Probable Rare Case of Cholecystitis After Exposure to Supratherapeutic Doses of Hydralazine

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Abstract

Objective: To report a rare case of cholecystitis in a patient who received supratherapeutic doses of hydralazine for 1 month. **Case Summary:** A 79-year-old woman was admitted with severe right upper quadrant abdominal pain. Three weeks prior, she suffered a similar episode and was told she had a buildup of sludge in her gall bladder. For the past month, she had inadvertently received 400 mg of hydralazine per day instead of 150 mg; she was also prescribed fenofibrate 145 mg daily. Her workup was remarkable only for a slightly elevated white blood cell count and gall bladder sludge and distention without common duct obstruction. She was diagnosed with cholecystitis and underwent a laparoscopic cholecystectomy within 72 hours of admission. She was subsequently discharged a day later with the corrected hydralazine dose, and she has not been readmitted to the hospital. **Discussion:** Hydralazine is a direct acting vasodilator that may also potentiate the effects of nitric oxide. Nitric oxide has been linked to decreased gall bladder motility in in vivo and in vitro studies. The Naranjo algorithm indicates that this is a probable adverse event of fenofibrate and of hydralazine; the Drug Interaction Probability Scale indicates that this case of cholecystitis was a possible result of the interaction between hydralazine and fenofibrate. Based on the time course of the patient's medication use and symptoms, hydralazine is more likely to be the cause of her cholecystitis than her other medications. **Conclusion:** Clinicians should be aware that high doses of hydralazine may inhibit gall bladder motility and contribute to the buildup of bile sludge.

Keywords

hydralazine, nitric oxide, cholecystitis

Hydralazine is a direct vasodilator that is used in select patients with hypertension or heart failure in doses up to 300 mg per day.^{1–3} Hydralazine's exact mechanism is not completely understood, although it has been shown to potentiate the effects of nitric oxide by inhibiting NADPH oxidase.⁴ There has also been conflicting evidence regarding the effect of hydralazine on clearance of nitric oxide in the vasculature.^{4–6} One of the most well-known drug-induced diseases caused by hydralazine is a syndrome that mimics systemic lupus erythematosus.³ To the best of our knowledge, there has been only one previous case report of hydralazine-induced cholecystitis.⁷ We present a rare case of cholecystitis, without evidence of liver injury or involvement of the upper biliary tract, in a patient who had ingested 400 mg of hydralazine per day for 1 month.

Patient Case

A 79-year-old woman who weighed 40.8 kg and had a history of hypertension, gastroesophageal reflux disease, and hyperlipidemia presented to the emergency department complaining of severe right upper quadrant abdominal pain

that radiated to her back, as well as nausea and vomiting. Approximately 3 weeks prior, she had suffered a similar painful episode and was told that she had sludge in her gall bladder; this evaluation was performed at an outside hospital, so specifics regarding medical decision making were unavailable. Pertinent vital signs and laboratory values are listed in Tables 1 and 2; all values were within normal limits, with the exception of a slightly elevated white blood count. A right upper quadrant ultrasound showed gall bladder sludge and distension with no renal calculi, sonographic Murphy's sign, or gallstones. A subsequent hepatobiliary scan showed no common duct obstruction.

The patient's medication list is detailed in Table 3. On further investigation, it was discovered that her medications had been stable for some time, with the exception of

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Table 1. Vital Signs on Admission.

Temperature (°F)	99.5
Blood pressure (mm Hg)	133/53
Heart rate (bpm)	74

Table 2. Selected Laboratory Values.

Parameter	Normal Values	Admission	Day of Surgery	POD 1	POD 2
WBC (1000/mm ³)	4.0-11.0	11.1	18.1	13.5	10.0
AST (U/L)	11-34	20		93	
ALT (U/L)	0-35	22		108	
Lipase (U/L)	5-61	71			
Total bilirubin (mg/dL)	≤1.3	0.3		0.3	
SCr (mg/dL)		0.7	0.5	0.7	

Abbreviations: POD, postoperative day; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SCr, serum creatinine.

Table 3. Drugs Prior to Admission.

Hydralazine 100 mg 4 times daily
Metoprolol tartrate 50 mg daily
Simvastatin 40 mg daily
Fenofibrate 145 mg daily
Amlodipine/valsartan/hydrochlorothiazide 10/320/25 mg daily
Aspirin 81 mg daily
Escitalopram 10 mg daily
Loratadine 10 mg daily

hydralazine. She had been taking hydralazine 50 mg 3 times daily for a year for her hypertension, but had been prescribed hydralazine 100 mg 4 times daily in error and had been taking this dose for 1 month prior to this admission. The dosage change occurred 1 week prior to the onset of her symptoms.

The patient was given pain control with hydromorphone and morphine and was given cefoxitin; she underwent a laparoscopic cholecystectomy within 72 hours of admission. On the day of surgery, her white blood cell count reached a maximum of 18.1. The gallbladder was found to be large, inflamed, and distended. Oozing sludge was found but no common bile duct obstruction or gallstones was discovered. The patient reported minimal pain postoperatively, and her white count resolved by postoperative day 2; she did have a transaminitis immediately postoperatively. The patient was discharged with her home medications, including the correct dose of hydralazine, 50 mg 3 times daily. Since that admission, the patient has not been readmitted to our hospital.

Discussion

The only previously reported case of hydralazine-induced cholecystitis described a patient who developed subacute cholecystitis and septic shock from cholangitis without stones or biliary duct obstruction.⁷ In that report, the patient was receiving standard dosing of hydralazine and her symptoms followed the course of her hydralazine exposure, dechallenge, and rechallenge; the patient was subsequently discharged and had no pain at the 3-month follow-up visit. The authors of that report concluded that hydralazine may have induced the patient's cholecystitis and cholangitis. The case that we report differs in that there was no associated cholangitis or transaminitis, and that our patient was not dechallenged and rechallenged, though there was a temporal relationship between her receipt of supratherapeutic doses of hydralazine and the onset of her symptoms.

The possible mechanism behind this adverse event may be related to the effect of nitric oxide in the gallbladder. Hydralazine has been shown to increase the effects of nitric oxide by inhibiting the production of superoxide.⁵ More important, Luman et al have identified that nitric oxide donors significantly decrease gall bladder emptying.⁶ It is possible that hydralazine may inhibit gall bladder emptying by this mechanism. While Luman et al infused very low doses of hydralazine in the human subjects as a hypotensive control agent (0.1 mg/min, increasing by 0.05 mg/min at 15-minute intervals), the median dose given was 0.1 mg/min, which is significantly less than the supratherapeutic hydralazine exposure of our patient.⁶

Fenofibrate may also have contributed to our patient's cholecystitis, as it can cause supersaturation of cholesterol in the bile and lead to gallstones and cholecystitis.^{8,9} The patient we describe had received fenofibrate for the past year without complication, and only developed symptoms of cholecystitis once she began taking supratherapeutic doses of hydralazine, which makes it less likely that fenofibrate was the cause of her symptoms.

To assess the likelihood of hydralazine, fenofibrate, or the combination of the 2 agents causing cholecystitis, we used the Naranjo algorithm and the Drug Interaction Probability Scale.^{10,11} An objective causality assessment of cholecystitis caused by either fenofibrate or hydralazine was probable.¹⁰ Furthermore, an objective causality assessment of cholecystitis caused by an interaction between fenofibrate and hydralazine was possible.¹¹ Because these assessments indicate that a single agent was more likely to cause our patient's symptoms and there is a temporal relationship between the patient's use of supratherapeutic doses of hydralazine and her symptoms, we believe that hydralazine is the most likely cause of cholecystitis in this case. A limitation of this analysis is that the patient was not able to be dechallenged and rechallenged so causality cannot be conclusively determined.

Conclusion

Hydralazine is used for several common disease states and has previously been associated with cholecystitis and cholangitis, possibly because of the role of hydralazine and nitric oxide in gall bladder function. Shortly after our patient began taking suprathreshold dose of hydralazine, she experienced symptoms indicative of cholecystitis, which has only been reported in the literature once. Clinicians should be aware that cholecystitis is a possible adverse drug event in patients receiving hydralazine.

Declaration of Conflicting Interests

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References

1. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guidelines for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;62:e147-e239.
3. Hydralazine [Package insert]. Hyderabad, India; Hetero Drugs Limited; September 2008.
4. Chirkov YY, De Sciscio M, Sverdllov AL, Leslie S, Sage PR, Horowitz JD. Hydralazine does not ameliorate nitric oxide resistance in chronic heart failure. *Cardiovasc Drugs Ther*. 2010;24:131-137.
5. Munzel T, Kurz S, Rajagopalan S, et al. Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase: a new action for an old drug. *J Clin Invest*. 1996;98:1465-1470.
6. Luman W, Ardill JEF, Armstrong E, et al. Nitric oxide and gall-bladder motor function. *Aliment Pharmacol Ther*. 1998;12:425-432.
7. Myers JL, Augur NA Jr. Hydralazine-induced cholangitis. *Gastroenterology*. 1984;87:1185-1188.
8. Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *Am J Med*. 1987;83:37-43.
9. The Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism. Experience in the Coronary Drug Project. *N Engl J Med*. 1977;296:1185-1190.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
11. Horn JR, Hansten PD, Chan L. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41:674-680.