

A possible increase in liver enzymes due to amlodipine: A case report

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Abstract

Amlodipine is a commonly prescribed antihypertensive drug, well tolerated and has rarely been attributed as a cause for elevated liver enzymes. Here, we present a 47-year-old male patient known to be hypertensive and admitted to our rehabilitation facility after an acute stroke. During his stay, amlodipine was started in addition to other antihypertensive medications to control his blood pressure. His liver transaminases after 4 days (notably alanine aminotransferase) were found to be markedly elevated. After reviewing the medications and investigating probable causes, amlodipine was suspended. After 5 days of suspending amlodipine, the transaminases started to trend downward. The Naranjo Adverse Drug Reaction Probability Scale and the Roussel Uclaf Causality Assessment Method were performed to assess causality in this suspected idiosyncratic drug-induced liver injury case. Both the scores denoted a probable amlodipine-induced liver injury. Previous case reports related to amlodipine-induced liver injury are mentioned and presented in the table below. In conclusion, amlodipine, though not well known to be hepatotoxic, can induce liver enzyme elevations in an idiosyncratic manner.

Keywords

Gastroenterology/hepatology, pharmacoepidemiology/drug safety

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Introduction

Drug-induced liver injury (DILI) is a drug reaction which can be potentially life-threatening, with features ranging from acute liver failure, jaundice and even culminating in death. The DILI is seen to occur between 5 and 90 days after drug ingestion.¹

Antimicrobials, antiepileptics, and herbal and dietary supplements are the most common therapeutic classes to cause DILI in the Western world.²

The estimated incidence in DILI is between 10 and 15 per 10,000 to 100,000 of persons exposed to prescription medications.^{3,4} Moreover, the most commonly cited cause for withdrawal of medications from the marketplace is secondary to DILI.⁵

DILI can be either intrinsic or idiosyncratic. Intrinsic DILI refers to injury with known hepatotoxic drugs in high doses, for example, acetaminophen, while idiosyncratic DILI (iDILI) occurs with agents not associated with liver injury and not dose-dependent.⁶ iDILI has been attributed to host susceptibility and environmental factors and presents with a wide variability in presentation, pattern of injury, latency and

severity. The presentations differ widely between drugs and even with the same drug.⁷ In our case report, we consider the DILI with amlodipine as an idiosyncratic reaction.

Amlodipine is a long-acting third-generation di-hydropyridine calcium channel blocker that acts through inhibition of calcium influx into vascular smooth muscle cells and myocardial cells, resulting in decreased peripheral vascular resistance.⁸

It was approved in the United States in 1992 and is widely in use, with numerous prescriptions filled yearly.⁹ Amlodipine is generally well tolerated with side effects which are due to its vasodilating properties. These include headache, flushing, dizziness, fatigue, nausea, diarrhea, palpitations, peripheral edema and rash.⁹

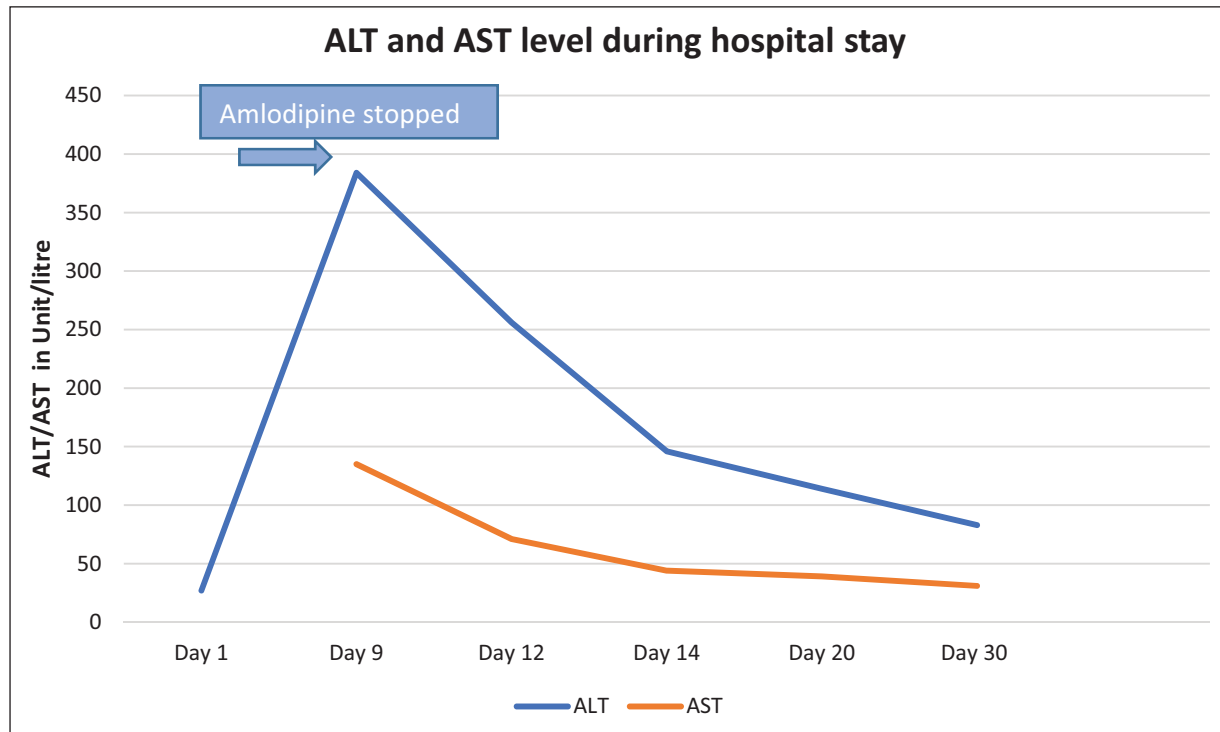
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Graph 1. AST and ALT trend after amlodipine withdrawal.

Amlodipine has rarely been attributed to increased liver enzymes.⁹ A search was done on different databases (MEDLINE, EMBASE and Cumulative Index of Nursing and Allied Health Literature) with the following keywords: Amlodipine, increase liver enzyme, acute liver injury and drug induced liver injury. Few published case reports are found on amlodipine hepatotoxicity.¹⁰⁻¹⁷ A search in the database 'LiverTox' identified only one report on amlodipine hepatotoxicity.¹⁷

We encountered an unusual case of iDILI in our patient in the stroke ward, which we attribute to amlodipine, prescribed for the management of hypertension.

Case presentation

Our case is of a 47-year-old male carpenter, known to be hypertensive since 2 years, but not compliant to his prescribed medication of enalapril. No history of recent infections, drug or alcohol consumption was given by the patient. He was admitted to emergency unit after left-sided weakness of upper and lower limbs, dysarthria and facial palsy. Blood pressure on presentation was 213/117 mmHg, which later lowered after labetalol infusion and hydralazine administration.

Computerized tomography scan revealed a right basal ganglia bleed of size 5×2 cm², and further management was done in the acute stroke unit.

The patient's blood pressure improved on the second day after admission, and intravenous labetalol and hydralazine were discontinued; the blood pressure was maintained with

the tablet enalapril. On day 4 after admission, 5 mg of amlodipine was started in addition to enalapril. The labs on initial admission revealed the following: total bilirubin, 10 μ mol/L; albumin, 37; and alanine transaminase (ALT), 27 U/L; alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were not checked at the time, and electrolytes, renal parameters and coagulation profile were normal.

After stabilization, by day 6, he was transferred for rehabilitation. The transfer medications comprised of 5 mg of amlodipine orally daily, 5 mg of enalapril orally daily, 40 mg of enoxaparin subcutaneous daily and 50,000 U of vitamin D2 (Ergocalciferol) orally every week.

Routine labs were repeated on the seventh day after the initial admission from acute care.

The results showed high ALT and AST at 449 and 271 U/L, respectively (with the upper limit of normal (ULN) range of laboratory ALT at 55 U/L and AST at 34 U/L). Total bilirubin was normal at 15 μ mol/L and the international normalized ratio (INR) was 1.2 (normal range). The calculated ALT/ALP ratio was 3, signifying a mixed picture of liver injury.

The patient did not report any symptoms of nausea, vomiting or abdominal pain. No rash, fever or enlarged lymph nodes were noted. He remained stable clinically, actively participating in his physical therapy programs. He denied alcohol consumption or smoking and did not give history of using herbal medications. No medications were started or adjusted during this time.

Labs were performed after 2 days which revealed the following: ALP at 133 U/L, ALT at 384 U/L and AST at 135 U/L.

Patient's medications and other causes for liver injury were evaluated. Amlodipine was suspended as it was the last medication to be introduced to the patient's medication list.

The repeated liver function showed an improvement after 5 days as illustrated in Graph 1.

Viral hepatitis serologies were negative for hepatitis A IgM antibody, hepatitis C antibody and hepatitis B surface antigen. The hepatitis E IgG antibody was reported as positive with hepatitis E IgM as negative, indicating a past infection. In addition, anti-mitochondrial antibody, anti-liver kidney microsomal antibody and antinuclear antibody were negative. Within 4 weeks of suspending amlodipine, both ALT and AST were decreased to values lower than three times the baseline. The patient was also informed about the effect of amlodipine before his discharge.

Discussion

iDILI is a diagnostic dilemma as no specific blood test, biomarkers or histologic features can identify a drug as the source of acute liver injury.⁶ The diagnosis is made upon clinical suspicion and exclusion of viral/autoimmune hepatitis and biliary obstruction, among others.¹⁸ A clinical history is also important to identify herbal, complementary medications and alcohol consumption.¹⁸

DILI is classified as hepatocellular, cholestatic or mixed types based on the level of transaminases, ALP and the ratio (R) of baseline ALT to baseline ALP. In hepatocellular-type DILI, ALT is ≥ 3 ULN, while $R \geq 5$; in cholestatic-type DILI, ALP is ≥ 2 ULN and $R \leq 2$; and in mixed-type DILI, ALT is > 3 ULN and ALP is > 2 ULN with $R > 2 < 5$. However, the degree of elevation in liver enzymes has poor correlation with severity of liver disease, and hepatitis patterns can vary along the course of time.¹⁸ Based on the lab values, our patient had a mixed-type DILI.

To aid in the diagnosis of DILI, a number of standard causality assessment methods have been developed. The Naranjo Adverse Drug Reaction Probability Scale (NADRPS), one of the earlier proposed score for assessment of adverse drug reactions, is commonly used.¹⁹ Its scores range from -4 to $+13$, where a score > 9 indicates a definite reaction; $5-8$ probable; $1-4$, possible; and 0 or less, doubtful.¹⁹

NADRPS, though easy to use, is not specifically developed for DILI diagnosis and has a lower predictive value.²⁰ The Council for International Organizations of Medical Sciences (CIOMS) or Roussel Uclaf Causality Assessment Method (RUCAM) is a standardized specific causality assessment in drug-induced or herbal-induced hepatotoxicity and is recommended as a guide to establish causality for suspected DILI.²¹ Its score below 3 is indicated as unlikely, $4-5$ as possible, $6-8$ as probable, and more than 8 as highly probable hepatotoxicity.

The CIOMS score was calculated at 6 for the patient, denoting a probable DILI.²¹ The NADRPS for the patient scored at 8 , signifying a probable DILI.

Clinicians should also keep in mind the phenomenon of adaptation or tolerance, which refers to the phenomenon of a drug causing mild elevations in ALT or AST.²² The elevated enzymes may then return to normal or remain at the same mildly elevated level while on the suspected medication. These elevations are asymptomatic and do not affect liver function.²² Elevated liver enzymes without symptoms may be part of an adaptation process and transaminases are usually less than five times the ULN.¹⁸ We assume that our patient did not have a tolerance phenomenon as his transaminases were eight times the ULN.

The concomitant medications given to the patient along with amlodipine were enalapril, vitamin D and enoxaparin. Vitamin D and enalapril are not commonly known to cause acute liver injury when searched in 'LiverTox' database. Review of case reports describes enalapril to cause a cholestatic liver injury.²³

Low-molecular-weight heparins (LMWHs) have been associated with elevated liver transaminases in $4\%-13\%$ of the patients.²⁴ The mechanism of action of liver injury is proposed to have a direct toxic effect on the hepatocytes which have been reproduced in animal models. LMWHs especially in the higher doses have been associated with transaminitis, more than five times the ULN. These elevations resolve once the LMWH has been suspended. The patient had a mixed picture of hepatic injury, with his enoxaparin given in a low dose for the prophylaxis of deep vein thrombosis. And despite not withholding the enoxaparin, the liver enzymes normalized, implying that enoxaparin is likely not the causative factor for iDILI.

A literature search done showed only a few case reports on amlodipine-associated elevations of liver enzymes. In the case reports by Lafuente and Egea, and Zinsser et al.,¹⁴ the patients had a cholestatic picture with a larger rise in bilirubin compared to our patient who solely had elevations in transaminases.¹⁰⁻¹⁴ The report by Demirci et al. shares similarities with our patient where amlodipine caused an isolated rise in ALT and AST within 1 week of starting the drug.¹⁶

The latency period from the introduction of amlodipine to the detection of the elevated liver enzymes is variable, ranging from 2 days to several years as described in Table 1.

AE Hammerstrom reported that after 48 h of amlodipine administration, the patient developed transaminitis of hepatocellular injury,¹⁵ while Zinsser et al. describe a patient who, after several years on amlodipine, developed a drug-related liver injury.

Amlodipine hepatotoxicity is not clearly understood, but the injury is likely due to the production of toxic intermediates in its metabolism.⁹ After screening concomitant drugs and ruling out other probable causes of liver injury, amlodipine was suspected. On suspending amlodipine, there was a marked improvement in liver enzymes, which normalized a month after initial elevation was seen. In our patient, considering the treatment history and the development of elevated transaminases soon after the initiation of amlodipine administration implies that it was liable for iDILI.

Table 1. Comparison of case reports of Amlodipine associated DILI.

| Case | Reference | Age (years) | Sex | Dose/regimen | Time to liver injury | Outcome | Type of injury | ALT | AST | ALP | Total bilirubin | Liver biopsy /histology |
|------|---------------------------------|-------------|-----|-----------------------------|----------------------|--|-----------------------|----------|----------|----------|-----------------|---|
| 1 | Hammerstrom ¹⁵ | 34 | M | Amlodipine 5 mg once | 2 days | LFT normalized | Hepatocellular injury | 630 IU/L | 269 IU/L | Normal | Normal | Hepatocellular injury with a possibility of drug injury |
| 2 | Demirci et al. ¹⁶ | 46 | M | Amlodipine 10 mg once | 1 week | LFT normalized | Hepatocellular injury | 519 IU/L | 923 IU/L | 102 IU/L | 1.44 mg/dL | Revealed lesions consistent with drug-induced hepatotoxicity |
| 3 | Zinsser et al. ¹⁴ | 87 | F | NA | Several years | LFT decreased; patient died from urosepsis | Hepatocellular injury | 300 U/L | 291 U/L | 1019 U/L | 20 µmol/L | Severe intra-hepatocellular and canalicular cholestasis with moderate inflammatory infiltrates without necrosis |
| 4 | Lafuente and Egea ¹¹ | N/A | N/A | Amlodipine 5 mg twice daily | 10 months | LFT normalized | N/A | 256 IU/L | 144 IU/L | N/A | 4 mg/dL | Not done |

ALT: alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; LFT: liver function test; NA: not available.

Summary

In conclusion, amlodipine, though not considered as hepatotoxic, can be attributed as a rare cause of iDILI. Clinicians can keep this in mind when approaching a patient with suspected iDILI. Further reports will also help to corroborate amlodipine-related liver injury.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

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Informed consent

Informed written consent for patient information to be published in this article was obtained retrospectively from the patient.

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