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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Amlodipine. [Updated 2016 Mar 1].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Amlodipine

Updated: March 1, 2016.

OVERVIEW

Introduction

Amlodipine besylate is a second generation calcium channel blocker that is used in the therapy of hypertension and angina pectoris. Amlodipine has been linked to a low rate of serum enzyme elevations during therapy and to rare instances of clinically apparent acute liver injury.

Background

Amlodipine (am loe' di peen) belongs to the dihydropyridine class of calcium channel blockers and is used in the treatment of both hypertension and angina pectoris. Like other calcium channel blockers, amlodipine acts by blocking the influx of calcium ions into vascular smooth muscle and cardiac muscle cells during membrane depolarization. This action causes relaxation of vascular and arterial smooth muscle cells, resulting in arterial vasodilation and a decrease in cardiac work and oxygen consumption. Amlodipine was approved in the United States in 1992 and it remains in wide use, with several million prescriptions filled yearly. Current indications include hypertension and coronary artery disease (angina pectoris). Amlodipine is available generically and under the brand name of Norvasc. Tablet strengths include 2.5, 5, and 10 mg. The recommended dose in adults is 2.5 to 10 mg once daily, usually starting with the lowest dose. Chronic therapy is typical. Recently, multiple fixed dose combinations of amlodipine with other agents have become available including amlodipine (5 or 10 mg) with aliskiren (150 or 300 mg: Tekamlo), aliskiren with hydrochlorothiazide (12.5 and 25 mg: Amturnide), atorvastatin (10, 20, 40 or 80 mg: Caduet and generic), benzapril (10, 20 or 40 mg: Lotrel, Amlobenz, and generic), benzapril and hydrochlorothiazide (12.5 and 25 mg: Tribenzor), olmesaran (20 and 40 mg: Azor), and telmisartan (40 or 80 mg: Twynsta), valsartan (160 and 320 mg: Exforge) and valsartan with hydrochlorothiazide (25 mg: Exforge HCT). Like most calcium channel blockers, amlodipine is generally well tolerated. Side effects are largely due to the vasodilating activities and can include headache, flushing, dizziness, fatigue, nausea, diarrhea, palpitations, peripheral edema and rash.

Hepatotoxicity

Chronic therapy with amlodipine is associated with a low rate of serum enzyme elevations at rates that are similar to matched control populations. The enzyme elevations are usually mild, transient and asymptomatic and may resolve even during continued therapy. Clinically apparent liver injury from amlodipine is rare and described only in isolated case reports. In the few idiosyncratic cases reported, the latency period to onset of liver injury was usually 4 to 12 weeks, but examples with prolonged latency have also been published (10 months and several years). The latency period is shorter with recurrence on reexposure, including several instances of recurrence after liver injury due to other calcium channel blockers. The pattern of serum enzyme elevations is

usually mixed or cholestatic. Rash, fever and eosinophilia have not been described and autoantibodies are not typical.

Likelihood score: C (probable but rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of amlodipine hepatotoxicity is not known, but liver injury is probably due to production of a toxic intermediate in its metabolism.

Outcome and Management

The severity of liver injury from amlodipine ranges from mild and transient serum enzyme elevations to self-limited jaundice. Complete recovery is expected after stopping the drug and recovery is usually rapid (4 to 8 weeks). Cases with chronic or fulminant liver injury due to amlodipine have not been reported. Little information is available on recurrence with rechallenge but there may be some degree of cross-sensitivity to hepatotoxicity with other calcium channel blockers.

Drug Class: Cardiovascular Agents, Calcium Channel Blockers

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

CASE REPORT

Case 1. Acute hepatitis-like syndrome attributed to amlopidine.

[Modified from: Basile C, Mascia E. Dihydropyridine calcium channel blockers: a rare and reversible cause of hepatotoxicity with cholestasis in a CAPD patient. Nephrol Dial Transplant 1999; 14: 2776-7. PubMed Citation]

A 76 year old man with diabetes and end-stage renal disease developed jaundice while on long term nifedipine therapy (60 mg daily for ~3 years) for hypertension. He was taking insulin, but no other medications. He had no risk factors for viral hepatitis and did not drink alcohol. Serum bilirubin was 2.5 mg/dL and rose over the next few months to 6.2 mg/dL. Tests for acute hepatitis A, B and C were negative and abdominal ultrasonography showed a normal liver and gallbladder. Nifedipine was stopped and he recovered rapidly. Several months later, amlodipine was started (10 mg daily) and within 6 weeks, he developed jaundice and a cholestatic pattern of serum enzyme elevations. Once amlodipine was stopped, liver tests improved and were normal three weeks later.

Key Points

Medication:	Nifedipine (60 mg daily) and then amlodipine (10 mg daily)
Pattern:	Cholestatic (R=0.3 and 0.8 during recurrence)
Severity:	2+ (jaundiced, but not hospitalized for liver injury)
Latency:	3 years for nifedipine, 2 months for amlodipine
Recovery:	3 to 4 weeks
Other medications:	Insulin

Laboratory Values

Date	Duration Therapy	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Long term therapy with nifedipine (60 mg daily)						

Table continued from previous page.

May 12, 1998	3 years		13	144	0.3	
Sep 9, 1998			47	783	0.5	
Dec 9, 1998			40	955	2.5	
Jan 11, 1999	3.5 years	0	79	...	6.2	
Nifepidine stopped January 11, 1999						
Jan 16, 1999		1 week	46	531	4.0	
Jan 23, 1999		2 weeks	45	419	1.8	
Feb 11, 1999		4 weeks	17	185	0.9	
Amlodipine (10 mg daily) started in late March, 1999						
Apr 10, 1999	2 weeks		43	398	0.6	
May 5, 1999	6 weeks	0	74	398	6.3	
Amlodipine stopped May 7, 1999						
May 11, 1999		4 days	70	399	5.4	
May 13, 1999		6 days	54	314	4.1	
May 28, 1999		3 weeks	19	181	1.3	
Normal Values			**<55**	**<250**	**<1.2**	

Comment

One of the few reports of acute liver injury with jaundice attributed to calcium channel blockers. The patient initially developed a cholestatic hepatitis while on long term nifepidine therapy. Liver tests because steadily worse and nifepidine was ultimately withdrawn, whereupon liver tests fell to normal within 4 weeks. There was a recurrence of liver injury within 2 to 6 weeks of restarting another calcium channel blocker with a similar pattern of liver test abnormalities and a similar rapid improvement upon stopping. Both nifedipine and amlodipine are dihydropyridines, but there structures are dissimilar.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Amlodipine – Generic, Norvasc®

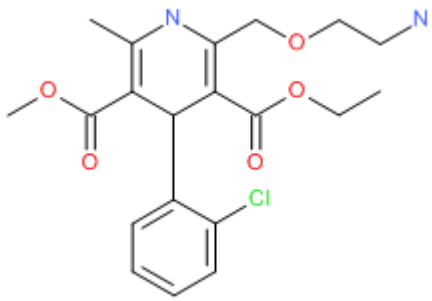
DRUG CLASS

Cardiovascular Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Amlodipine	88150-42-9	C20-H25-C1-N2-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 01 March 2016

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, diltiazem, nifedipine, bepridil and verapamil have been incriminated in instances of hepatic injury; amlodipine is 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; amlodipine 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).

Osterloh I. The safety of amlodipine. Am Heart J 1989; 118:1114-9. PubMed PMID: 2573265.

(Analysis of adverse events in a pooled database of 2495 patients treated with amlodipine and ~1800 controls reported similar rate of ALT elevations with amlodipine [4.3%] as with hydrochlorthiazine [6.3%], and no serious liver toxicity).

de Luis DA, Aller R, Moreira V. Hepatic toxicity and amlodipine. Med Clin (Barcelona). 1998; 110: 638-9 [Spanish]. PubMed PMID: 9656204.

(66 year old man developed serum enzyme elevations 3 months after starting amlodipine [bilirubin normal, ALT 211 U/L, Alk P 369 U/L], resolving within 2 months of stopping).

Basile C, Mascia E. Dihydropyridine calcium channel blockers: a rare and reversible cause of hepatotoxicity with cholestasis in a CAPD patient. Nephrol Dial Transplant 1999; 14: 2776-7. PubMed PMID: 10534534.

(76 year old man developed jaundice 3 years after starting nifedipine [bilirubin 6.2 mg/dL, ALT 79 U/L, Alk P 955 U/L], resolving within 1 month of stopping and recurring within 6 weeks of starting amlodipine [bilirubin 6.3 mg/dL, ALT 74 U/L, Alk P 398 U/L], resolving in 3 weeks: Case 1).

Lafuente NG. Calcium channel blockers and hepatotoxicity. Am J Gastroenterol 2000; 95: 2145. PubMed PMID: 10950093.

(69 year old developed jaundice 10 months after starting amlodipine [bilirubin 4.0 mg/dL, ALT 256 U/L, Alk P 344 U/L]; subsequent switching to diltiazem caused a similar pattern of injury after 5 months [bilirubin 3.3 mg/dL, ALT 355 U/L, Alk P 415 U/L], resolving in several weeks of stopping).

Khemissa-Akouz F, Ouguergouz F, Sulem P, Tkoub el M, Vaucher E. Amlodipine-induced acute hepatitis. Gastroenterol Clin Biol 2002; 26: 637-8. French. PubMed PMID: 12193867.

(77 year old man developed jaundice one month after starting amlopidine [bilirubin 7.4 mg/dL, ALT 30 times ULN, Alk P 2 times ULN, ANA positive], resolving within 8 weeks of stopping).

Lopez Vivancos J, Bara Olivan B, Muniz Garcia R. [Toxic hepatitis caused by amlodipine] Gastroenterol Hepatol 2002; 25: 112. Spanish. PubMed PMID: 11841767.

(66 year old man developed asymptomatic enzyme elevations 2 months after starting amlodipine [bilirubin normal, ALT 267 rising to 694 U/L, Alk P 367 U/L], resolving within 3 months of stopping).

Zinsser P, Meyer-Wyss B, Rich P. Hepatotoxicity induced by celecoxib and amlodipine. Swiss Med Wkly 2004; 134:201. PubMed PMID: 15106034.

(87 year old woman developed jaundice and pruritus after several years of amlodipine therapy [bilirubin 20.8 mg/dL, ALT 300 U/L, Alk P 1019 U/L]; after withdrawal she began to recover, but then developed urosepsis and died 3 weeks after presentation).

ALLHAT. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981-97. PubMed PMID: 12479763.

(Large controlled trial of antihypertensive agents including amlodipine which included 33,357 participants; no mention of ALT elevations or liver related adverse events).

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).

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 PMID: 16165719.

(Summary of 25 years of adverse drug reaction reporting in Sweden identified 103 cases of drug induced acute liver failure; only one case was possibly linked to a calcium channel blocker--felodipine).

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 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, but amlodipine was not implicated in any case, despite being among the top 10 most commonly prescribed drugs in Iceland).

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 amlodipine or other calcium channel blockers).

Demirci H, Polat Z, Kantarcioglu M, Kekilli M, Uygun A, Bagci S. Short-term amlodipine induced liver injury : an extremely rare acute complication. Acta Gastroenterol Belg 2013; 76 (4): 441. PubMed PMID: 24592551.

(46 year old man was found to have abnormal liver tests one week after switching from ramipril to amlodipine [bilirubin 1.4 mg/dL, ALT 923 U/L, Alk P 102 U/L, INR 1.02], resolving within 3 weeks of stopping).

Hammerstrom AE. Possible amlodipine-induced hepatotoxicity after stem cell transplant. Ann Pharmacother 2015; 49: 135-9. PubMed PMID: 25239629.

(34 year old man with leukemia and graft-vs-host disease after hematopoietic cell transplant developed ALT and AST elevations without jaundice a few days after starting high doses of methylprednisolone and amlodipine [for hypertension], values improving wihtin two weeks of stopping amlodipine and decreasing the dose of corticosteroids).

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, amlodipine was implicated as probable in one case and as definite or highly likely in none).