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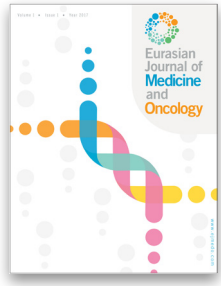

Case Report

Oral Amiodarone-induced Liver Injury with Gamma Glutamyl Transferase Elevation: A Case Report

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Abstract

Amiodarone-induced hepatotoxicity varies from asymptomatic serum aminotransferase elevation to severe liver disease. Aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase are known to be elevated in amiodarone-induced liver damage. However, no study in the literature has reported that gamma glutamyl transferase (GGT) is elevated in this condition. Described is the case of an 82-year-old female patient with elevated GGT while using oral amiodarone for rapid response atrial fibrillation. The GGT level decreased after amiodarone was discontinued. GGT elevation was considered to be a potentially prominent drug side effect according to the Council for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method scale. GGT is found in biliary epithelial cells and hepatocytes. GGT elevation may be due to drug or alcohol use. Histological changes in alcoholic liver disease and those in liver injury due to amiodarone toxicity are similar. It is thought that amiodarone-induced liver injury and GGT elevation are related to this histological similarity.

Keywords: Amiodarone, drug-induced liver injury, gamma glutamyl transferase

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Amiodarone is a commonly used antiarrhythmic drug. The frequency of side effects of amiodarone is related to total drug exposure.[1] Amiodarone causes 25% asymptomatic elevation of serum aminotransferase and causes less than 3% severe hepatic disease.[1] Liver toxicity is usually transient and improves after dose reduction or release.[1] It is known that aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) increase in amiodarone-induced liver damage. However, in our literature review, there is no literature with gamma glutamyl transferase (GGT) elevation due to amiodarone. In this case, we present the case of a patient with GGT elevation induced by oral amiodarone.

Case Report

An 82-year-old female with shortness of breath, cough, and sputum was admitted to our clinic with a diagnosis of pneumonia. On physical examination, blood pressure was 120/90 mmHg, fever was 37.1°C, and heart rate was 91/min. The patient's pulse was arrhythmic. There was bilateral diffuse rales and rhonchi in the lung of the patient, pretibial edema was ++/++. She had a history of type 2 diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, and hypertension. The drugs used were amiodarone 200 mg/day, valsartan-hydrochlorothiazide 160-12.5 mg/day, metoprolol 25 mg/day, atorvastatin 10 mg/day, and metformin 1 g/day. Her

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Table 1. Liver enzymes during treatment of the patient

Duration of hospitalization	GGT (U/L)	ALT (U/L)	ALP (U/L)	AST (U/L)	LDH (U/L)
First day	54	21	100	13	243
Eighth day	83	17	70	11	290
Thirteenth day	304	38	56	15	363
Fifteenth day	1445	90	97	59	437
Nineteenth day	1977	80	164	64	411

laboratory test results were as follows: C-reactive protein, 26.6 mg/dl; urea, 76.4 mg/dl; erythrocyte sedimentation rate, 36; white blood cell count, 16.3×103/μL; and hemoglobin, 11.1 g/dL. Other laboratory findings were within normal limits. Abdominal ultrasonography showed that liver parenchyma echogenicity was compatible with grade 2-3 fatigue. Based on these findings, levofloxacin 500 mg/day, salbutamol four times daily 100 mcg inhaler, enoxaparin twice daily 0.4 ml, methylprednisolone once daily 80 mg, furosemide twice daily 40 mg, and budesonide twice daily 100 mcg inhaler were added to the medical treatment of the patient along with the previous medications. Elevated levels of liver enzymes, especially GGT, were found in the patient's daily follow-up. ALT, AST, and LDH increased three times, and GGT increased approximately 35 times (Table 1). It was estimated that the drug toxicity caused the elavation of GGT. Levofloxacin, amiodarone, atorvastatin, and metformin were discontinued. A week later, GGT reduced from 1900 to 637 U/L. Amiodarone 200 mg/day was started again to control the patient's heart rate. However, 5 days after the start of amiodarone, the GGT level increased to 877–910 U/L. In order to evaluate the side effect of the drug, the adverse effects related to the evaluation using the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale. Scale score was 10 points and this score shows ''highly probable" adverse drug reaction. Therefore, amiodarone was stopped. Digoxin was added to control the patient's heart rate. The GGT level then decreased to 270 U/L. The pneumonia symptoms improved, edema decreased, and breathlessness improved. The patient was offered to come to the control and was discharged. The GGT level was found to be 66 U/L in the control examination of the patient approximately 2 months later.

Discussion

Long-term oral amiodarone treatment has several side effects such as thyroid dysfunction, photosensitivity, corneal microdeposits, pulmonary toxicity, and hepatotoxicity.[1] The frequency of drug side effects is related to total drug exposure.[1] Liver toxicity in these patients is usually transient and improves after dose reduction or discontinuation.[1] Amiodarone is removed by the bilious system. Because of the long half-life of amiodarone, the side effects sometimes continue for months after the drug is discontinued. Typical histological findings of amiodarone-associated acute hepatitis are steatohepatitis and phospholipidosis.[3, 4] The amiodarone can be caused by several mechanisms of phospholipidosis in the liver; first, amiodarone directly inhibits phospholipase enzyme (especially lysosomal phospholipase), and second, amiodarone binding to phospholipids leads to the formation of a drug–phospholipid complex that is more resistant to phospholipases.[9-11] These changes are similar to those found in alcoholic liver disease.

The presence of phospholipid-loaded lysosomal lamellar bodies on electron microscopy may aid in distinguishing amiodarone hepatotoxicity from alcoholic liver disease.[12-14] In this case, the duration of the use of amiodarone was approximately 6 months and the liver had stage 2-3 steatosis. It has been reported that the use of low-dose oral amiodarone (200 mg/daily) stimulated the formation of steatohepatitis.[8] In our present case, steatosis was thought to facilitate amiodarone toxicity. The criteria for establishing a causal relationship between amiodarone and hepatotoxicity are the exclusion of other drugs and non-drug causes, suspicion of drug initiation, improvement of drug release, and onset of drug hepatotoxicity again.[2] Different algorithms are used to determine the causal relationship between a drug and its side effects according to these criteria.[5-7] We used the CIOMS/RUCAM scales to assess drug-induced liver injury and the result from the scale was "highly probably" adverse drug reaction (Scale score was 10 points).[17, 18] Fonseca et al.[1] reported that ALT, AST, and LDH levels were increased to more than 50 times in amiodarone-induced hepatitis because of amiodarone and that GGT and ALP levels were normal. However, there is no study in the literature on the possibility of isolated GGT elevation.

GGT is found in biliary epithelial cells and hepatocytes.[15] Increased isolated GGT may be due to drug induction. However, amiodarone is a CYP1A2, CYP2C9, and CYP2D6 inhibitor.[16] Increased isolated GGT may be due to alcohol use. However, our patient did not consume alcohol. Histological changes in alcoholic liver disease and those in liver injury due to amiodarone toxicity are similar.[12-14] We think that the reason for the elevation of isolated GGT bound to amiodarone is related to this histological similarity.

Conclusion

The use of oral amiodarone is safer than intravenous amiodarone. There are several side effects along with the cumulative effect of long-term oral amiodarone

therapy. However, it should not be forgotten that oral amiodarone-induced liver damage may occur early in patients with steatosis in the liver, as observed using ultrasonography. It may be thought that this liver damage may occur as an isolated GGT elevation at subject with steatohepatitis.

Disclosures

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Conflict of Interest: None declared.

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