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Predictors of intravenous amiodarone induced liver injury

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KEYWORDS

Intravenous amiodarone;
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Abstract *Background:* Intravenous (IV) amiodarone may be associated with liver injury that may necessitate drug discontinuation. The prediction of amiodarone induced liver injury (AILI) and its severity may help careful patient monitoring or the choice of other measures alternative to amiodarone in high risk patients. Little is known regarding predictors of AILI.
Objectives: To address the predictors of AILI and its severity.
Methods: The study included 180 patients indicated for IV amiodarone therapy who were divided into 2 groups: cases (90 patients) who developed AILI, and controls (90 patients) who did not develop AILI. AILI was defined as aminotransferase (ALT and AST) elevation by $\geqslant 2$ folds of baseline levels. Severe AILI was defined as enzyme elevation by >5 folds of baseline values.
Results: Multivariate analysis showed that the presence of cardiomyopathy ($P = 0.032$), congestive hepatomegaly ($P = 0.001$), increasing baseline total bilirubin ($P < 0.0001$), direct current cardioversion ($P = 0.015$), and increasing dose of amiodarone ($P = 0.014$) to be independent predictors for AILI. Regarding severity of AILI, inotropic support ($P = 0.034$), congestive hepatomegaly ($P = 0.012$), increasing baseline total bilirubin ($P = 0.001$), and increasing dose of amiodarone ($P = 0.002$) were found to be independent predictors for severe AILI. Among cases, linear regression analysis showed that baseline ALT was the only significant independent predictor of post-amiodarone ALT ($P < 0.0001$), while baseline AST ($P < 0.0001$) and EF ($P = 0.012$) were the only significant independent predictors of post-amiodarone AST.
Conclusions: Compromised cardiac, hepatic, and hemodynamic conditions, with increasing dose of IV amiodarone were associated with AILI. Severity of liver injury had linear relationship with baseline aminotransferase levels and left ventricular systolic function.
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1. Introduction

Drug induced liver injury (DILI) due to oral amiodarone was extensively studied. However, the available data regarding acute hepatotoxicity form intravenous (IV) amiodarone are not far beyond case reports.[1–16] The mechanisms of liver injury

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with IV amiodarone are controversial. Ischemic injury due to compromised hemodynamic conditions may have a role.[5] Solubilizers in the IV amiodarone preparation such as polysorbate 80 were reported to be responsible for hepatotoxicity, possibly due to immune-mediated alteration of hepatocellular membrane.[6,16] Importantly, the mechanism of injury with IV amiodarone is different from that in chronic exposure to oral therapy; therefore, acute hepatic injury following IV amiodarone does not preclude subsequent oral therapy.[6,17]

Acute elevation of liver enzymes following IV amiodarone use ranged from mild asymptomatic to severe life threatening, and frequently necessitates drug discontinuation. In most of the reported cases, the liver injury occurred within 24–48 h of therapy and reversed within 2–3 weeks of discontinuation.

Parenteral amiodarone is commonly used in critically ill and hemodynamically unstable intensive care unit patients. Therefore, multiple factors may predispose patients to IV amiodarone induced liver injury (AILI). Possible predisposing factors for AILI were variably reported in different case studies. Underlying liver injury from heart failure, high dose of IV amiodarone, hypotension from ventricular arrhythmias (VAs), and postoperative therapy following coronary artery bypass grafting (CABG) were observed in case reports.[4,8,18,19] Up to our knowledge, there are no prospective clinical studies that addressed the predictors of AILI.

2. Methods

The study included 180 intensive and coronary care unit patients who received IV amiodarone therapy. Patients were divided into 2 groups:

- Cases: Included 90 patients who developed AILI defined as acute rise in serum aminotransferase levels by at least 2 folds of the baseline levels within 24–48 h of IV amiodarone therapy.
- Controls: Included 90 patients who did not develop AILI.

Patients with underlying decompensated liver cell failure, hepatic coma, active hepatitis, patients with >5 fold elevation of aminotransferases relative to upper limit of normal (ULN), patients who had acute myocardial infarction (MI) within the past 3 days, and those who received multiple ($>$one) direct current (DC) shocks were not enrolled in the study.

2.1. Clinical assessment

Patients were subjected to history taking and physical examination emphasizing on risk factors (such as hypertension, diabetes mellitus, smoking), signs of underlying liver disease, heart failure, concomitant drug therapy.

2.2. Laboratory investigations

Before initiation of IV amiodarone therapy, liver function tests, viral markers, hemoglobin level, serum creatinine, serum sodium and potassium, INR, and random blood sugar were measured. Liver function tests and viral markers included the following:

- Aminotransferases: Baseline ALT (alanine aminotransferase) and AST (aspartate aminotransferase) were measured using standard reagents by reaction rate assay based on the conversion of NADH to NAD.[20] Upper limit of normal (ULN) values was 44 IU/L for ALT and 34 IU/L for AST. Post-amiodarone aminotransferase levels were taken on the same day, 24, and 48 h following IV amiodarone. Peak levels were taken as post-treatment values.
- Other liver function tests included serum total and direct bilirubin (reference levels up to 1.2 and 0.3 mg/dl respectively), serum albumin (reference range 3.5 to 5.5 g/dl), and INR (international normalized ratio) that was considered high if >1.5.
- Viral markers: Included hepatitis B virus (HBV) surface antigen detected by ELISA (enzyme linked immunosorbent assay), and hepatitis C virus (HCV) antibody detected by EIA (enzyme immunoassay).

Severity AILI was graded according to rise in aminotransferase level. Due to inclusion of patients with elevated baseline aminotransferase levels, the severity grading was classified based on changes relative to their baseline value rather than ULN as follows [21]:

- Grade 1: 1.25–2.5 folds of baseline value.
- Grade 2: 2.6–3.5 folds of baseline value.
- Grade 3: 3.6–5 folds of baseline value.
- Grade 4: >5 folds of baseline value.

2.3. Radiologic investigations

Transthoracic echocardiography was done to all patients. Left ventricular dimensions were measured by M-mode in short axis parasternal view. Left ventricular ejection fraction (EF) was calculated by M-mode in case of normal regional wall motions and by 2D (modified Simpson's equation) in the presence of segmental wall motion abnormalities. Valve assessment including morphology, motion, transvalvular flow, and valve regurgitation was done. Structural heart disease was defined as the presence of dilated chambers, akinetic segments, low EF ($<50\%$), or any significant (more than moderate) valve lesion. Cardiomyopathy (CM) was defined as dilated left ventricle (LV) with or without low EF.

Abdominal ultrasound was done to assess liver size and parenchyma, any abdominal fluid collection, or splenomegally. Congestive hepatomegaly was defined as increased liver size (with or without splenomegally), attributed to right sided heart failure or severe tricuspid regurge on echocardiography, with tender hepatomegaly and hepatojugular reflux on physical examination.

2.4. Amiodarone therapy and in-hospital course

Amiodarone was given by IV loading of 5 mg/kg as a 30 min IV infusion, followed by infusion of 10 mg/kg/day over 24–48 h. Indication of therapy was documented by 12-lead surface electrocardiogram (ECG). The duration, total dose received, and the need of amiodarone discontinuation were recorded. Causes of discontinuation included significant liver injury defined as >10 fold rise in aminotransferases relative to ULN, hemodynamically significant bradyarrhythmias, ineffec-

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