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Felodipine

Updated: January 11, 2017.

OVERVIEW

Introduction

Felodipine is a second generation calcium channel blocker and commonly used antihypertensive agent. Felodipine therapy has been associated with a low rate of serum enzyme elevations, but has not been convincingly linked to instances of clinically apparent, acute liver injury.

Background

Felodipine (fe loe' di peen) belongs to the dihydropyridine group of calcium channel blockers (with amlodipine, isradipine and nifedipine) and is used primarily in the therapy of hypertension. Like other calcium channel blockers, felodipine acts by blocking the influx of calcium ions into vascular smooth muscle and cardiac muscle cells during depolarization, which results in arterial vasodilation and decrease in cardiac work and oxygen consumption. Felodipine was approved in the United States in 1991 and currently more than 3 million prescriptions are filled yearly. The current sole indication is treatment of hypertension, either alone or with other antihypertensive agents. Felodipine is available in multiple generic forms and under the commercial name Plendil in 2.5, 5 and 10 mg extended release tablets. The recommended dose in adults is 2.5 to 10 mg once daily, generally starting at the lowest dose and adjusting upward. Like other calcium channel blockers, felodipine is generally well tolerated, but side effects can include dizziness, flushing, headache, fatigue, nausea, diarrhea, peripheral edema, palpitations and rash.

Hepatotoxicity, Outcome and Management

Felodipine therapy has been associated with low rates of serum enzyme elevations (<1% to 5%) which in many studies were no higher than occurred with placebo. ALT elevations were usually mild, asymptomatic and transient and often resolved even with continuation of therapy. Despite 20 years of clinical use, cases of clinically apparent liver injury due to felodipine have not been published. Thus, acute liver injury due to felodipine must be rare, if it occurs at all.

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

Felodipine, however, can have significant drug-drug interactions. Felodipine is metabolized by the cytochrome P450 enzyme, CYP3A4, which is found in intestine and liver. Grapefruit juice can increases felodipine levels by inhibiting expression of intestinal CYP3A4 which ordinarily metabolizes it. Similarly, systemic drugs that inhibit CYP 3A4 (such as itraconazole or cimetidine) can increase and drugs that stimulate CYP 3A4 (such as phenytoin or phenobarbital) can lower felodipine levels significantly. Because felodipine can interact with other

agents that are metabolized by the hepatic microsomal enzyme system, it may affect the risk of hepatotoxicity with other agents.

Drug Class: Cardiovascular Agents, Calcium Channel Blockers

Other Drugs in the Subclass, Calcium Channel Blockers: Amlodipine, Diltiazem, Isradipine, Nicardipine, Nifedipine, Nimodipine, Nisoldipine, Verapamil

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Felodipine – Generic, Plendil®

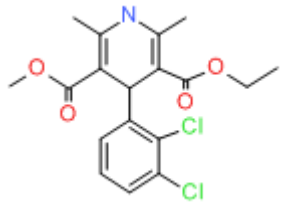
DRUG CLASS

Cardiovascular Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Felodipine	72509-76-3	C18-H19-C12-N-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 11 January 2017

Zimmerman HJ. Calcium channel blockers. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 646-7.

(Expert review of hepatotoxicity published in 1999; among calcium channel blockers, only diltiazem, nifedipine, bepridil and verapamil have been incriminated in instances of hepatic injury; felopidine not mentioned).

De Marzio DH, Navarro VJ. Calcium channel blockers. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 524.

(Review of hepatotoxicity of calcium channel blockers; diliazem and verapamil have been implicated in causing cholestatic liver injury in a small number of patients; felodipine is not specifically mentioned).

Michel T, Hoffman BB. Calcium channel antagonists. Treatment of myocardial ischemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 755-60.

(Textbook of pharmacology and therapeutics).

Edgar B, Lundborg P, Regardh CG. Clinical pharmacokinetics of felodipine. A summary. Drugs 1987; 34: (Suppl 3): 16-27. PubMed PMID: 3327676.

(Review of pharmacokinetics of felodipine; felodipine is highly protein bound and is extensively metabolized by the liver).

Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. J Clin Invest 1997; 99: 2545-53. PubMed PMID: 9153299.

(Pharmacokinetic study in 10 volunteers demonstrated downregulation of enterocyte CYP 3A4 by grapefruit juice and a three fold increase in bioavailability of felodipine).

Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC, Michelsen EL. Enalapril-Felodipine ER Factorial Study Group. Long-term efficacy, tolerability, and safety of the combination of enalapril and felodipine ER in the treatment of hypertension. Clin Ther 1998; 20: 527-38. PubMed PMID: 9663368.

(Among 507 patients treated with felodipine and enalapril for an average of 8 months, one patient stopped therapy because of a rise in ALT [from 72 to 93 U/L]).

McClennen W, Wilson T. National Trial Group. Felodipine extended release versus conventional diuretic therapy for the treatment of systolic hypertension in elderly patients. Clin Invest Med 1998; 21: 142-50. PubMed PMID: 9627768.

(Among 216 patients with hypertension treated with either felodipine or diuretics for 8 weeks, ALT or AST levels became elevated in 5-6% of felodipine- vs 1-2% of diuretic treated patients, but none required early discontinuation).

Black HR, Elliott WJ, Weber MA, Frishman WH, Strom JA, Liebson PR, Hwang CT, Ruff DA, Montoro R, DeQuattro V, Zhang D, Schleman MM, Klibaner MI. One-year study of felodipine or placebo for stage 1 isolated systolic hypertension. Hypertension 2001; 38: 1118-23. PubMed PMID: 11711508.

(In a controlled trial of felodipine vs placebo in 171 patients with hypertension, "there were no clinically meaninful changes from baseline" of ALT or AST).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but none were attributed to a calcium channel blocker).

Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 2005; 23: 2157-72. PubMed PMID: 16269957.

(A trial in 9800 patients treated with diuretics with or without felodipine for an average of 3 years reported no liver related adverse events).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101.

PubMed Citation (Summary of 25 years of adverse drug reaction reporting in Sweden identified 103 cases of drug induced acute liver failure; felodipine was possibly linked one case, but another hepatotoxic agent was being used [details not provided]).

Frishman WH, Hainer JW, Sugg J; M-FACT Study Group. A factorial study of combination hypertension treatment with metoprolol succinate extended release and felodipine extended release results of the

Metoprolol Succinate-Felodipine Antihypertension Combination Trial (M-FACT). Am J Hypertens 2006; 19: 388-95. PubMed PMID: 16165719.

(In a controlled trial of multiple combinations of metoprolol and felodipine or placebo in 1092 patients with hypertension, no liver related side effects were reported).

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 Citation

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, calcium channel blockers were implicated as a sole agent in 2 cases [1 amlodipine, 1 verapamil] and as one of several agents in 2 cases [both amlodipine]).

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, none of which were attributed to a calcium channel blocker).

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, none of which was attributed to a calcium channel blocker or other antihypertensive medication).

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; one case was attributed to verapamil, but none were linked to felodipine or other calcium channel blockers).

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, 39 [4%] were due to antihypertensive agents including 4 due to calcium channel blockers [amlodipine in 1 and verapamil in 3 instances]).