Liver injury after the intravenous amiodarone administration in patient with impaired heart function

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ABSTRACT
While many adverse effects have been associated with long-term oral amiodarone therapy, acute hepatotoxicity from intravenous administration of amiodarone is a rare side effect. This case report focuses on a 78-year-old critically ill female, who underwent several urgent surgical procedures and had elevated liver aminotransferases concentrations after the intravenous administration of amiodarone for the treatment of atrial fibrillation. Also, the patient developed heart failure with reduced left ventricular systolic function. Immediately after the discontinuation of amiodarone therapy, liver aminotransferases levels began to decline. Our case suggests that regular monitoring of hepatic function is required in patients receiving intravenous amiodarone, especially in the setting of impaired heart function and possible liver hypoperfusion.

Key words: amiodarone, hepatotoxicity, heart failure.

Introduction
Amiodarone is a class III antiarrhythmic drug that prolongs intranodal conduction and refractoriness of the atrioventricular node. It is metabolised in the liver to N-desethylamiodarone, a metabolite primarily excreted in bile. (1) Amiodarone is used to treat ventricular and supraventricular tachyarrhythmias and is thought of as one of the safest antiarrhythmic agents, in particular in patients with a low ejection fraction (EF) or clinical heart failure. (2) In patients with pre-existing left ventricular dysfunction amiodarone may exert negative inotropic effects. (2) During long-term oral therapy, accumulation of the drug in tissues may be responsible for thyroid dysfunction, corneal microdeposits, skin manifestations, gastrointestinal disturbances and pulmonary and hepatic toxicity. (3) The most prominent adverse effect of intravenous (i.v.) amiodarone therapy is hypotension which occurs in 26% of patients and is presumably caused by solvents used in the preparation. Hypotension appears more frequently in patients with EF less than 35%, critically ill patients and postcardiac surgery patients. (2) Proarrhythmic effects may occur manifested as “torsades de pointes” or ventricular fibrillation. (4) An asymptomatic rise of liver aminotransferases occurs in about 25% of patients receiving oral amiodarone, whereas severe liver injury with potentially fatal complications and cirrhosis occurs in less than 1% of patients. (5,6) Elevated bilirubin levels may be the first sign of toxic effects. Bilirubin levels may stay elevated after discontinuation of the drug because of its long half-life. (7) Though less common, cases of acute hepatotoxicity after i.v. amiodarone have also been reported. In two patients fatal hepatocellular necrosis has been reported. (4) Abnormal liver function tests occur in 1 to 5% of patients receiving i.v. amiodarone. (4,8) The diluent polysorbate 80 present in the i.v. form of the drug is presumably responsible for the hepatotoxic effects. (9) Polysorbate 80 has been associated with E-ferol syndrome described in infants after the i.v. usage of vitamin E. This syndrome shares similar clinical features with the acute amiodarone hepatotoxicity. (9)

Case report
A 78-year-old female was admitted to the intensive care unit (ICU) prior to an urgent surgical procedure due to rectal prolapse. Her past medical history included chronic obstructive pulmonary disease and osteoporosis without known cardiovascular diseases. Her home medications included theophylline and raloxifene. She has no history of alcohol abuse. Initial laboratory tests in the ICU were within normal reference range, and liver aminotransferases levels were slightly elevated (table 1). At admittance she...
presented atrial fibrillation (AF) with a rapid ventricular rate. After the i.v. dose of 300 mg of amiodarone and initial stabilization, a rectal excision with loop sigmoidostomy was performed. At the time she was hypotensive, and noradrenalin in a continuous infusion was administered until the following day. On the third postoperative day Hartmann’s operation was performed due to the prolapsed stoma. Also, she developed left brachial artery thrombosis which was treated by Fogarty thrombectomy. On the following day she became hypotensive again with a heart rate of 180/min. An echocardiogram of the heart showed reduced systolic function of the nondilated left ventricle with EF of 25-30%. A bolus dose of 300 mg of amiodarone was administered and a continuous infusion was started. Synchronized electrical cardioconversion was attempted unsuccessfully. Because of persistent hypotension and signs of heart failure, noradrenalin and dobutamin were initiated (table 1). An amiodarone infusion was continued for the next two days along with vasoactive therapy. On the third day after the start of the amiodarone infusion, elevated levels of liver enzymes were observed (table 1). Amiodarone was suspected to be the cause of liver injury and infusion was discontinued. The total dose of administered amiodarone was 1842 mg over a period of 55 hours. Liver transaminases were checked daily and a steady decline in their values was observed with a return to baseline after eight days (table 1). Eventually, the patient’s medical condition worsened with a perforation of the transverse colon and she died from severe sepsis complications.

**Discussion**

Liver injury after parenteral amiodarone therapy presents with acute elevation of liver aminotransferases within 1-3 days, which was noticed in our case as well. (10) Ischemic hepatitis, as the most common cause of elevated aminotransferases in hospitalized patients, shares many clinical and histological characteristics with amiodarone hepatotoxicity. (10) It is characterized by acute elevation of liver transaminases which return to baseline values within days following circulatory progress. It has been hypothesized that acute liver injury after the amiodarone administration is more likely a result of liver

<table>
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<th>ICU days</th>
<th>ALT U/L</th>
<th>AST U/L</th>
<th>GGT U/L</th>
<th>LDH U/L</th>
<th>AP μmol/L</th>
<th>HR/min</th>
<th>BP</th>
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<th>BP/HF control</th>
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<td>amiodarone 300 mg</td>
<td>noradrenaline 0-08 μg/kg/min</td>
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<td>54</td>
<td>171</td>
<td>10</td>
<td>90-150</td>
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<tr>
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<td>60</td>
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<td>7</td>
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<td>↓↓</td>
<td>bisoprolol 2.5 mg amiodarone 10.2 μg/kg/min</td>
<td>noradrenaline 0.04 μg/kg/min dobutamine 6.4 μg/kg/min</td>
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<td>1070</td>
<td>1718</td>
<td>104</td>
<td>551</td>
<td>93</td>
<td>30</td>
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<td>8</td>
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<td>113</td>
<td>511</td>
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ALT - alanine aminotransferase, AP - alkaline phosphatase, AST - aspartate aminotransferase, BIL - bilirubin, U/L - units per liter, BP - blood pressure, GGT - gamma glutamile transferase, HF - heart function, HR - heart rate, ICU – intensive care unit, LDH - lactate dehydrogenase, SE cardioconversion - synchronized electrical cardioconversion.
ischemia than drug toxicity, since most patients receiving amiodarone also have chronic cardiovascular illnesses. (10) Whether acute aminotransferases elevation in our patient was a result solely of amiodarone hepatotoxicity is arguable. Although acute elevation of liver aminotransferases was noticed after the initiation and a decline in their values was noticed in a 12-hour period after stopping the amiodarone infusion, the patient was haemodynamically compromised. Her aminotransferases levels were moderately elevated before receiving amiodarone which may be attributable to ischemic hepatitis. Normalization of aminotransferases levels within days may have also been a result of circulatory improvement. A total dose of administered amiodarone in the period of 55 hours was in accordance with recommendations from the literature. (4) Nevertheless, for the patient who weighed 39 kg it may have been excessive and contributed to liver injury.

**Conclusion**

Many critically ill patients receive i.v. amiodarone for the treatment of acute arrhythmias in the setting of impaired heart function. Intravenously administered amiodarone may have direct toxic effects or may damage liver tissue in the presence of liver ischemia due to heart failure. Our case suggests that regular monitoring of liver function is necessary to prevent severe liver injury when amiodarone is administered parenterally in patients with impaired heart function.

**REFERENCES**