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Case Report
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Esomeprazole Induced Liver Injury

Santosh Raj Sharma, Dhuha Alhankawi and James Park*

Department of Hepatology, New York University, USA

Abstract

Proton Pump Inhibitors (PPIs) are one of the most widely prescribed medications. Recently PPIs have been linked to causing dementia, vitamin B_{12} deficiency, *Clostridium difficile*, interstitial nephritis, osteopenia etc. We present a case of a 65 years old female who developed biopsy proven Acute Liver Failure (ALF) after starting Esomeprazole a PPI. The liver recovered after Esomeprazole was stopped. Our case provides convincing evidence that Esomeprazole could be linked to liver injury. Once thought the safest and the most prescribed group of medications, is it time to add one more adverse effect on their extensive list of adverse effects?

Introduction

Esomeprazole is a medication of the Proton Pump Inhibitor (PPI) family used to treat Gastroesophageal Reflux Disease (GERD) and peptic ulcer disease by inhibiting H+/K+ ATP in the gastric parietal cells [1]. Owing to its effectiveness in acid suppression, it became the best-selling drug in the world [2]. Recent studies have raised the concern of safety of PPIs with association of numerous diseases like dementia, vitamin B_{12} deficiency, hypomagnesaemia, interstitial nephritis, gastric carcinoid tumor, bone fractures, cardiovascular risk, *clostridium difficile* infection and community acquired infection [3-6]. Drug Induced Liver Injury (DILI) is the commonest cause of liver failure and many medications are known to cause DILI [7]. Despite the wide use Esomeprazole it has not been associated with liver injury. Esomeprazole was not mentioned as a drug to cause liver injury in a large study on drugs causing liver injury [8]. Nonetheless it was associated with rise in serum Alanine Aminotransferase (ALT) in less than 1% of the patients [9]. Interestingly there are cases reported of PPIs causing liver injury [9,10].

We present a case of a 65 years old female, who presented with acute liver failure after receiving Esomeprazole therapy.

Case Presentation

A 65-year-old female with no known liver disease presented with jaundice, dark urine and light stool 3 days after starting Esomeprazole for heartburn which prompted her to stop the medication and seek medical attention. Outpatient laboratory studies were significant for total bilirubin of 12.4 mg/dl, AST 374 U/L, ALT 678 U/L, ALP 114 (U/L) and INR of 2. The patient was immediately sent to emergency department by her primary physician for further evaluation. Her mental status remained intact. Inpatient studies laboratory studies showed consistent elevation of liver test as well as positive ANA (antinuclear antibody) of 1:320 and AMA (Antimitochondrial Antibody) of 1:20. Due to concern for drug induced liver injury and possible autoimmune liver disease given positive autoimmune markers, liver biopsy was performed which showed acute cholestatic hepatitis compatible with Drug Induced Liver Injury (DILI). She received supportive care and daily repeat in liver enzymes. The patient's serum aminotransferase levels improved to AST 113 U/L, ALT 278 U/L respectively and total bilirubin of 10 upon discharge. At outpatient visit 6 week later, her labs were back to normal.

Discussion

DILI is the most common cause acute hepatitis in the United States accounting for 10% to 13% of all the cases [11,12]. DILI can be broadly classified into predictable (for example dose dependent liver injury of Tylenol) or unpredictable (where the effect of drug is unknown) [13]. Though not clearly understood, the possible mechanisms of DILI are impaired intracellular calcium homeostasis causing disarray of actin fibrils leading to cell rupture and cell lysis, loss of villous processes and disruption of transport pumps, stimulation of apoptotic pathways by tumor necrosis factors and mitochondrial dysfunction reducing the ATP production [7]. In general adults are more commonly affected than children (except valproic acid) and women are more commonly affected

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Correspondence:
Santosh Raj Sharma, Department of Hepatology, New York University, New York, USA, Tel: 3033303782; E-mail: santosh.sharma@nyumc.org

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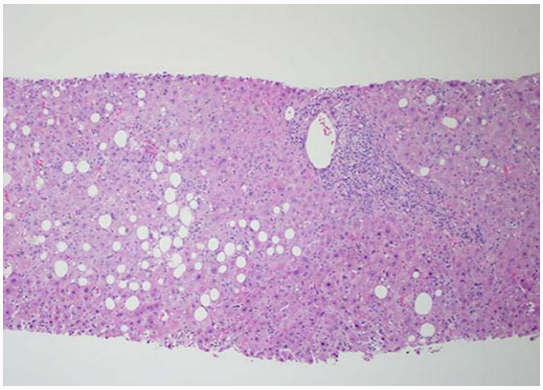

Figure 1: The normal architecture of the liver is preserved without scarring. There is marked portal and lobular inflammatory infiltrates and mild steatosis.

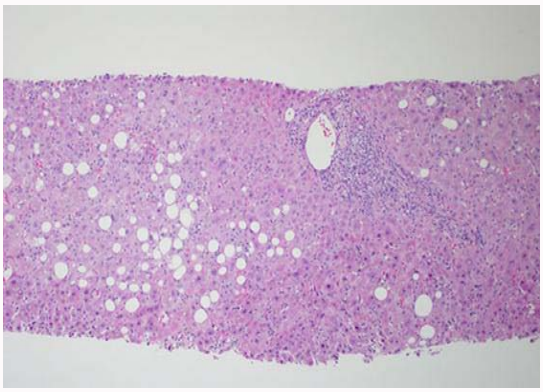

Figure 2: Portal tracts contain a mild mixed inflammatory infiltrate including eosinophils (thin arrow). Lobular hepatitis is evidenced by collections of pigment laden macrophages (angled arrow), focal mixed inflammatory infiltrates and scattered acidophil bodies (thick arrow).

than men [11]. The mode of injury can be cytotoxic, cholestatic, or mixed [12]. Based on the pattern of injury DILI can be classified into acute, hepatocellular (ALT>3 times upper limit), cholestatic (ALP>2X upper limit), mixed (elevated ALP and ALT), chronic, steatohepatitis, microvesicular steatosis, granulomatous hepatitis, sinusoidal obstruction syndrome, fibrosis, hepatic adenoma and autoimmune hepatitis [14].

More than 1000 medications are known to cause liver injury and they are classified to one of the patterns of DILI but none of the PPIs including Esomeprazole are classified into any patterns [7,14]. Based on the type of pattern of liver injury different drugs might have different presentations [14]. The association of esomeprazole responsible for the liver injury in our case can be supported by the following points [10]: a) no prior history of liver disease b) no serological evidence of viral hepatitis c) imaging studies did not reveal bile duct abnormalities d) No other drugs taken before the event e) no herbal medication taken before having symptoms f) occurred after administration of Esomeprazole g) liver enzymes improved after discontinuation of Esomeprazole h) liver biopsy was suggestive of Drug Induced Liver Injury.

In our case patient had hyperbilirubinemia with markedly elevated with liver enzymes (ALT>AST) but alkaline phosphatase was only minimally elevated. Autoimmune parameters like ANA and AMA were also positive. This raises the possibility that Esomeprazole

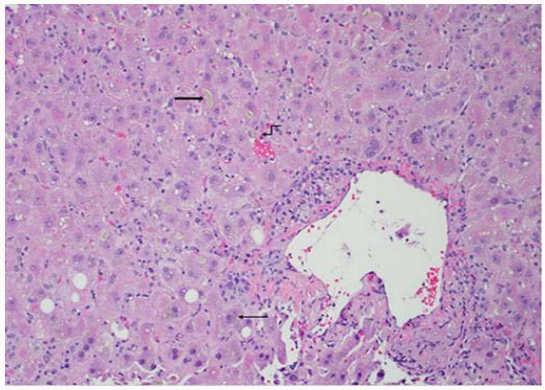

Figure 3: Cholestatic features are evidenced by prominent bilirubinostasis in zone 3 hepatocytes (thin arrow), focal canalicular bile plugs (thick arrow) and bile pigment in macrophages (angled arrow).

causing cytotoxic liver injury with autoimmune hepatitis. A case was published of possible liver injury caused by Esomeprazole in a pregnant female concomitantly taking metoclopramide and pyrazinamide unlike our case [7]. The ALT and AST was elevated to 267 and 137 respectively (much lower than in our case) and ALP was minimally elevated. Esomeprazole was switched to Pantoprazole and patient had normalization of the LFTs. It is unclear if they discontinued or continued the other two medications [7]. Naranjo Adverse Drug Reaction Probability scales were used to justify as probable Esomeprazole liver injury [7]. Another case was reported where 1 dose of 20 mg Esomeprazole used in conjunction with chemotherapy (Paclitaxel) let to cytolytic liver injury [15]. After discontinuing the Esomeprazole, the liver enzymes normalized despite continuing the chemotherapy [15]. A study reported a case of Pantoprazole causing autoimmune hepatitis where ALT was 1520, AST was 1419, ALP was 396, GGT was 715 µmol/l and ANA titer was 1:640. This was the other case where liver biopsy was performed showing drug induced autoimmune hepatitis. Patient was treated with immunosuppressive therapy and successively recovered with normalization of the liver function tests over a period of several months [10] (Figure 1-3).

Histologic appearance of DILI is variable and is based on the mode of injury [16]. Almost 90% of the cases manifest as acute hepatocellular injury [16]. It leads to hepatocellular necrosis/apoptosis, steatosis and cellular degeneration [16]. The hepatocellular injury can affect single or a group of hepatocytes leading to confluent necrosis followed by bridging necrosis, sub-massive and massive necrosis resulting in acute liver failure [16]. Most DILI related hepatocellular injuries recover without fibrosis [17]. Even when there is suspicion of DILI, other causes of hepatitis esp. viral hepatitis need to be ruled out [18]. Most of the cases will show improvement with just discontinuation of the offending drug, bilirubin value more than 3 g/l has mortality of more than 10% [18]. Drug induced Acute Liver Failure has high mortality which prompts early diagnosis and treatment including referral to liver transplantation [14].

Studies have already raised the concern the safety of PPIs in cirrhotic patients [19]. There are not enough evidences to link PPIs including Esomeprazole to acute liver failure, however cases are emerging. Our case is a biopsy proven case of Esomeprazole causing liver injury. It provides convincing evidence that Esomeprazole could be linked to liver injury. Once thought the safest and the most prescribed group of medications, is it time to add one more adverse effect on their extensive list of adverse effects?

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