Effect of esomeprazole on some liver enzymes in patients with peptic ulcer

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Keywords:
Peptic Ulcer, Esomeprazole, Liver Enzymes, PPIs.

\textbf{ABSTRACT}

Esomeprazole is a proton pump inhibitor (PPIs) successfully used to inhibit gastric acid secretion and treat peptic ulcers and other acid-related disorders. However, the studies of the effect of esomeprazole on liver enzymes are limited. This study aims to investigate the effect of esomeprazole on liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphates (ALP) in peptic ulcer patients. Twenty-nine omeprazole users and twenty-four health control were recruited from outpatient clinics. Serum levels of liver enzymes Alanine transferase (ALT), aspartate transferase (AST), and alkaline phosphates (ALP) were evaluated at least 2 months after the medication use. Serum levels of ALP (74.31\pm 19.63 U/L, P<0.0001) were significantly higher in esomeprazole users compared to non-users. While serum levels of ALT (16.07\pm 6.3 U/L, P=0.008) were significantly lower in esomeprazole users. Serum AST levels (18.86\pm 6.4 U/L, p= 0.192) were not changed between the 2 groups. Whilst this study did not confirm the hepatotoxicity of esomeprazole on the liver, it could indicate that esomeprazole might affect the liver. Further research is required to determine whether esomeprazole is hepatotoxic or not.

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1. Introduction

The rate of peptic ulcer disease (PUD) has been estimated to be about 5-10% in the general population's lifetime time, with an annual incidence of 0.1-0.3% \cite{1,2}. Nevertheless, the number is declining due to the decrease in infection rate and the availability of effective treatment for Helicobacter pylori (H. pylori) \cite{3}, and the innovation of new therapies \cite{2}. Many drugs are used in the management of PUD such as proton pump inhibitors (PPIs), H2 receptor blockers, sucralfate, and antibiotics if the patient is H. pylori-positive. The PPIs, such as omeprazole, lansoprazole, esomeprazole... etc, are prescribed as a gold-standard therapy for PUD, as they potentially provide stronger acid suppression, and recovery rates and symptom relief compared to H2 blockers \cite{4}. The mechanism of PPI depends on the binding to the cysteine residues of the proton pump leading to inhibition of the gastric H+/K+-ATPase and thereby suppressing gastric acid production \cite{5}. Esomeprazole (the S-isomer of omeprazole) was developed to increase the efficacy of PPI in the treatment of acid-related disease \cite{6}. This is because It has been reported that esomeprazole undergoes a slower metabolic rate compared to omeprazole in the liver, and therefore it leads to a higher
plasma concentration resulting in more effective control of gastric acid secretion [7]. Even though esomeprazole is well tolerated by most users, it has been associated with uncommon side effects such as “abdominal pain, nausea, dyspepsia, diarrhoea, headache intolerance, malaise, and pruritis” [8]. However, some studies reported that PPI might be related to a number of serious but uncommon side effects such as “acute and chronic kidney disease, hypomagnesemia, liver injury, pneumonia, and osteoporotic fractures” [9], [10]. However, the effect of esomeprazole on liver enzymes is still unknown and since the liver is the primary site of esomeprazole metabolism, it is imperilled to drug-induced toxicity.

Liver enzymes, such as “aspartate aminotransferase (AST), alanine aminotransferase (ALT), and Alkaline phosphatase (ALP)” are the most frequently used markers in liver function tests. They are used as a diagnostic tool for liver diseases and monitoring side drug effects [11]. Therefore, the objective of this study is to investigate if liver enzymes (AST, ALT, and ALP) are changed in peptic ulcer patients treated with esomeprazole.

2. MATERIALS AND METHODS
This prospective observational study was conducted on patients with a PUD who were recruited from outpatient clinics in Mosul city (North of Iraq), between 2020 and 2021. Only those patients with no chronic diseases or polypharmacy, non-lactating mother, and non-pregnant were enrolled in the present study. The patient should be on esomeprazole therapy for at least two months (40 mg per day; Nexium, AstraZeneca, UK).

Fifty-three subjects were included in the study. They were divided into 2 groups; group 1 consisted of 29 subjects, mean age of 35.14±16.6, who used 40mg/ day of esomeprazole. Group 2 consisted of 24 subjects, mean age of 41.54±11.05 years, who were non-esomeprazole-users as a control group.

For liver enzyme detection, venous blood samples were withdrawn from patients and control groups, serum was separated and samples were frozen for future analysis. Determination of ALT, AST and ALP in serum were measured according to the manufacturer's instructions using colourimetric assays using a kit supplied by Thermo Fisher Scientific [THS] Infinity™ ALT (GPT) Liquid Stable Reagent, InfinityTM AST (GOT) Liquid Stable Reagent, and Alkaline Phosphatase (ALP) Reagent respectively.

The results were cited as mean ± standard deviation. Quantitative data were analysed by the chi-square test. Comparisons between users and non-users were done with an independent t-test for age, weight, and liver enzymes. A value of P < .05 was considered significant.

3. Results
Characteristics of the participants (esomeprazole users and non-users) are shown in Table 1. The 2 groups were matched regarding age and Body weight as evident by a non-significant difference between the 2 groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=24)</th>
<th>Esomeprazole users (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of esomeprazole users and control
Female 12 16

Age (years) 39.29 ±9.9 35.14 ±16.6 0.287

Weight(kg) 68 ±7.11 65.28 ±13.06 0.272

The mean levels of ALP increased significantly in esomeprazole users compared with the control group (non-users). Whereas the mean levels of ALT were significantly lower in esomeprazole users than in the control group. However, there were no significant changes in Aspartate transaminase as shown in Table 2 and Figure 1.

Table 2. Liver enzyme levels (IU/L) in the studied group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (n=24)</th>
<th>Esomeprazole users (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>53.25±16.22</td>
<td>74.31±19.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST</td>
<td>21.17±5.85</td>
<td>18.86±6.64</td>
<td>0.192</td>
</tr>
<tr>
<td>ALT</td>
<td>20.88±6.38</td>
<td>16.07±6.30</td>
<td>0.008</td>
</tr>
</tbody>
</table>

The results represent the mean ± standard deviation

![Figure 1](image)

**Figure 1.** The effect of esomeprazole on serum ALP, AST, and ALT levels.

Data are presented as Mean ±SD. Statistical significance was evaluated with a t-test. *** represent p<0.001
and represent **** p<0.001.

4. Discussion
The liver is one of the most susceptible organs to drug adverse reactions because of its vital role in drug metabolism. The effect of medication on the liver can lead to liver injury that might necessitate withdrawal of the medication. Drug-induced liver injury (DILI) is unpredictable and classified into cholestatic, hepatocellular, and mixed, which is usually based on alteration in blood levels of ALP and ALT [12]. Therefore, studying esomeprazole’s effect on the liver was anticipated, as it is a widely prescribed treatment for peptic ulcers and other acid-related diseases.

Although, PPIs have been considered to be safe medications with no notable side effects when used in the long term. However, a large-scale epidemiologic study suggests that PPI use was related to a higher risk of fatty liver disease compared with non-use of PPIs [13]. A study by AL-Hadrawy and AL-Turfi showed that rats treated with esomeprazole for the long term (3 months) had significantly higher ALT, ALP and total bilirubin levels in comparison with short-term exposure (2 weeks) and non-exposed animals. Moreover, long-term exposure induced histological changes in the liver including blood vessel congestion and hepatic cell degradation [14]. Likewise, a case study reported abnormal liver function tests and significantly high AST, ALT and ALP levels in a female patient who used esomeprazole for 3 days and liver biopsy confirmed acute cholestatic hepatitis consistent with DILI. However, the liver functions back to normal after 6 weeks of esomeprazole cessation [15]. In addition, [16] reported a significantly higher liver enzyme in a pregnant woman taking esomeprazole which then markedly improved within days following the withdrawal of the drug. In England, a Prescription-Event Monitoring Study examined the safety profile of esomeprazole prescribed by health professionals had reported 3 cases with abnormal liver function test. one case noted that liver function test was back to normal after switching to a different medication while the abnormality in the second cases was attributed to atorvastatin use. Hence, the abnormal liver function test was resolved without stopping treatment in the third case [8]. On the same scale, a “Cross-Sectional Study” used the FDA Adverse Event Reporting System database to assess the relationship between PPIs use and hepatotoxicity-related adverse effects using the reporting odds ratio (ROR). The study showed that the top five hepatotoxicity-related adverse effects signals triggered by PPIs were “hepatitis cholestatic, cholestasis, fulminant hepatitis, subacute hepatic failure, and acute hepatitis”. Esomeprazole showed the highest ROR of 21.556 in the cholestasis signal [17].

Recent literature has reported esomeprazole-induced liver damage in patients with other underlying conditions. [18] reported patients with chronic liver disease who used PPI had a 67% increased risk of developing hepatocellular carcinoma and a 57% higher mortality rate than chronic liver disease patients not using PPI. In another study, PPI use was considered a risk factor in patients with liver cirrhosis as its use was associated with a higher mortality rate in cirrhosis patients compared to non-users [19]. The increase in mortality rate might be associated with increased risks of hepatic encephalopathy in cirrhotic individuals using PPI [20]. A Recent systemic review suggested that PPIs modified the structure and role of the intestinal microflora which were related to adverse effects in liver diseases. Also, PPI may raise the hazard of spontaneous bacterial peritonitis infection and hepatic encephalopathy. In addition, PPIs influenced the “direct-acting antiviral” routine in “chronic hepatitis C” individuals. Also, PPI was linked with an increased risk of liver abscess. Furthermore, PPIs could predispose metabolic risk events, for instance, put on weight liver and steatosis [20]. So far, the findings from the above studies and meta-analysis sought to evaluate the impact of PPI on the liver, there is inadequate evidence to confirm that PPI use increases the incidence of liver complications and mortality.
The results of this experimental study showed patients using esomeprazole had significantly higher ALP in comparison with non-users, but there was no statistically significant difference between the 2 groups regarding AST. The results also revealed serum ALT level was significantly lower in esomeprazole users than non-users. Though, liver enzymes in both groups were within the normal range. The increase of ALP in this study was in accordance with other studies [14], [15]. Nevertheless, the ALP was the only enzyme that is significantly higher in esomeprazole users, this might indicate that the source might not be from the liver. ALP can be found in the liver, bone, intestine, placenta and leukocytes [21]. Therefore, further investigations are required to examine the effect of esomeprazole on the liver for example gamma-glutamyl transpeptidase (GGT) and 5'-nucleotidase (5NT). These enzymes increase in concordance with the liver ALP [21]. In addition, the significantly lower ALT levels in esomeprazole users might be attributed to other causes such as vitamin B6 deficiency [22], regular exercise [23], chronic kidney disease [24], and zinc deficiency [25].

The limitation of the present study is the sample size was small and to confirm our result we do advise conducting a large-scale multicentre study to obtain more accurate results. Our study lack comparison with other PPIs especially the prototype, omeprazole. Moreover, the ulceration in different patients could be at a different level of severity which could interfere with digestion and food consumption, thereby subsequently responsible for liver damage effects.

PPIs are a very effective therapy for PUD, therefore, the side effects profile needs to be titrated to the individual patients i.e. contraindication should only be advised when there are obvious liver abnormalities. We do advise using different remedies to mitigate liver injury induced by esomeprazole, the might includes, vitamins [26], [27], minerals [28], [29], or herbal remedies [30].

5. Conclusion
This study could not conclude the effect of esomeprazole on liver enzymes. Future larger studies and more parameters are required to better understand and evaluate the hepatotoxicity of esomeprazole on the liver.

6. References


