

Fatal gastrointestinal bleeding and perforated duodenal ulcer: a rare complication of deferasirox in a patient with liver cirrhosis.

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Abstract

We report here a case of deferoxamine (DFX) related gastrointestinal bleeding and duodenal perforation in a cirrhotic patient after the use of deferasirox for secondary hemochromatosis. Duodenal ulcer bleeding and perforation is noted as a rare adverse event in the scientific product information of deferasirox, in our current knowledge, this is the first case-report on this adverse drug reaction at adult patients. Clinicians must be aware that deferasirox use in a cirrhotic patient may have a potential risk of complicated gastrointestinal ulceration. It is recommended that patients undergoing treatment with deferasirox especially with liver cirrhosis are monitored regularly for adverse events.

Keywords: Gastrointestinal bleeding, Duodenal ulcer, Deferasirox, Liver cirrhosis.

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Introduction

Patients receiving multiple transfusions for anemia are at a great risk of developing secondary hemochromatosis. Iron overload represents a major concern in secondary hemochromatosis because it is a leading cause of morbidity and mortality in patients who do not receive proper iron chelation therapy [1]. The oral iron chelator deferasirox is licensed in over 70 countries worldwide [2]. Before deferasirox was approved, two other iron-chelating agents were licensed for treatment of iron overload, namely desferoxamine and deferiprone. Deferasirox is a novel iron chelator which can be administered once daily orally, resulting in an increased survival for secondary hemochromatosis these patients [3]. The main adverse events of deferasirox are transient gastrointestinal complaints [4,5]. Gastrointestinal bleeding and perforation related to deferasirox has been reported in children [6,7]. Best to our knowledge gastrointestinal bleeding and perforation has never been reported in the adult. We report here a case of deferoxamine related gastrointestinal bleeding and duodenal perforation in a cirrhotic patient treated with deferasirox for secondary hemochromatosis.

Case Report

A 69-year-old female was diagnosed with haemolytic anaemia and subsequently received multiple red blood cell transfusions (36 units in two year) at another hospital. She was sent our clinic for the suspicion of chronic liver disease. Patient was hospitalized. She had type 2 diabetes mellitus (DM) and metabolic syndrome. She was using subcutaneous insulin analogues; amlodipine besilat and proton pump inhibitor. The

body mass index of the patient was 32. No active alcohol or illicit drug use was reported. Laboratory studies revealed that AST/ALT levels were 87/65 U/L respectively. Ferritin levels were 2480 g/L, Fe was 150 µg/dL and total iron binding capacity was 90 µg/dL and transferrin saturation was 55%. Ultrasound of the liver revealed a heterogeneous parenchyma structure, an irregular edge and grade III steatosis, spleen length was 140 mm. Gastroscopy showed grade 1 esophageal varices, without other pathological features. Other reasons that may lead to cirrhosis were investigated. Chronic viral hepatitis panel for hepatitis B and C were negative. The laboratory tests for Wilson disease, hemochromatosis and α 1-antitrypsin deficiency were unrevealing. Hemochromatosis gene analysis (C282Y and H63D mutations) was negative. Magnetic resonance imaging demonstrated decreased signal intensity in the affected liver parenchyma on the in-phase images compared with the out-of-phase images (Figure 1). Child and MELD scores of the patient were 6 (A) and 10 respectively. We decided that the reason of chronic liver disease could be the combined effects of nonalcoholic steatohepatitis and secondary hemochromatosis due to excessive blood transfusion which caused iron overload. The cause of anemia was investigated. Laboratory studies about hemolysis showed that the haptoglobin level was very low and LDH and indirect bilirubin levels were high. Coombs test was positive. Serological markers for anti-nuclear antibody (ANA), Epstein Barr virus and cytomegalo virus were negative. We decided to start deferasirox at a dose of 1 g/day for secondary hemochromatosis. Two weeks later after starting deferasirox she was admitted to our institution with abdominal pain and melena. She denied any use of nonsteroidal anti-inflammatory medications, acetylsalicylic acid, bisphosphonates, antibiotics

or other medications. Laboratory studies showed anemia (Hgb 5.7 mg/dl) and leukocytosis ($21400/\text{mm}^3$) with a neutrophil predominance. Kidney functions were normal. Upper gastrointestinal endoscopy revealed a large ulcer at the bulb of the duodenum which expands till the second part of the duodenum. There was no active bleeding but a large fixed coagulum at this area. There is no sign of variceal bleeding. Pantoprazole infusion was started and 4 units of red blood cell transfusion were given. The day after, her abdominal pain persisted; at physical examination rebound tenderness was observed. Abdominal X Ray scan showed subdiaphragmatic free air (Figure 2). Emergency surgical consultation was done but she was transferred to the intensive care unit because of the hypovolemic shock before the surgical operation. A diagnosis of deferasirox-induced gastrointestinal bleeding and perforation was therefore made. The patient was unresponsive to the intravenous fluids infusion of and to the vasopressive treatment. The patient died before emergency surgery could be performed.

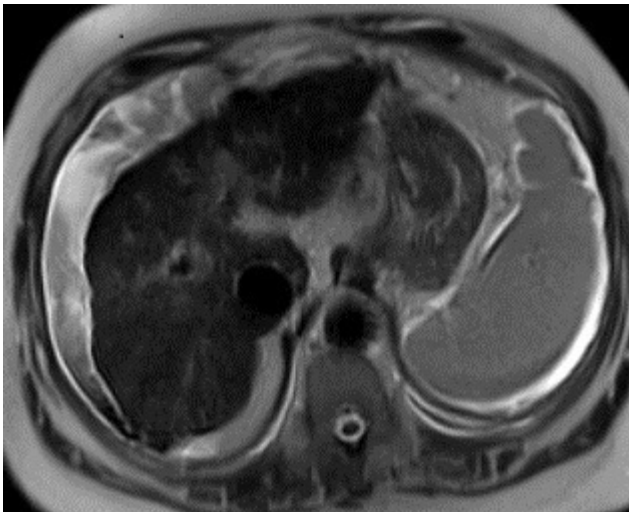


Figure 1. MRI view of liver cirrhosis.

Discussion

Patients with cirrhosis are at risk for both variceal and non-variceal causes of upper gastrointestinal bleeding; however, only variceal bleeding has been widely studied. Nevertheless, there remains one third of non-variceal upper gastrointestinal bleeding in cirrhotic patients due to peptic ulcers (PU) as reported in the literature [8]. In addition, bleeding PU has been associated with substantial morbidity and mortality in cirrhotic patients [9]. Peptic ulcers have frequently been associated with liver cirrhosis. There is a 5- to 8-fold increased risk of duodenal ulcers in patients with cirrhosis compared with the general population [10,11]. Patients with cirrhosis and bleeding peptic ulcers had a mortality rate of 20%, which was higher than that in patients without cirrhosis [12]. The factors which are responsible for the increased prevalence of peptic ulcers in patients with cirrhosis are still unknown. It has been demonstrated that the gastric mucosa of rats with portal hypertension is more susceptible to aggressive agents, such as bile acid and alcohol than that of healthy rats [13,14].

Long-term transfusion therapy leads to iron overload and results in significant morbidity and mortality if left untreated [15]. Using iron-overload chelation therapy improves patient survival [16,17]. Deferasirox is highly selective for ferric iron, with which it forms a stable complex in a 2:1 ratio. The deferasirox-ferric iron is eliminated predominantly through feces. Its high bioavailability and long half-life means it is suitable as a once-daily oral treatment [18]. In the literature, in relation to about adverse effect deferasirox, Huang et al., found significant higher risk of GI bleeding associated with deferasirox use [19].

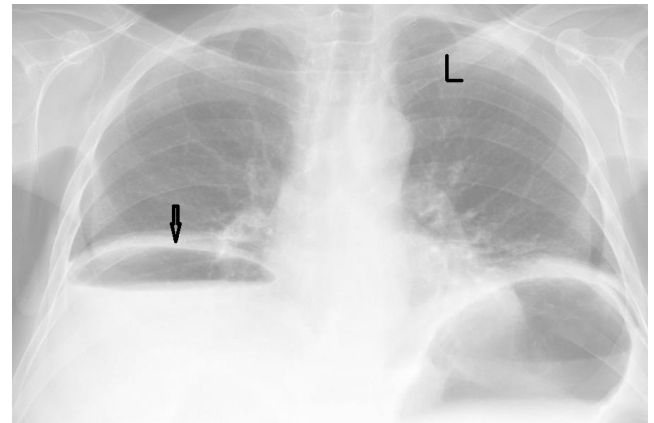


Figure 2. X-Ray view of subdiaphragmatic free air.

To our best knowledge, we report the first case of gastrointestinal bleeding and perforation associated with the use of deferasirox in an adult patient. Other potential causes of gastrointestinal bleeding and perforation like non-steroidal anti-inflammatory medications have been ruled out in our case. In our case portal hypertension induced gastropathy and thrombocytopenia might have induced tendency to gastrointestinal ulceration. Our case illustrates these potential risk factors for deferasirox-induced gastrointestinal bleeding and perforation. We must be aware that this single case report does not prove any causality link with gastrointestinal ulcer and deferasirox. Clinicians must be aware that deferasirox use in a cirrhotic patient may have a potential risk of complicated gastrointestinal ulceration. Careful monitoring is mandatory for patients undergoing treatment with deferasirox especially in patients with portal hypertension associated with liver cirrhosis.

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