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# Hydralazine

Updated: March 24, 2018.

# OVERVIEW

## Introduction

Hydralazine is a commonly used oral antihypertensive agent that acts by inducing peripheral vasodilation. Hydralazine has been linked to several forms of acute liver injury as well as a lupus-like syndrome.

## Background

Hydralazine (hye dral' a zeen) is a phthalazine derivative and antihypertensive agent which acts by direct relaxation of arteriolar smooth muscle, probably by alteration in intracellular calcium signaling. Hydralazine was one of the first oral antihypertensive medications introduced into clinical medicine and was first used in the late 1950s, but was officially approved for use in the United States in 1984. The vasodilation caused by hydralazine is followed by reflex sympathetic response that may partially reverse its antihypertensive effects. Nevertheless, when combined with other antihypertensive medications, hydralazine is effective in lowering blood pressure and it is still widely used, with more than 2 million prescriptions for hydralazine being filled yearly in the United States. Hydralazine is available in generic forms and under the brand name of Apresoline in tablets of 10, 25, 50 and 100 mg as well as in parenteral forms. The typical dose is 10 mg four times daily initially, with subsequent increases to a maximum of 200 mg daily. Common side effects include dizziness, headache, tachycardia, orthostatic hypotension, flushing, nausea and gastrointestinal upset.

## Hepatotoxicity

Serum aminotransferase elevations during hydralazine therapy are considered uncommon. However, hydralazine has been clearly linked to cases of acute liver injury with jaundice as well as a delayed lupus-like syndrome. Two clinical patterns of hepatic injury have been described, associated with either a short (2 to 6 weeks) or long (2 months to more than a year) latency period. The clinically apparent liver injury is usually hepatocellular, although cholestatic forms have also been reported (Case 1). In cases with a short latency period, rash, fever and eosinophilia are common and the onset is typically abrupt and severe, and recovery is rapid. In cases with a longer latency (Case 2), the onset is more typically insidious, liver biopsy may resemble chronic hepatitis and demonstrate fibrosis, and autoantibodies are often present. The late form of hepatitis may also accompany the lupus-like syndrome that occurs with hydralazine, particularly in high doses when given for 6 months or more. Recovery can be prolonged. Autoantibodies to isoforms of the P450 system (CYP 1A2) have been identified in patients with hepatotoxicity due to the structurally related antihypertensive agent dihydralazine (available in Europe, but not the United States) and which is associated with a higher rate of hepatotoxicity than hydralazine.

Likelihood score: A (well established cause of clinically apparent liver injury).

## Mechanism of Injury

The cause of the acute liver injury due to hydralazine appears to be due to its metabolism to an immunologic adduct that can result in an immunoallergic hepatitis or a more delayed lupus- and/or an autoimmune hepatitis-like syndrome. Hydralazine, like isoniazid, is metabolized by N-acetyltransferase (NAT) and hepatic injury may be more frequent with specific genetic variants in NAT activity.

## Outcome and Management

Fatal instances of liver injury due to hydralazine have been reported, but most cases begin to resolve within a few days of stopping the medication. In patients with signs and symptoms of hypersensitivity, corticosteroids are often used and anecdotal results suggest that they are beneficial in speeding recovery. The duration of therapy with corticosteroids, however, should be kept to a minimum and careful follow up after stopping is prudent. While liver histology can resemble chronic hepatitis and include hepatic fibrosis, persistent injury and vanishing bile duct syndrome have not been reported after hydralazine induced liver injury. Reexposure to hydralazine results in prompt recurrence, that can be severe. There does not appear to be cross reactivity of hepatic injury with other medications or antihypertensive agents, but there may be cross reactivity to other phthalazines such as dihydralazine and possibly to isoniazid.

Drug Class: Antihypertensive Agents

# CASE REPORTS

## Case 1. Rapid onset of acute cholestatic hepatitis due to hydralazine.

[Modified from: Myers JI, Augur NA. Hydralazine-induced cholangitis. Gastroenterology 1984; 87: 1185-8. PubMed Citation]

A 59 year old woman with coronary artery disease and hypertension was started on hydralazine and developed fever, malaise, and right upper quadrant pain 8 days later. She was admitted for suspected cholecystitis, but ultrasound of the abdomen showed no abnormalities of the biliary system. She had no history of alcohol abuse or liver disease and was known to have normal liver tests in the past. On admission, she had leukocytosis, the total serum bilirubin was 5.2 mg/dL, alkaline phosphatase 540 U/L and AST 141 U/L (Table). Hydralazine was stopped and she recovered rapidly. After discharge, she restarted hydralazine on her own and rapidly developed symptoms again with nausea, vomiting, fever and hypotension. She was febrile and jaundiced, but had no rash or eosinophilia. Autoantibodies were negative. She underwent exploratory laparotomy which was unrevealing; the gallbladder was removed but there were no stones and no biliary dilatation by intraoperative cholangiography. A liver biopsy showed intrahepatic cholestasis. She recovered rapidly and three months later, when readmitted for coronary artery bypass surgery, her liver tests were back to baseline values.

### Key Points

| | |
|---|---|
| Medication: | Hydralazine |
| Pattern: | Cholestatic (R=1.1) |
| Severity: | Moderate (3+; jaundice and hospitalization) |
| Latency: | 8 days; 2 days on rechallenge |
| Recovery: | Within 1-3 months |
| Other medications: | None mentioned |

## Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | Pre | 41 | 145 | 0.7 | |
| Developed fever and right upper quadrant pain 8 days after starting hydralazine | | | | | |
| 8 days | 0 | 141 | 540 | 5.2 | US normal |
| 14 days | 4 days | 48 | 141 | 1.7 | |
| Unintentional rechallenge with hydralazine for 1-2 days | | | | | |
| 24 (1 day) | 0 | 92 | 244 | 3.5 | Cholecystectomy |
| 35 (11) days | 10 days | 53 | 237 | 0.7 | |
| 3 months | 3 months | 23 | 127 | 0.6 | |
| **Normal Values** | | **<50** | **<115** | **<1.2** | |

## Comment

An example of hydralazine induced liver injury with a short latency (8 days), mild immunoallergic features (fever) and a cholestatic pattern of liver enzymes. She had immediate recurrence of injury on mistakenly restarting the drug. Patients with drug induced liver injury should be specifically warned about restarting the medication and should specifically search out and discard any residual medication that might still be in home medicine cabinets. The recurrence of jaundice was interpreted as cholecystitis and she underwent an unnecessary cholecystetomy. This example demonstrates how early and accurate diagnosis of drug induced liver injury can help avoid unnecessary, invasive diagnostic or therapeutic interventions.

# Case 2. Cholestatic hepatitis due to hydralazine with delayed onset.

[Modified from: Hassan A, Hammad R, Cucco R, Niranjan S. Hydralazine-induced cholestatic hepatitis. Am J Ther 2009; 16: 371-3. PubMed Citation]

A 63 year old woman with hypertension and end-stage renal disease on dialysis developed epigastric pain and jaundice approximately 12 weeks after starting hydralazine. She had no previous history of liver disease and was known to have normal serum aminotransferase and alkaline phosphatase levels. Abdominal CT scans and magnetic resonance cholangiopancreatography were normal and "no other laboratory evidence of cholestatic jaundice was found." Serum bilirubin levels continued to rise (Table). Hydralazine was suspected as the cause of the liver injury and, indeed, serum enzyme elevations and bilirubin began to fall when it was stopped. Three months later serum bilirubin and alkaline phosphatase had fallen to baseline values.

## Key Points

| | |
|---|---|
| Medication: | Hydralazine |
| Pattern: | Cholestatic (R=1.7) |
| Severity: | Moderate (3+; jaundice and hospitalization) |
| Latency: | 10 weeks according to figure, 5 months according to text |
| Recovery: | 9 weeks |
| Other medications: | None mentioned |

## Laboratory Values

| Time After Starting | Time After Stopping | ALT* (U/L) | Alk P* (U/L) | Bilirubin* (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | Pre | 20 | 175 | 0.8 | Hemodialysis |
| 5 days | 0 | 25 | 180 | 0.5 | |
| Hydralazine (75 mg three times daily) started | | | | | |
| 10 weeks | 0 | 210 | 820 | 3.5 | Admitted for jaundice |
| 11 weeks | 0 | 110 | 740 | 4.1 | Ultrasound normal |
| 12 weeks | 0 | 100 | 760 | 6.2 | MRCP normal |
| Hydralazine stopped | | | | | |
| 13 weeks | 1 week | 50 | 640 | 2.1 | |
| 15 weeks | 3 weeks | 50 | 390 | 1.1 | |
| 18 weeks | 6 weeks | 30 | 210 | 0.6 | |
| 21 weeks | 9 weeks | 20 | 120 | 0.5 | |
| **Normal Values** | | **<40** | **<130** | **<1.2** | |

*Some values estimated from figures 1 and 2.

## Comment

The onset, clinical features, course and prompt improvement with stopping therapy are typical of hydralazine induced liver injury presenting after several months of therapy. Typically, cases with a longer latency period are associated with a hepatocellular pattern of serum enzyme elevations, autoantibodies and often present insidiously with fatigue rather than abrupt onset of fever, rash and jaundice. In this case report, the injury pattern was cholestatic and results of autoantibody testing and immunoglobulin levels were not provided.

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Hydralazine – Generic, Apresoline®

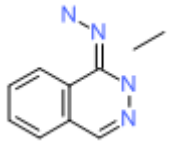
**DRUG CLASS**

Antihypertensive Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Hydralazine | 86-54-4 | C8-H8-N4 |  |

## ANNOTATED BIBLIOGRAPHY

References updated: 24 March 2018


Zimmerman HJ. 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. 655-6.

*(Expert review of hepatotoxicity published in 1999 mentions that more than 50 cases of hepatic injury due to hydralazine had been reported, rates being ~0.5%, usually arising within a few weeks, hepatocellular and accompanied by fever and eosinophilia, rare fatal instances have occurred).*

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic medications. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

*(Review of hydralazine hepatotoxicity, mentions that hydralazine hepatotoxicity is extremely variable manifesting itself with hepatocellular, cholestatic, hypersensitivity, or autoimmune features).*

Michel T, Hoffman BB. Treatment of myocardial ischemia and hypertension. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 745-88.

*(Textbook of pharmacology and therapeutics).*

Jori GP, Peschile C. Hydralazine disease associated with transient granulomas in the liver. A case report. Gastroenterology 1973; 64: 1163-7. PubMed PMID: 4706137.

*(52 year old woman developed fever and arthralgias 6 months after starting hydralazine with 10% eosinophilia, bilirubin 1.2 mg/dL, ALT 85 U/L, Alk P 3 times ULN, granulomas on biopsy, resolving within 6 weeks of stopping as proven by repeat liver biopsy).*

Perry HM. Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. Am J Med 1973; 54: 58-72. PubMed PMID: 4581906.

*(Among 371 patients treated with hydralazine for 2 months to 20 years, late toxic effects developed in 12% resembling lupus or rheumatoid arthritis, clinical hepatitis in 2; almost all were ANA positive and all ultimately resolved after stopping).*

Irias JJ. Hydralazine-induced lupus erythematosus-like syndrome. Am J Dis Child 1975; 129: 862-4. PubMed PMID: 50009.

*(9 year old girl developed arthralgias, fever, splenomegaly and ANA-positivity with normal serum enzymes and no jaundice 9 months after starting hydralazine; symptoms resolved within 1 and serology within 11 months of stopping).*

Knoblauch M, Cueni B, Spycher M, Schmid M. [Dihydralazine-induced acute hepatitis with IgM deficiency]. Schweiz Med Wochenschr 1977; 107: 651-6. German. PubMed PMID: 867010.

*(Two patients, one man and one woman both with IgM deficiency, developed elevations in bilirubin [1.9 and 12.7 mg/dL], ALT [135 and 530 U/L] and Alk P [1-2 times ULN] 6 months and two weeks after starting hydralazine, and both had more rapid recurrence on restarting).*

Bartoli E, Massarelli G, Solinas A, Faedda R, Chiandussi L. Acute hepatitis with bridging necrosis due to hydralazine intake. Report of a case. Arch Intern Med 1979; 139: 698-9. PubMed PMID: 443977.

*(59 year old woman developed abdominal pain and nausea within days of starting hydralazine [bilirubin rising from 1.3 to 8.9 mg/dL, ALT to 150 U/L], improving upon stopping and more severe recurrence on restarting; biopsy showed acute hepatitis with bridging hepatic necrosis, and follow up biopsy on methyldopa was markedly improved).*

Itoh S, Yamaba Y, Ichinoe A, Tsukada Y. Hydralazine-induced liver injury. Dig Dis Sci 1980; 25: 884-7. PubMed PMID: 7438960.

*(68 year old man developed jaundice and fever, 3 years after starting hydralazine [bilirubin 8.1 mg/dL, ALT >300 U/L, Alk P 297 U/L], resolving rapidly on stopping, recurring within 2 weeks of rechallenge; case documented with four liver biopsies).*

Barnett DB, Hudson SA, Golightly PW. Hydralazine-induced hepatitis? Br Med J 1980; 280: 1165-6. PubMed PMID: 7388447.

*(37 year old woman developed nausea 2 weeks after starting hydralazine; restarting led to rise in ALT [11 to 504 U/L] and Alk P [153 to 1077 U/L] within 3 days without jaundice, and with rapid resolution on stopping).*

Mölleken K, Rüger K. [Rare liver damage caused by antihypertensive and anti-arrhythmic agents]. Z Gesamte Inn Med 1980; 35: 296-9. German. PubMed PMID: 7405322.

*(33 year old developed abdominal pain, weakness and jaundice 3-4 weeks after starting dihydralazine [bilirubin 5.7 mg/dL, ALT 295 U/L, Alk P 58, eosinophils 2%], resolving within 3 weeks of stopping).*

Forster HS. Hepatitis from hydralazine. N Engl J Med 1980; 302: 1362. PubMed PMID: 7374684.

*(37 year old man developed malaise 6 months after starting hydralazine [bilirubin normal, ALT 207 U/L, slight Alk P elevation, ANA-positivity], improving on stopping but recurrence of fever, rash and eosinophilia within hours of rechallenge).*

Itoh S, Ichinoe A, Tsukada Y, Itoh Y. Hydralazine-induced hepatitis. Hepatogastroenterology 1981; 28: 13-6. PubMed PMID: 7216134.

*(Three patients, 2 women, 1 man, ages 51-59 years, developed jaundice after 2, 10 and 24 months of hydralazine therapy with submassive necrosis on liver biopsy; resolving slowly).*

Stewart GW, Peart WS, Boylston AW. Obstructive jaundice, pancytopenia and hydralazine. Lancet 1981; 8231: 1207. PubMed PMID: 6112544.

*(63 year old man developed fever and abdominal pain 10 days after starting hydralazine [peak bilirubin 3.8 mg/dL, Alk P 1470 U/L, AST 257 U/L], resolving within two weeks of stopping).*

Mansilla-Tinoco R, Harland SJ, Ryan PJ, Bernstein RM, Dollery CT, Hughes GRV, Bulpitt CJ, et al. Hydralazine antinuclear antibodies and the lupus syndrome. Br Med J 1982; 284: 936-9. PubMed PMID: 6802356.

*(Among 221 patients treated with hydralazine, 60% developed ANA-positivity arising after 2-6 months, lower rate in blacks and rapid acetylators; 7 [3%] developed lupus-like syndrome).*

Pariente EA, Pessayre D, Bernuau J, Degott C, Benhamou JP. Dihydralazine hepatitis: report of a case and review of the literature. Digestion 1983; 27: 47-52. PubMed PMID: 6884586.

*(50 year old developed jaundice 3 months after starting dihydralazine [bilirubin 12.3 mg/dL, AST 68 times ULN, Alk P 1.5 times ULN], and had a severe recurrence upon restarting).*

Roschlau G. [Dihydralazine-induced hepatitis with bridging necrosis. A clinico-pathologic survey of 20 cases]. Zentralbl Allg Pathol 1983; 127: 385-93. German. PubMed PMID: 6880446.

*(20 cases of dihydralazine liver injury, with abrupt onset and jaundice arising at 2-8 weeks or with more insidious onset after 4-12 months; bridging necrosis frequent on liver biopsy; relapse occurs with reexposure with either form).*

Rice D, Burdick CO. Granulomatous hepatitis from hydralazine therapy. Arch Intern Med 1983; 143: 1077. PubMed PMID: 6679226.

*(51 year old woman developed fever and nausea 10 days after starting hydralazine [bilirubin 5.8 mg/dL, ALT 574 U/L, Alk P 212 U/L], biopsy showing granulomas, resolving within a month of stopping).*

Myers JI, Augur NA. Hydralazine-induced cholangitis. Gastroenterology 1984; 87: 1185-8. PubMed PMID: 6479540.

*(59 year old woman developed fever and right upper quadrant pain 8 days after starting hydralazine [bilirubin 5.2 mg/dL, AST 141 U/L, Alk P 540 U/L], with rapid recurrence after inadvertent rechallenge, rapid recovery: Case 1).*

Reinhardt M, Machnik G, Krombholz B, Jahn G. [The so-called dihydralazine hepatitis. A contribution to the pathogenesis]. Dtsch Z Verdau Stoffwechselkr 1985; 45: 283-94. PubMed PMID: 4092653.

*(14 cases of dihydralazine liver injury, 12 women and 2 men; ages 31-84 years, injury arising 1-10 weeks after starting, resolving in all after stopping, liver biopsy usually showing bridging necrosis and two showing fibrosis).*

Kunze KD, Porst H, Tschöpel L. [Morphology and pathogenesis of liver injury produced by dihydralazine, propranolol and ketophenylbutazone]. Zentralbl Allg Pathol 1985; 130: 509-18. PubMed PMID: 3841742.

*(Results of lymphocyte stimulation tests in 28 cases of drug induced liver injury; positive in 18 cases of dihydralazine hepatotoxicity which were also characterized by bridging necrosis and cholangitis on liver biopsy).*

Hod M, Friedman S, Schoenfeld A, Theodor E, Ovadia J. Hydralazine-induced hepatitis in pregnancy. Int J Fertil. 1986; 31: 352-5. PubMed PMID: 2898436.

*(Among 38 women given hydralazine during pregnancy, 5 developed right upper quadrant pain 2-4 weeks after starting [bilirubin 1.5-2.1 mg/dL, AST 280-314 U/L, decrease in platelet counts], resolving within 2 days of Caesarian section and stopping hydralazine, making it unclear whether the HELPP syndrome or drug induced liver injury was the cause).*

Machnik G, Bergert A, Justus J, Kunze P, Müller R, Reinhardt M, Schulz H, et al. [Drug-induced hepatitis after dihydralazine treatment with fatal consequences]. Zentralbl Allg Pathol 1988; 134: 167-77. German. PubMed PMID: 3420978.

*(3 cases of dihydralazine induced liver injury in 60-79 year old hypertensive patients, arising 1-12 months after starting dihydralazine [bilirubin 12.4, 18.1 and 8.3 mg/dL, ALT 5340, 392 and 102 U/L, Alk P 224, 277 and 138 U/L], liver biopsies showing bridging or confluent necrosis, all three dying of complications of hepatic injury).*

Roschlau G, Hass S, Schmehl V. [Chronic drug-induced hepatitis caused by dihydralazine]. Dtsch Z Verdau Stoffwechselkr 1988; 48: 41-6. German. PubMed PMID: 3371237.

*(2 cases; 52 year old woman found to have elevations in ALT and bilirubin 3 years after starting dihydralazine, with biopsy showing chronic hepatitis with bridging fibrosis; 74 year old woman developed jaundice after 2 years of dihydralazine therapy, with biopsy showing chronic hepatitis and bridging fibrosis; symptoms and laboratory abnormalities resolved completely with stopping therapy).*

Shaefer MS, Markin RS, Wood RP, Shaw BW Jr. Hydralazine-induced cholestatic jaundice following liver transplantation. Transplantation 1989; 47: 203-4. PubMed PMID: 2643228.

*(16 year old boy treated with iv hydralazine for hypertension 1-3 days after liver transplantation developed flushing, rash and rise in bilirubin levels, but role of hydralazine versus other factors was unclear).*

Bourdi M, Larrey D, Nataf J, Bernuau J, Pessayre D, Iwasaki M, Guengerich FP, et al. Anti-liver endoplasmic reticulum autoantibodies are directed against human cytochrome P-450IA2. A specific marker of dihydralazine-induced hepatitis. J Clin Invest 1990; 85: 1967-73. PubMed PMID: 2347920.

*(Serum from 5 patients with dihydralazine induced liver injury arising 2-6 months after starting therapy were found to have antibodies to human CYP 1A2, which inhibited its enzymatic activity).*

Roschlau G, Baumgarten R, Fengler JD. [Dihydralazine hepatitis. Morphologic and clinical criteria for diagnosis]. Zentralbl Allg Pathol 1990; 136: 127-34. German. PubMed PMID: 2327183.

*(70 cases of dihydralazine induced hepatitis with confluent or bridging necrosis found between 1981 and 1985; more frequent in women than men).*

Stumpf JL. Fatal hepatotoxicity induced by hydralazine or labetalol. Pharmaco-therapy 1991; 11: 415-8. PubMed PMID: 1745625.

*(73 year old man developed jaundice 5 months after starting hydralazine and 2 months after starting labetalol [bilirubin 26 mg/dL, ALT 4590 U/L, Alk P 346 U/L], with progressive hepatic failure and death 11 days later).*

Bourdi M, Gautier JC, Mircheva J, Larrey D, Guillouzo A, Andre C, Belloc C, et al. Anti-liver microsomes autoantibodies and dihydralazine-induced hepatitis: specificity of autoantibodies and inductive capacity of the drug. Mol Pharmacol 1992; 42: 280-5. PubMed PMID: 1513326.

*(Analysis of antibodies from 6 patients with dihydralazine induced liver injury showed reactivity to CYP 1A2 and not 1A1; antibodies inhibited enzyme activity; anti-CYP1A2 could also be induced in rats given dihydralazine).*

Tameda Y, Hamada M, Takase K, Nakano T, Kosaka Y. Fulminant hepatic failure caused by ecarazine hydrochloride (a hydralazine derivative). Hepatology 1996; 23: 465-70. PubMed PMID: 8617425.

*(Among 16 patients with acute liver failure possibly due to medications, 7 had received ecarazine [a derivative of hydralazine] for 11 days to more than a year with jaundice and high ALT levels and progression to hepatic failure, despite stopping the medication; autoantibodies frequent as was massive or bridging necrosis; 4 died).*

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 done in the United States between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but no case was attributed to hydralazine).*

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, one case was attributed to hydralazine).*

Hassan A, Hammad R, Cucco R, Niranjan S. Hydralazine-induced cholestatic hepatitis. Am J Ther 2009; 16: 371-3. PubMed PMID: 19092641.

*(63 year old developed abdominal pain and jaundice ~3 months after starting hydralazine [peak bilirubin 6.5 mg/dL, ALT ~400 U/L, Alk P ~825 U/L], resolving within 9 weeks of stopping: Case 2).*

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, one of which was attributed to hydralazine).*

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

*(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; none were attributed to hydralazine).*

Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology 2010; 51: 2040-8. PubMed PMID: 20512992.

*(Retrospective analysis of 261 cases of autoimmune hepatitis, 24 [9%] of which were due to a medication; 11 nitrofurantoin and 11 minocycline, but none to hydralazine).*

Fleming P, Marik PE. The DRESS syndrome: the great clinical mimicker. Pharmacotherapy 2011; 31: 332. PubMed PMID: 21361742.

*(44 year old woman with a hemorrhagic stroke and sepsis developed fever, exfoliative rash, facial edema and eosinophilia 3 weeks after starting hydralazine, but also while receiving vancomycin making attribution difficult).*

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 none were attributed to hydralazine).*

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, including 4 [2%] to antihypertensive agents [methyldopa, enalapril and verapamil], but none to hydralazine).*

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 [4.3%] were attributed to antihypertensives including 8 to hydralazine and 11 to methyldopa).*

deLemos AS, Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. Semin Liver Dis 2014; 34: 194-204. PubMed PMID: 24879983.

*(Review of drug induced liver injury with autoimmune features includes a case of hydralazine jaundice arising 3 weeks after stopping a 10 week course of hydralazine [bilirubin 19.8 mg/dL, ALT 1005 U/L, Alk P 239 U/L, INR 2.0, ANA 1:160], with progressive liver injury necessitating liver transplantation 2 months later).*

Alansari A, Quiel L, Boma N. A one-two punch: hydralazine-induced liver injury in a recovering ischemic hepatitis. Am J Ther 2016; 23: e1094-5. PubMed PMID: 25423497.

*(77 year old woman with cardiomyopathy and atrial fibrillation had elevations in serum ALT [391 U/L] which improved with control of heart rate but worsened again 4 days after starting hydralazine [peak ALT 359 U/L], ultimately resolving 1 month after stopping).*

Harati H, Rahmani M, Taghizadeh S. Acute cholestatic liver injury from hydralazine intake. Am J Ther 2016; 23: e1211-4. PubMed PMID: 26291593.

*(75 year old African American woman developed jaundice 10 weeks after starting hydralazine [bilirubin 22.0 mg/dL, ALT 242 U/L, Alk P 166 U/L, INR 1.23, ANA negative], that improved with prednisone therapy and stopping hydralazine, all tests being normal 5 weeks later).*

de Boer YS, Kosinski AS, Urban TJ, Zhao Z, Long N, Chalasani N, Kleiner DE, et al.; Drug-Induced Liver Injury Network. Features of autoimmune hepatitis in patients with drug-induced liver injury. Clin Gastroenterol Hepatol 2017; 15: 103-12. PubMed PMID: 27311619.

*(Among 7 patients with hydralazine induced liver injury enrolled in a US prospective database [Chalasani 2015], 5 were women, 4 white and 3 black, ages 42 to 72 years, latency to onset of 2 weeks to 7 months, 5 with jaundice [bilirubin 0.3 to 29.7 mg/dL, ALT 132 to 2018 U/L, Alk P 188 to 607 U/L] and 1 with acute liver failure requiring liver transplantation [deLemos 2014]; 3 had autoimmune features, but ANA levels tended to decrease with recovery).*