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CASE REPORT

Rhabdomyolysis after midazolam administration in a cirrhotic patient treated with atorvastatin

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Abstract

The administration of statins in patients with liver disease is not an absolute contraindication. Hepatotoxicity is a rare and often dose-related event and in the literature there are only a few described cases of fatal rhabdomyolysis in patients with chronic liver disease after statin administration. During treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, the factors responsible for myopathy may either be related to the patient, or due to interactions with other medications that are metabolic substrates of the same isozymes and therefore able to increase blood statin concentration. The most important side effects consist of increased transaminase levels, abdominal pain or muscle weakness, increased serum levels of creatine kinase and rhabdomyolysis. In this article we report a case of fatal rhabdomyolysis with acute renal failure after gastric endoscopy, where midazolam was used as a sedation agent in a patient with chronic liver disease treated with a high dose of atorvastatin. Therefore, we suggest paying particular attention to the potential risks of associating atorvastatin and midazolam in patients with chronic liver disease who need to undergo gastric endoscopy.

Key words: Rhabdomyolysis; Chronic liver disease; Statins; Midazolam; Alcoholic liver cirrhosis

Core tip: When dealing with alcoholic liver disease, clinicians need to pay particular attention to the administration of drugs, their dosage, interactions and metabolism to avoid severe adverse reactions. Cirrhotic patients on treatment with statins (particularly atorvastatin) are at high risk of developing fatal rhabdomyolysis and acute renal failure when midazolam is used to allow gastric endoscopy.

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INTRODUCTION

Statins are widely used to treat hypercholesterolemia, therefore reducing cardiovascular risk. Currently, there are no trials on the safety of statins in chronic liver disease. Although hepatotoxicity represents a rare event (< 2%) and is often dose-dependent, adverse effects or even death have been described in patients suffering from liver disease.

The concomitant use of other drugs that are metabolic substrates of the same isoenzymes, as cytochrome P-450 and isoenzyme CYP3A4, can increase statin concentration and consequently elevate the risk of myopathy. The most important side effects consist of increased transaminase levels, abdominal pain or muscle weakness,

Table 1 Biochemical analysis on different days

	ER	Before EGDS	1st day after EGDS	2nd day after EGDS	6th day after EGDS	ICU
ALT (UI/L)	146	52	70	130	207	827
AST (UI/L)	125	117	191	240	927	2075
Total bilirubin (mg/dL)	1.2	2.73	3.39	4.51	6.1	7.44
Direct bilirubin (mg/dL)	0.2	1.86	2.12	3.01	3.8	5.87
INR	1.75	1.7	1.58	1.6	1.68	6.11
Fibrinogen (g/L)	3.52	-	-	-	-	0.58
Platelets (mm^3)	115	54	49	45	70	40
D-dimer (ng/mL)	2557	-	-	-	-	9000
ATⅢ (%)	-	-	-	-	-	20
Myoglobine (ng/mL)	175	198	22.899	25.981	> 30.000	> 30.000
CK (U/L)	81	95	3.298	5.876	38.289	89
CK-MB (ng/mL)	4.2	4.1	14.01	25.03	73.59	68.72
Troponin T HS (mg/L)	0.022	0.025	0.061	0.043	0.189	1.53
LDH (UI/L)	240	286	358	470	1603	2084
Creatinine (mg/dL)	1.1	1.3	1.3	1.3	3.14	3.8
BUN (mg/dL)	45	60	61	59	161	78
Calcium (mg/dL)	8.8	8.4	-	-	6.7	4.4
Diuresis (cc)	-	2000	1300	1000	150	300
BP (mmHg)	90/50	115/60	105/55	95/60	75/50	60/40

EGDS: Esophagogastroduodenoscopy; ICU: Intensive care unit; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ATⅢ: Antithrombin Ⅲ; CK: Creatine kinase; INR: International normalized ratio; Troponin T HS: High sensitivity troponin T; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; BP: Blood pressure; ER: Emergency room.

increased levels of creatine kinase and rhabdomyolysis[1,2].

CASE REPORT

A 67-year-old man was admitted to an internal medicine ward at our hospital for syncope. In the emergency room (ER) the patient was oriented, apyretic and had pale skin. His blood pressure was 90/50 mmHg, and he had arrhythmia (80 bpm), swollen abdomen and peristalsis.

Laboratory findings demonstrated abnormal alanine transaminase (146 IU/L), aspartate aminotransferase (125 IU/L), D-dimer (2557), creatine kinase-MB (4.2 ng/mL), platelets (115 × 10^3/μL), glucose (195 mg/dL), myoglobin (175 ng/mL), international normalized ratio (1.75), and high sensitivity troponin T (0.022 mg/L) values (Table 1).

Chest X-ray and brain computed tomography (CT) scans were performed, which showed no notable findings. The patient was admitted to our department for further investigation and treatment. This patient had a history of hospitalization for myocardial infarction three months earlier (treated by percutaneous transluminal coronary angioplasty with implantation of two drug-eluting stents), arterial hypertension, type Ⅱ diabetes mellitus (diagnosed about 7 years earlier) and a more recent diagnosis of chronic atrial fibrillation (AF). Patient's medications included carvedilol 50 mg/d, digoxin 0.125 mg, ramipril 10 mg, duoplavin 75/100 mg, furosemide 25 mg, canrenon 100 mg, pantoprazole 40 mg, insulin, and atorvastatin 40 mg. Our examination revealed that the patient presented with low blood pressure, and physiological anamnesis outlined a history of alcohol abuse (about 2 L of wine for the last 30 years). Electrocardiogram (ECG) showed AF at a frequency of 73 bpm, and a Holter monitor confirmed AF. Ambulatory blood pressure monitoring showed recurrent episodes of hypotension. Carotid ultrasonography and electroencephalography showed no abnormalities consistent with syncope. For this reason, we reduced the dosage of antihypertensive medications (ramipril 5 mg, carvedilol 25 mg) and treated the patient with intravenous fluid administration. During hospitalization, because of persistently elevated transaminase levels, the patient underwent hepatobiliary ultrasonography, which showed increased liver size with heterogeneous echogenicity, irregular surface, but no focal lesions. The average velocity in the portal vein was 8.2 cm/s (normal values ⩾ 14 cm/s). Spleen size was increased, and mild ascites was present.

Therefore markers for viral hepatitis were sought and found to be negative, and thus the patient was diagnosed with alcoholic liver cirrhosis.

During his second day of hospitalization, the patient reported localized muscle pain in the lower limbs associated with intense weakness. Since statin-induced myopathy was suspected, muscular enzymes were assayed and the results were within reference intervals. Nonetheless, atorvastatin administration was discontinued. The next day the patient underwent esophagogastroduodenoscopy (EGDS) under sedation with midazolam (at a dose of 2 mg), which revealed congestive gastropathy in absence of esophageal varices. The day after the examination the patient complained of a further increase in muscle pain with extension to the upper limbs: muscular enzymes levels increased, as showed in Table 1. In the following days, despite the discontinuation of the statin, muscle pain did not regress, and neither did muscle enzymes levels return within reference values (Table 1).

Suspecting a possible drug interaction, digoxin was

suspended too, which is a known common substrate of atorvastin cytochrome (CYP 3A4). However laboratory test values and the patient's condition did not improve. Moreover, six days after EGDS, clinical findings of myoglobinuria, oligo-anuria, acute kidney injury and elevated levels of muscle enzymes (Table 1) suggested the diagnosis of rhabdomyolysis, with the indication to begin hemodialysis (HD).

The patient underwent HD treatment for 5 consecutive days with worsening of pain and persistently elevated muscle enzymes. The condition eventually deteriorated into disseminated intravascular coagulation (DIC). ECG showed a new-onset diffuse ST and T wave changes, and prolonged Q-T interval (0.54 s) associated with severe metabolic acidosis.

The patient was transferred to the intensive care unit (ICU). Biochemical values are reported in Table 1. The patient died the next day, 9 d from the diagnosis of rhabdomyolysis.

DISCUSSION

The use of statins in patients with chronic liver disease is not an absolute contraindication: recommendations suggest to start with low doses, making sure that the patient does not consume alcohol and does not suffer from acute hepatitis. In the literature there are only a few described cases of fatal rhabdomyolysis in patients with liver disease treated with statins[3]. Recent studies suggest that even in liver disease patients, especially those suffering from non-alcoholic steatohepatitis, the indication to use statins stands strong because of the increased cardiovascular risk in these subjects[4].

During treatment with statins, the factors responsible for myopathy may be related to the patient (age, female sex, alcoholism, hypothyroidism, systemic diseases, family history of myopathy, high consumption of grapefruit juice, large physical activity, major surgery, *etc.*) or to interaction with other medications (fibrates, cyclosporine, antifungals, macrolides, protease inhibitors, nefazodone, amiodarone, verapamil, *etc.*)[1]. In our case, we assume that the development of rhabdomyolysis was related to several contributing factors such as the high dose of atorvastatin in a patient with undiagnosed chronic liver disease.

The benefits associated with the use of statins in lowering cholesterol levels and preventing cardiovascular disease still remain superior to their potential risk of hepatotoxicity in patients with chronic liver disease. However, in the course of acute viral or alcoholic hepatitis, HMG-CoA reductase inhibitors should be avoided until liver function is restored[5]. In fact, although major trials have excluded patients with a history of active liver disease, other studies recommended to start with low doses of statins, making sure that the patient does not take alcohol, and to check serum transaminase levels after the first two weeks of therapy, and then each month for three months, eventually reducing the interval to four times a year. If serum transaminase levels are doubled or tripled compared to reference, therapy should be discontinued until normalization of liver enzymes, and then the use of another statin is reconsidered[1,2].

In our case, the trigger for the onset of rhabdomyolysis followed by overt DIC and multi organ failure may have been the use of midazolam, metabolized by the same isoenzyme that is responsible for the metabolism of atorvastatin.

Statins are inhibitors of HMG-CoA reductase undergoing first-pass hepatic metabolism. Excluding pravastatin, other molecules of this class are subject to phase 1 hepatic metabolism mediated by CYP 450 isoenzymes. Isoenzyme CYP3A4 is responsible for atorvastatin, lovastatin and simvastatin metabolism, while fluvastatin and rosuvastatin are metabolized mainly by CYP2C9 isozyme.

Although serum levels of atorvastatin and midazolam were not checked, we assume that the concomitant use of drugs that are substrates of the same CYP isoenzymes, as midazolam and atorvastatin, can dangerously increase statin concentration in the blood and consequently the risk of myopathy.

There are some reports of rhabdomyolysis caused by propofol[6] and its interaction with other statins[7], but this is the first case report documenting rhabdomyolysis after atorvastatin and midazolam administration.

Furthermore, patients with alcohol use disorders (AUD) are at high risk for rhabdomyolysis secondary to toxic effects of ethanol in the muscle, metabolic disturbances, alcohol withdrawal syndrome and sepsis.

In this case report, the fatal outcome of drug-induced rhabdomyolysis may have been promoted by the presence of pre-DIC condition due to liver cirrhosis: the association of both conditions escalated to multiple organ failure.

In conclusion, particular attention must be paid to the potential risks of associating statins, such as atorvastatin, with other drugs especially in patients with AUD and chronic liver disease. The use of midazolam as a sedation agent should be avoided in patients needing EGDS while treated with statins.

COMMENTS

Case characteristics

The patient complained of muscle pain in the lower and upper limbs associated with intense weakness.

Clinical diagnosis

Clinical findings included elevated transaminases and muscle enzymes, myoglobinuria, oligo-anuria, acute kidney injury, disseminated intravascular coagulation, prolonged Q-T interval (0.54 s) and severe metabolic acidosis.

Differential diagnosis

Rhabdomyolysis in the presence of pre-disseminated intravascular coagulation (pre-DIC) condition due to secondary toxic effects of ethanol in the muscle, metabolic disturbances, alcohol withdrawal syndrome and sepsis.

Laboratory diagnosis

Findings demonstrated elevated transaminases, muscle enzymes, serum creatinine, myoglobinuria, and disseminated intravascular coagulation.

Imaging diagnosis

Hepatobiliary ultrasonography showed increased liver size with heterogeneous echogenicity and irregular surface, and the average velocity in the portal vein

was low. Increased spleen size and mild ascites were also present.

Treatment

Atorvastatin and other drugs metabolized by the same cytochrome isozyme were discontinued; fluid IV administration and hemodialysis were given.

Related reports

The concomitant use of substrates of the same isozymes (CYP3A4), such as midazolam and atorvastatin, can increase statin blood concentration and consequently the risk of myopathy.

Experiences and lessons

The indication for the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in cirrhotic patients must be evaluated by physicians on the basis of clinical necessity. It is correct to start with low-dose drug administration while monitoring transaminases. Finally, it is appropriate to evaluate simultaneous administration of other drugs metabolized by the same cytochrome, therefore reducing the risk of moderate and severe interactions.

Peer review

It was a nicely written case report. It suggests that rhabdomyolysis may have been related to the simultaneous administration of atorvastatin and midazolam in a patient with alcoholic liver disease.

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