Case Report

Losartan-induced Ischemic Hepatocellular Hepatotoxicity: A Case Report and Literature Review

Moh'd Z. Al-Halawani, Mohammad Thawabi, Fady Asslo, Hamid Shaaban, Fayez Shamoon, Walid J. Baddoura

Department of Internal Medicine, St. Michael's Medical Center, Seton Hall University School of Health and Medical Sciences, South Orange, NJ, USA

Abstract

With the increasing use of various medications and supplements nowadays, the incidence of abnormal liver function tests and frank hepatic injury is has been increasing. Medications are now considered one of the most common causes of acute hepatic failure in the United States. Losartan was the first angiotensin 1 (AT1) receptor blocker approved by FDA for the treatment of arterial hypertension. It is a well-tolerated medication with few significant adverse effects. However, losartan-related hepatotoxicity has been reported rarely. We report a case of acute hepatic injury in an adult patient treated with losartan as a monotherapy for arterial hypertension.

Keywords: Drug-induced liver injury, hepatitis, losartan

Introduction

Losartan was the first angiotensin 1 (AT1) receptor blocker approved by Food and Drug Administration (FDA) for the treatment of arterial hypertension. It is a well-tolerated medication with few significant adverse effects. However, losartan-related hepatotoxicity has been reported rarely. We report a case of acute hepatic injury in an adult patient treated with losartan as a monotherapy for arterial hypertension.

Case Report

A 65-year-old Hispanic female with a medical history of hypertension presented with acute abdominal pain associated with nausea and nonbilious emesis of 2 days duration. The pain was not associated with fever, chills, or jaundice. Four months prior to her presentation, she was started on losartan 50 mg monotherapy for her hypertension. She denied taking any other medications or supplements. The patient had no history of tobacco smoking or alcohol intake. On review of systems, the patient denied any episodes of palpitation or light-headedness in the past. Physical examination was remarkable for epigastric and right upper quadrant tenderness. Initial laboratory results revealed elevated liver enzymes, with aspartate aminotransferase 1018 IU/L (Normal 15-41 IU/L), alanine transaminase 1184 IU/L (normal 14-54 IU/L), alkaline phosphatase (ALP) 142 IU/L (Normal 38-126 IU/L), bilirubin total 2.7 mg/dL (normal 0.4-2.0 mg/dL), bilirubin direct 1.3 mg/dL (normal 0.1–0.5 mg/dL), with normal levels of total protein, albumin, and prothrombin time. On further laboratory work-up, the patient had normal serum levels of amylase and lipase, negative viral hepatitis (A, B and C) panel, nondetectable acetaminophen serum level, undetectable antinuclear antibody and anti-smooth muscle antibody titers, and normal white cell and eosinophilic counts.

Hepatobiliary iminodiacetic acid/hepatobiliary scan was done and revealed a patent cystic duct; and a magnetic resonance cholangiopancreatography showed normal common bile duct diameter without any filling defects.

The decision was made to hold losartan on admission as it was the only medication she was exposed to. During her hospital stay, the clinical symptoms and laboratory findings improved rapidly within the first 4 days of hospitalization [Table 1]. The patient underwent liver biopsy on day 8. Of note, liver biopsy revealed normal hepatic tissue without abnormal findings. The patient was discharged home on the 9th day without re-challenge with losartan.

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/2249-4863.141635

Address for correspondence: Dr. Hamid Shaaban, Department of Internal Medicine, Saint Michael's Medical Center, 111 Central Avenue, Newark, NJ 07102, USA.
E-mail: hamidshaaban@gmail.com

Discussion

Losartan was the first AT1 receptor blocker to be approved by FDA in 1995 for the treatment of arterial hypertension, reduction of the stroke risks in patients with hypertension or left ventricular hypertrophy, and treatment of diabetic nephropathy. In addition, losartan has other beneficial effects not seen in other medications of the same class such as uricosurea and attenuation of platelet aggregation.[1] Losartan was initially evaluated for its safety in 4058 patients with no recorded hepatotoxicity. However, postmarketing data reveals that losartan has been associated with occasional elevation of liver enzymes.[2]

Drug related hepatotoxicity is a fairly uncommon problem, as it occurs in one in 10,000-100,000 patients using prescribed medications.[3] However, it is now considered as one of the most common causes of acute liver failure in the United States.[4] The clinical course of drug related hepatic injury can be described as hepatocellular, cholestatic, or mixed depending on the clinical symptoms, laboratory profiles and/or histological findings. A hepatocellular injury is characterized by a disproportionate elevation of aminotransferases when compared to ALP, while in cholestatic injury there is a disproportionate elevation of ALP when compared to aminotransferases. Mixed injury is a combination of both. Liver biopsy has been considered as an important assist in the diagnosis of drug related hepatic injury, however, its role in the diagnosis and causality assessment is unclear.[4]

Different host-related, genetic and environmental risk factors play a role in drug related hepatotoxicity. Other risk factors include age, gender, race, tobacco smoke, alcohol intake and co-administration of other medications. However, the effects of these factors vary between different medications, and are not helpful in assessing the likelihood of drug related hepatotoxicity in individual cases.[5]

Discontinuation of the offending agent, dechallenge, is the first step once the diagnosis of drug related hepatotoxicity is suspected. Improvement can be seen within hours or days after stopping the medication. In minority of patients, acute liver failure may occur, which require emergent liver transplant. Re-challenge with the same medication is discouraged since it may lead to recurrent hepatic injury and possible hepatic failure.

To the present date, drug-induced hepatic injury in association with angiotensin receptor blockers (ARBs) use was reported in 17 cases; 5 cases with losartan use, 5 cases with irbesartan use, 4 cases with candesartan use and 3 cases with valsartan use. The most common pattern of the liver injury was hepatocellular; however, cholestatic and mixed patterns were also observed. The mechanism of liver injury was not well defined, but mostly resembled an idiosyncratic reaction. Onset of hepatotoxicity was variable, consisting with idiosyncratic reactions and arising as early as 8 days and up to 6 months after therapy initiation with an ARB. Normalization of liver enzymes was seen on average between 2 and 4 months after stopping the medication[6-11] [Table 2].

In our case, the patient had a hepatocellular pattern of injury as evident by the marked elevation of aminotransferases, reaching

Table 1: Pattern of liver enzymes during the hospital stay

Liver function parameters	Day 1	Day 2	Day 3	Day 4
ALT (IU/L)	1184	682	342	266
AST (IU/L)	1018	231	70	42
ALP (IU/L)	142	132	110	94
Total bilirubin (mg/dL)	2.7	2.3	0.9	0.8

ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase

Table 2: Case reports of angiotensin receptor blockers related hepatotoxicity

Case number	Drug/dose	Age/sex	Onset of symptoms	ALT (IU/L)	AST (IU/L)	Total bilirubin (mg/dL)	ALP (IU/L)	Biopsy	Re-challenge
Our case	Losartan/50 mg	65/female	4 months	1184	1018	2.7	142	No	No
1 [7]	Losartan/50 mg	55/female	3 weeks	650	635	1.3	396	No	No
2 [7]	Losartan/50 mg	46/female	3 months	311	300	NA	NA	No	No
3 [8]	Losartan/50 mg	46/male	1 month	2574	2042	9.6	738	No	Yes
4 [9]	Losartan/150 mg	77/male	3 weeks	410	115	1.7	Normal	Yes	No
5 [10]	Losartan/50 mg	52/female	5 months	941	1093	8.9	419	Yes	Yes
6 [11]	Irbesartan/300 mg	62/female	1 month	NA	177	23.6	3173	Yes	No
7 [12]	Irbesartan/300 mg	56/male	8 days	2646	1438	7.5	305	yes	No
8 [13]	Irbesartan/300 mg	59/NA	20 days	1378	1347	8.5	244	No	No
9 [14]	Irbesartan/300 mg	69/male	1 month	1449	821	31	515	Yes	No
10 [15]	Irbesartan/150 mg	51/female	3 weeks	890	237	NA	NA	No	No
11 [16]	Candesartan/NA	70/female	2 weeks	244	441	21	221	No	No
12 [17]	Candesartan/16 mg	41/female	5-6 months	2700	1600	20	321	No	No
13 [18]	Candesartan/16 mg	61/female	1 month	918	1367	15.9	142	Yes	No
14 [19]	Candesartan/16 mg	82/male	3 weeks	272	111	8.2	1045	No	No
15 [20]	Valsartan/80 mg	54/female	5 months	1664	738	23.5	385	Yes	No
16 [21]	Valsartan/NA	52/female	1 month	780	1292	4.5	1840	No	No
17 [22]	Valsartan/80 mg	47/male	2 weeks	776	360	4.8	268	No	No

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase

around 50 times the upper normal limit, with disproportionate elevation in bilirubin and ALP, which were minimally elevated making any extra hepatic obstruction unlikely. Hepatocellular injury with this high magnitude of aminotransferases elevation reaching >50 times the upper normal limit is usually seen with ischemic hepatopathy. Other causes of hepatocellular injury with marked aminotransferases elevation such as acute viral hepatitis, acetaminophen toxicity, autoimmune hepatitis, alcoholic hepatitis, Wilson disease, malignant infiltration, biliary obstruction, and sepsis were excluded by patient's presentation and diagnostic investigations. The temporal relationship between the onset of drug intake, the clinical presentation, the rapid clinical recovery and laboratory normalization after losartan discontinuation, with ruling out other causes of acute hepatitis are highly suggestive of a losartan-related liver injury. Applying the Council of International Organizations of Medical Science/ Roussel Uclaf Causality Assessment Method scale for causality assessment of drug-induced hepatotoxicity yields >8 points for this reaction falling in the "highly probable" category.[12]

In summary, losartan and other ARBs are well-tolerated commonly used medications. However, in the presence of an unexplained liver injury, the possibility of drug related hepatotoxicity should be always ruled out in patients treated with losartan or other ARBs despite its rarity. To the best of our knowledge, we are reporting the 6th case of losartan-induced hepatitis and possibly the first report of a losartan-induced ischemic liver injury in the adult population.

References

1. Ripley E, Hirsch A. Fifteen years of losartan: What have we learned about losartan that can benefit chronic kidney disease patients? Int J Nephrol Renovasc Dis 2010;3:93-8.
2. Cozaar prescribing information by Merck and Co., Inc. Available from: http://www.merck.com/product/usa/pi_circulars/c/cozaar/cozaar_pi.pdf. [Last revised on October 2013; last accessed on May 2014].
3. Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis 2002;22:145-55.
4. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003;349:474-85.
5. Fontana RJ, Seeff LB, Andrade RJ, Björnsson E, Day CP, Serrano J, *et al.* Standardization of nomenclature and causality assessment in drug-induced liver injury: Summary of a clinical research workshop. Hepatology 2010;52:730-42.
6. Nygaard B, Strandgaard S. Marked hepatotoxicity associated with losartan treatment. Blood Press 1996;5:190-1.
7. Bosch X. Losartan-induced hepatotoxicity. JAMA 1997;278:1572.
8. Tabak F, Mert A, Ozaras R, Biyikli M, Ozturk R, Ozbay G, *et al.* Losartan-induced hepatic injury. J Clin Gastroenterol 2002;34:585-6.
9. Andrade RJ, Lucena MI, Santalla F. Hepatic injury associated with losartan. Ann Pharmacother 1998;32:1371.
10. Hariraj R, Stoner E, Jader S, Preston DM. Drug points: Prolonged cholestasis associated with irbesartan. BMJ 2000;321:547.
11. Andrade RJ, Lucena MI, Fernández MC, Vega JL, García-Cortés M, Casado M, *et al.* Cholestatic hepatitis related to use of irbesartan: A case report and a literature review of angiotensin II antagonist-associated hepatotoxicity. Eur J Gastroenterol Hepatol 2002;14:887-90.
12. 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;46:1323-30.

How to cite this article: Al-Halawani MZ, Thawabi M, Asslo F, Shaaban H, Shamoon F, Baddoura WJ. Losartan-induced ischemic hepatocellular hepatotoxicity: A case report and literature review. J Fam Med Primary Care 2014;3:272-4.

Source of Support: Nil. **Conflict of Interest:** None declared.