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Case Report

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# HYPERACUTE HYDRALAZINE INDUCED LIVER INJURY

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## ABSTRACT

Drug induced liver injury secondary to Hydralazine use, although rare, has been documented. Of those cases described, the time course for liver injury is either a short (2-6 weeks) or long (2-12 months) latency period after starting the drug. We report a case of a patient who, after being treated with Hydralazine, developed an acute liver injury on a timeline that wasn't previously described. A 64-year-old African American female with a past medical history remarkable for coronary artery disease and hypertension presented to our hospital complaining of chest pain. She was admitted for management of NSTEMI. During the course of her stay, the patient was noted to have hypertensive urgency and antihypertensive regimen including Hydralazine was started. After receiving multiple doses of hydralazine, the liver transaminases began to trend upward, peaking within 24 hours of starting the drug. Establishing causality of liver injury to hydralazine was done by using the RUCAM scoring system. By doing so, this case presents the possibility of a "hyperacute" timeline for Hydralazine induced liver damage, in this case, within 24 hours of starting hydralazine.

**KEYWORDS:** Hydralazine, drug-induced, liver injury, DILI, autoimmune, hepatitis.

## INTRODUCTION

Hydralazine is a vasodilator that is indicated for the treatment of hypertension. It acts primarily as a direct vasodilator of arteries and arterioles by causing smooth muscle relaxation. Common adverse effects of hydralazine include headache, reflex tachycardia, and drug-induced Lupus. However, acute autoimmune hepatotoxicity is a rare side effect with few reported cases.

## CASE REPORT

A 64-year-old African American female with a past medical history remarkable for coronary artery disease, anomalous right coronary artery arising from the left coronary sinus, and hypertension presented to our hospital complaining of chest pain. The patient described that she had two episodes of intense angina-type chest pain over the past 24 hours. In the ED, the patient was afebrile with a blood pressure of 182/93 mm Hg, a regular heart rate of 64 bpm, a respiratory rate of 21 rpm, and an oxygen saturation of 99% on room air. On physical exam she was drowsy, lethargic, and had a smell of alcohol on her breath. Her cardiovascular exam was benign with regular rate and rhythm and radial pulses 2+ bilaterally. Her gastrointestinal examination showed a non-distended abdomen, normoactive bowel sounds, and no tenderness to palpation. Her labs on admission were notable for elevated troponin I levels of 0.466 ng/mL, 0.728 ng/mL, and finally 0.770 ng/mL. Her AST, ALT, and ALP were 32 U/L, 21 U/L, and 70 U/L, respectively, and her alcohol level was 283 mg/dL. Home medications at the time of admission included aspirin 81 mg daily, atorvastatin 80 mg daily, hydrochlorothiazide 25 mg daily, and sublingual nitroglycerin 0.4 mg PRN. The patient had reported nonadherence with her medications. During the course of her stay, the patients' blood pressures were elevated with systolic pressures ranging from 190 - 204 mm Hg. Medication treatment that was initially started on hospital day 2 included hydralazine 50 mg orally PRN, amlodipine 10 mg orally daily, captopril 25 mg orally every 8 hours, and metoprolol tartrate 12.5 mg every 8 hours. On day 3 patient's blood pressures were still not at goal. So her antihypertensive regimen was escalated by changing metoprolol tartrate to carvedilol 3.125 mg orally twice daily and increasing the dose of captopril to 50 mg. Additionally, the hydralazine dosing was changed to 50 mg orally every 6 hours. Following these changes, her blood pressures trended down to a range of 179 -188 mm Hg. Later, additions to her hypertension regimen were made, which included hydrochlorothiazide 25 mg orally daily and transdermal nitroglycerin 0.1 mg. Both of these medications failed to control her pressures.

After receiving several doses of hydralazine, the liver transaminases began to trend upward, peaking at AST

and ALT of 378 and 253, respectively (Table 1, Figure 1). The atorvastatin that the patient had been on was discontinued in response to this. Despite discontinuing the common hepatotoxic agents, the LFTs continued to trend up the following day: the AST, ALT, and ALP were 327 U/L, 202 U/L, and 179 U/L, respectively. At this point, our team consulted the gastroenterology service and obtained a right upper quadrant abdominal ultrasound. The finalized impression was described as a normal size liver with smooth echotexture and no evidence of advanced cirrhosis or hepatic steatosis, and no cholelithiasis or acute cholecystitis. A hepatitis work up checking for Hepatitis A, Hepatitis B and Hepatitis C was also ordered which was negative. The consult team provided a recommendation of stopping the hydralazine due to suspicion of a drug-induced autoimmune hepatitis etiology. Antinuclear antibody (ANA) was subsequently ordered and resulted positive in a speckled pattern. The ANA titer was 1:160. Other markers associated with autoimmune hepatitis were negative, which included Anti-Smith antibody, Anti-Mitochondirial antibody and a Liver-Kidney Microsome Type 1 antibody. After stopping hydralazine, the liver transaminases started to trend downward each day with a final drop in AST, ALT, and ALP of 74%, 35%, and 20%, respectively. The bilirubin levels remained within normal range the entire hospitalization.

## RESULTS

**Table 1: Liver Function Tests over hospital course.**

| | Day1 | Day 2 (Hydralazine Started) | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
|---|---|---|---|---|---|---|---|---|
| AST* (U/L) | 32 | 29 | 59 | 327 | 378 | 100 | 48 | 35 |
| ALT* (U/L) | 21 | 19 | 31 | 202 | 253 | 164 | 104 | 84 |
| Alk Phos* (U/L) | 70 | 74 | 86 | 179 | 207 | 166 | 150 | 131 |
| T. Bili* (mg/dL) | 0.2 | 0.5 | 0.4 | 0.4 | 0.3 | 0.3 | 0.2 | 0.2 |

*Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (Alk Phos), and total bilirubin (T. Bili)

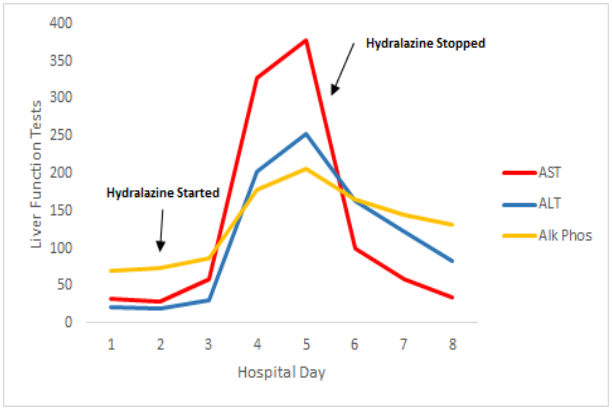


**Fig. 1: Liver Function Tests (AST, ALT, and Alk Phos)* over hospital course.**

### Diagnostics

Ultrasound: liver was normal in size with smooth contours and normal parenchyma. No intrahepatic or extrahepatic biliary ductal dilation. Common bile duct was normal size (0.3 cm). No cholelithiasis or acute cholecystitis. Duplex analysis showed normal hepatic, portal, and splenic vessel flow.

## DISCUSSION

Drug induced liver injury (DILI) accounts for up to 30% of cases of acute hepatitis and is the leading cause of acute liver injury in the United States.[1] In most cases, there is a difficulty in establishing causality of the offending drug as there are not any specific diagnostic tests which do so. Therefore, we will establish a link between the use of hydralazine in this patient with her hepatic injury by process of exclusion of other possible sources of hepatic injury.

In response to the elevated liver function tests (LFT), our team discontinued the atorvastatin on hospital day 3 to exclude other sources of hepatic injury; no other inpatient medications were sources of possible hepatotoxicity and therefore were continued. Of note, the patient had been taking atorvastatin for years with no previous LFT elevation upon chart review. Despite this discontinuation, on day 4, the labs showed the LFTs were continuing to elevate. It was here that hepatitis A/B panels were ordered, which returned negative as previously stated. With statin-induced liver injury and viral hepatitis excluded, other drug-induced liver injury (DILI) was suspected. To establish causality, we used the RUCAM scale. The calculated score of 9 was consistent with a highly probable likelihood that the hepatotoxicity was secondary to a medication, most likely hydralazine.

With hydralazine being the leading differential as the cause of hepatotoxicity in this case, the timing of the DILI after the start of hydralazine should be addressed. Timing for DILI secondary to hydralazine toxicity has been described based on published case reports and tends to occur in one of two clinical patterns: those with short or long latency periods.[2,3] Evidence of injury usually occurs 2-6 weeks (short latency) after receiving hydralazine, or 2 months to more than a year after (long latency). Short latency presents with liver damage that is generally abrupt and associated with rash, fever, and eosinophilia. Recovery after stopping hydralazine is usually rapid. Cases of long latency tend to have a more subacute onset, can be associated with lupus-like symptoms and autoantibodies, and patients generally recover over a longer period of time. For example, Hassan et al. described a case of a patient who presented 5 months after receiving Hydralazine and recovery

occurred over a period of 4 weeks after stopping the drug.[4]

In our case, the patient did not fit either pattern previously described in other case reports. Hydralazine was started while the patient was in the hospital and an observed hepatocellular pattern of liver injury developed overnight. When compared to the short latency cases described in the literature, our patient presented much more acutely and lacked symptoms of fever, rash, and eosinophilia. Additionally, there were positive ANA antibodies present that overlap with reported cases of patients presenting with long latency of liver damage.

Liver injury is not an uncommon complication for many medications. However, common culprits of drug-induced liver injury have been researched more thoroughly than rare medications. For example, acetaminophen is not only responsible for the greatest number of drug-induced liver injuries, but it is also one of the best studied. Due to its wide availability as an over-the-counter medication, as well as its deleterious side effect, details such as NAPQI mediating hepatocyte death in acetaminophen toxicity, as well as the timeline for liver injury, has been well established in numerous reviews. On the other hand, the data available on the intricacies of a liver injury mechanism in drugs that are uncommon causes of hepatocyte death, such as hydralazine, is much less robust.[5]

## CONCLUSIONS

Our patient showed evidence of hydralazine-induced liver injury with an abnormal timeline of presentation based on the timing of her transaminits with respect to the dosing and resolution of the drug in addition to ruling out other causes of hepatotoxicity. This case suggests there may be more acute forms of liver damage secondary to hydralazine use not previously described.

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