity was not mentioned).

Cardozo L, Hall T, Ryan J, Ebel Bitoun C, Kausar I, Darekar A, Wagg A. Safety and efficacy of flexible-dose fesoterodine in British subjects with overactive bladder: insights into factors associated with dose escalation. Int Urogynecol J 2012; 23: 1581-90. PubMed PMID: 22576329.

(Among 331 adults with overactive bladder treated with fesoterodine for 12 weeks, 30% complained of dry mouth and 9% of constipation: no mention of jaundice, ALT elevations or hepatic side effects).

Dell'Utri C, Digesu GA, Bhide A, Khullar V. Fesoterodine in randomised clinical trials: an updated systematic clinical review of efficacy and safety. Int Urogynecol J. 2012;23:1337-44. PubMed PMID: 22411206.

(Systematic review of the safety and efficacy of fesoterodine from 7 controlled trials of 8-12 weeks of treatment in more than 6000 patients; "No clinically relevant changes in vital signs, laboratory or electrocardiogram parameters occurred in any of the studies").

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 mirabegron or drugs for overactive bladder syndrome).

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.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, but none were attributed to drugs used for overactive bladder syndrome).

Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, Odeyemi I, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol. 2014;65:755-65. PubMed PMID: 24275310.

(Systematic review of literature on medical therapies for overactive bladder identified 44 controlled trials demonstrating similar efficacy among 6 anticholinergics and a single beta-3 adrenergic agonist [mirabegron] when compared to placebo, but less dry mouth with mirabegron than with anticholinergic agents; no mention of ALT elevations or hepatotoxicity).

Wyndaele JJ, Schneider T, MacDiarmid S, Scholfield D, Arumi D. Flexible dosing with fesoterodine 4 and 8 mg: a systematic review of data from clinical trials. Int J Clin Pract. 2014;68:830-40. PubMed PMID: 24754814.

(Systematic review of publications on "flexible dosing" [4 or 8 mg daily] of fesoterodine in therapy of overactive bladder syndrome suggested that optimal dosing varies by individual and flexible dosing results in higher response rates without worsening of adverse events; no mention of ALT elevations or hepatoxicity).

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: 1340-1352.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 mirabegron or other agents for overactive bladder syndrome).

Thiagamoorthy G, Cardozo L, Srikrishna S. Drug therapy for an overactive bladder. Womens Health (Lond) 2015; 11: 445-8. PubMed PMID: 26238677.

(Overactive bladder is defined as urinary urgency, usually with frequency and nocturia with or without incontinence in the absence of infection or other known cause, medical therapy being use of anticholinergics or beta-3 adrenergic receptor agonists such as mirabegron or vibegron which have fewer side effects than typical anticholinergics).

Ramsay S, Naud É, Simonyan D, Moore K, Bolduc S. A randomized, crossover trial comparing the efficacy and safety of fesoterodine and extended-release oxybutynin in children with overactive bladder with 12-month extension on fesoterodine: The FOXY study. Can Urol Assoc J. 2020;14:192-198. PubMed PMID: 31977308.

(Among 60 children with overactive bladder syndrome treated with fesoterodine [4 mg] or oxybutynin [50 mg] daily for 2 months, with subsequent cross over to the other medication for 2 months followed by 12 months of treatment with fesoterodine, both drugs led to similar improvement in symptoms, and both were well tolerated; one patient developed ALT elevations on fesoterodine, but no details of degree and duration of abnormalities were provided).

Drugs for overactive bladder. .Med Lett Drugs Ther. 2023;65:41-45. PubMed PMID: 36897601.

(Concise review of drugs approved for therapy of overactive bladder in the US including anticholinergic agents [darifenacin, fesoterodine, oxbutynin, solifenacin, tolterodine and trospium] and beta-3 adrenergic receptor agonists [mirabegron and vibegron], including clinical efficacy, safety, and costs; no mention of ALT elevations or hepatotoxicity of any of the agent discussed).