

Proton pump inhibitors in liver cirrhosis: a review of benefits and harms

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Contributions: (I) Conception and design: X Qi; (II) Administrative support: X Qi; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: J Zhu; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Proton pump inhibitors (PPIs) are acid suppressants, which can effectively control gastric acid secretion through inhibiting the H⁺/K⁺ ATPase of parietal cells. In recent years, PPIs are extensively prescribed in patients with liver cirrhosis. The impact of PPIs in such patients is controversial. Helicobacter pylori eradication and reduction of endoscopic treatment related complications are the potential benefits of PPIs in liver cirrhosis. By contrast, bone fracture, clostridium difficile infection (CDI), spontaneous bacterial peritonitis (SBP), and hepatic encephalopathy (HE) are the potential harms of PPIs in liver cirrhosis. Further, prospective studies are required to refine the special indications and contra-indications for PPIs in cirrhotic patients.

Keywords: Proton pump inhibitors (PPIs); liver cirrhosis; helicobacter pylori eradication; endoscopic treatment; bone fracture; clostridium difficile infection (CDI); spontaneous bacterial peritonitis (SBP); hepatic encephalopathy (HE)

Received: 01 January 2017; Accepted: 08 March 2017; Published: 30 March 2017.

doi: 10.21037/amj.2017.03.04

View this article at: <http://dx.doi.org/10.21037/amj.2017.03.04>

Introduction

Liver cirrhosis

Liver cirrhosis is the end-stage of liver disease, in which the liver is gradually shrunk and is separated by broad fibrotic bands related to extensive necrosis and regenerative nodules of liver cells (1). Liver cirrhosis can result in hepatic encephalopathy (HE) and spontaneous bacterial peritonitis (SBP), which are associated with a high mortality (2). The overgrowth of intestinal bacteria and the development of bacterial translocation increase the risk of infection and HE in cirrhotic patients (3-5). The severity of liver cirrhosis is positively associated with the development of small intestinal bacterial overgrowth (6). On the other hand,

intestinal permeability is often increased in patients with cirrhosis, which leads to the translocation of bacteria and endotoxins into the portal venous system, thereby impairing the immunity (7,8).

Proton pump inhibitors (PPIs)

PPIs are effective acid suppressants that are widely prescribed for managing various acid related disorders. As the front-line choice of therapy, they block gastric acid secretion through inhibiting the H⁺/K⁺ ATPase of parietal cells (9) and are metabolized in the liver by the CYP450 cytochrome (10).

The use of PPIs is common in cirrhotic patients

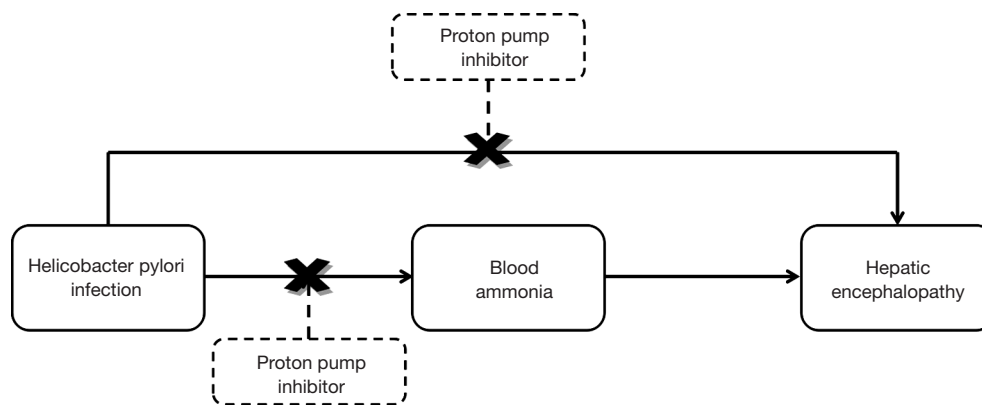


Figure 1 Possible relationship between proton pump inhibitor and decreased risk of hepatic encephalopathy.

at present. However, the prescription of PPIs in such patients is often lacking of specific indications, such as gastroesophageal reflux disease, peptic ulcers, non-variceal upper gastrointestinal bleeding, and bleeding prophylaxis in selected users of nonsteroidal anti-inflammatory drugs (11-15). Recent studies suggested that the use of PPIs might decrease the abundance and diversity of gut microbiota and lead to the growth of pathogens and the overgrowth of unhealthy species (16-18). Long-term use of PPIs may increase the incidence of bone fracture (19), clostridium difficile infection (CDI) (20,21), HE (22), and SBP (23,24), which may be related to the overgrowth of bacteria (3,25).

The purpose of this paper is to review the potential benefits and harms of PPIs in liver cirrhosis.

Potential benefits of PPIs

Peptic ulcer treatment and helicobacter pylori eradication

Recent studies found that liver cirrhosis increased the risk of peptic ulcers (26,27). The prevalence of peptic ulcers is higher in decompensated cirrhosis than in compensated cirrhosis (28). Currently, PPIs are the mainstay treatment option of peptic ulcers in the general population (29-31).

Cirrhotic patients also have a high proportion of helicobacter pylori infection. Helicobacter pylori promotes the conversion of urea into ammonia, which enters into the systemic circulation. Helicobacter pylori infection contributes to the development of hyperammonemia (32,33) and subsequent episodes of HE (34,35) in cirrhosis. Helicobacter pylori eradication has been improved by PPIs-based triple therapy (36). Notably, blood ammonia

concentration is significantly reduced after PPIs-based triple treatment in cirrhotic patients (34,35). As well known, the application of PPIs triple therapy can effectively treat helicobacter pylori infection which can increase the risk of HE. Therefore, it might be true that PPIs reduce the risk of HE in patients with helicobacter pylori infection (*Figure 1*).

A meta-analysis by Vergara *et al.* pointed out that helicobacter pylori infection was a risk factor for developing peptic ulcers in cirrhotic patients (37). Similarly, Calvet *et al.* showed that helicobacter pylori seropositivity was an independent risk factor for increasing the rate of peptic ulcers in patients with cirrhosis [odds ratio (OR)=1.7; 95% confidence interval (CI)=1.02–2.81] (38). Thus, helicobacter pylori eradication with PPIs treatment should be necessary. By contrast, some studies showed that the prevalence of helicobacter pylori infection was not significantly different between cirrhotic patients with and without peptic ulcers (39,40). Additionally, a recent prospective cohort study found that helicobacter pylori eradication could not effectively prevent from the recurrence of peptic ulcer in patients with cirrhosis (41).

Endoscopic treatment

Endoscopic treatment, including endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and endoscopic variceal obturation (EVO), can effectively prevent and control variceal haemorrhage in patients with liver cirrhosis. According to the current U.K. practice guideline, due to the potential harms of PPIs, they are not recommended for acute variceal bleeding unless patients are accompanied by peptic ulcer (42). However, post-EVL or EIS ulcer bleeding is life-threatening and gastric

acid is a significant risk factor which delays post-EIS ulceration healing (43). Therefore, PPIs may be appropriate after endoscopic treatment on the basis of the following considerations.

First, some evidence regarding the use of PPIs after EIS was controversial. Some studies found that omeprazole was effective for preventing from and healing of post-EIS ulcerations (44-46). In contrast, Garg *et al.* revealed that the use of omeprazole was not significantly effective in preventing from post-EIS ulceration in patients with portal hypertension (47).

Second, the evidence uniformly supported the use of PPIs for reducing the risk of complications after EVL. A randomized controlled trial demonstrated that pantoprazole reduced the size of post-EVL ulcerations, rather than the number of ulcerations or symptoms (48). Hidaka *et al.* suggested that the long-term use of PPIs decreased the risk of variceal hemorrhage or severe medical complications after EVL (49). A more recent study with 505 cirrhotic patients also showed that non-use of PPIs was an independent risk factor associated with bleeding after prophylactic EVL by multivariate logistic analysis (50).

Third, to our knowledge, the evidence from the only one study demonstrated that PPIs treatment was effective for prolonging the re-bleeding interval ($P=0.008$), but not the re-bleeding rate after EVO in cirrhotic patients (51).

In summary, PPIs may be appropriate for reducing the risk of complications after endoscopic treatment.

Potential harms of PPIs

Osteoporosis and bone fracture

Osteoporosis refers to an abnormal condition that the bone becomes weak and can be easily broken, reduces the life quality, and increases the risk of bone fracture. Some researchers suggested that the use of PPIs should increase the risk of bone fracture (19,52) and observed a dose- or duration-response effect of PPIs on the risk of bone fracture (53-57). The potential mechanism should be that PPIs influenced the bone metabolism by inhibiting the vacuolar H^+ -ATPase of osteoclasts, thereby leading to the occurrence of osteoporosis (58). By contrast, others suggested a reduced relationship between PPIs use and bone fracture after adjusting the confounding factors (59,60). Three meta-analyses showed that the use of PPIs was a risk factor of bone fracture, but the occurrence of bone fracture might be unrelated to the dosage or

duration of PPIs (61-63). In addition, Itoh *et al.* indicated that bisphosphonate combined with PPIs increased the bone mineral density than bisphosphonate alone in patients with osteoporosis (64).

Liver cirrhosis is a risk factor for the development of osteoporosis and bone fracture. In a large nationwide population-based and case-control study, Tsai *et al.* found that cirrhotic patients had a higher risk of bone fracture than non-cirrhotic patients (65). Similarly, Bang *et al.* also found that liver cirrhosis was a predisposing factor of bone fracture (66). The potential mechanisms include (I) a reduced calcium and phosphate absorption (67); (II) effect of bilirubin on the osteoblast viability (68); (III) poor nutritional and dietary (69); and (IV) effect of increased inflammation on the bone mineral density (70,71). By contrast, there was no significant association between bone mineral density and primary biliary cirrhosis (72,73).

Taken together, the current evidence indicated two important aspects: (I) an association between PPIs and bone fracture; and (II) an association between liver cirrhosis and bone fracture. Thus, we hypothesized that the use of PPIs might aggravate the risk of bone fracture in cirrhosis (*Figure 2*), but the direct evidence was lacking.

CDI

The incidence of CDI is being increased in this world. In the general population, the association between PPIs with CDI is a bit controversial. Some studies showed that PPIs therapy was prone to CDI (74-77) due to the overgrowth of gut microbiota (17). PPIs therapy elevates the pH value and promotes the survival of clostridia species (78). By contrast, a population-based study showed that PPIs were not associated with CDI after adjusting the confounding factors (79).

Liver cirrhosis leads to a higher risk of healthcare-associated and hospital-acquired bacterial infections (80). The incidence of CDI has been increased among the cirrhotic patients. Cirrhotic patients with CDI are prone to worse outcomes (20,81-83). A large study, using Nationwide Inpatient Sample database, revealed that CDI was a predictive factor of mortality in cirrhotic patients (20). CDI was prone to higher mean length of stay and hospital charges in cirrhotic patients (20). A retrospective study with 162 cirrhotic patients admitted to a tertiary care center revealed that the proportion of PPIs use was significantly higher in cirrhotic patients with CDI than in those without CDI (20). Besides, a multivariable analysis demonstrated

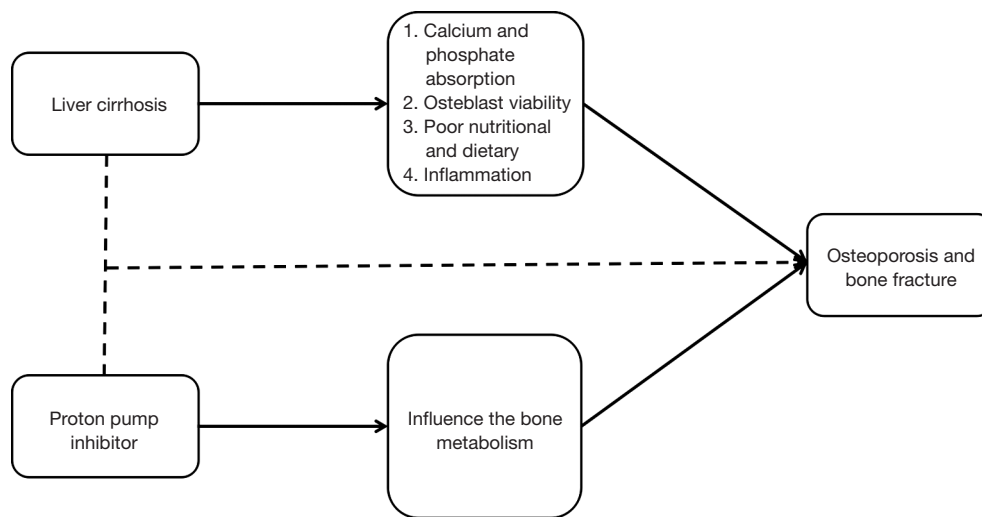


Figure 2 Possible relationship between proton pump inhibitor and increased risk of bone fracture in patients with liver cirrhosis.

that PPIs use promoted the development of CDI in cirrhotic outpatients (20). Certainly, further studies are needed to analyze a causal relationship between PPIs and CDI in patients with cirrhosis.

SBP

As one of the serious complications of liver cirrhosis, SBP is related to a high morbidity and mortality in the absence of appropriate therapy. PPIs can promote the small intestinal bacterial overgrowth (84) and altered intestinal motility, which might be the pathogenesis of SBP. Some evidence had shown that PPIs treatment was a predisposing factor for the development of SBP in patients with cirrhosis (12,24,85-88). Two case-control studies found that cirrhotic patients with SBP had a higher proportion of PPIs use than those without SBP (85,89). Three meta-analyses identified that the use of PPIs increased the incidence of SBP in cirrhotic patients (24,86,90). Xu *et al.* (24) showed that PPIs increased the risk of SBP. Similar results were obtained by Deshpande *et al.* that the application of acid-suppressive drugs increased the occurrence of SBP in cirrhotic patients (86). Besides, the prescription of PPIs had a higher risk of SBP compared with histamine H₂ receptor blockade therapy (86). The occurrence of SBP might be related to the dosage and duration of PPIs. The Taiwan National Health Insurance Research database showed a significant association between long-term PPIs treatment (>180 days) and incidence of SBP [adjusted hazard ratio (aHR) =2.28, 95% CI =1.37-3.78] by using multivariate Cox regression (87). Similar results were

shown by Chang *et al.* that prolonged PPIs use increased the incidence of SBP in cirrhotic patients (88).

In contrast, more recently, in a multicenter prospective study from Argentina, Terg *et al.* found that the prescription of PPIs was not significantly different between patients with and without SBP (91). A larger meta-analysis with 8,145 patients confirmed that PPIs use was prone to a higher risk of SBP only in case-control studies rather than in cohort studies (92). The association between SBP and PPIs would be diminished, if only high-quality data were analyzed (93).

HE

HE is a complex, reversible, and lethal syndrome of neuropsychiatric abnormalities due to acute and chronic liver dysfunction or a variety of portosystemic shunt. The impact of PPIs on the development of HE may be explained by the two following mechanisms.

First, high blood ammonia is one of the potential pathogenesis of HE (94). High ammonia levels interfere with the brain energy metabolism and produce the central inhibitory effect by an imbalance of excitability and inhibitory neurotransmitter. Additionally, small intestinal bacterial overgrowth is a risk factor of minimal HE in cirrhotic patients (95). PPIs alter the gastrointestinal motility and affect the mucosal barrier (96), thereby increasing the absorption of nitrogenous substances. PPIs also promote the overgrowth and translocation of bacteria (84). Thus, PPIs may increase the risk of HE.

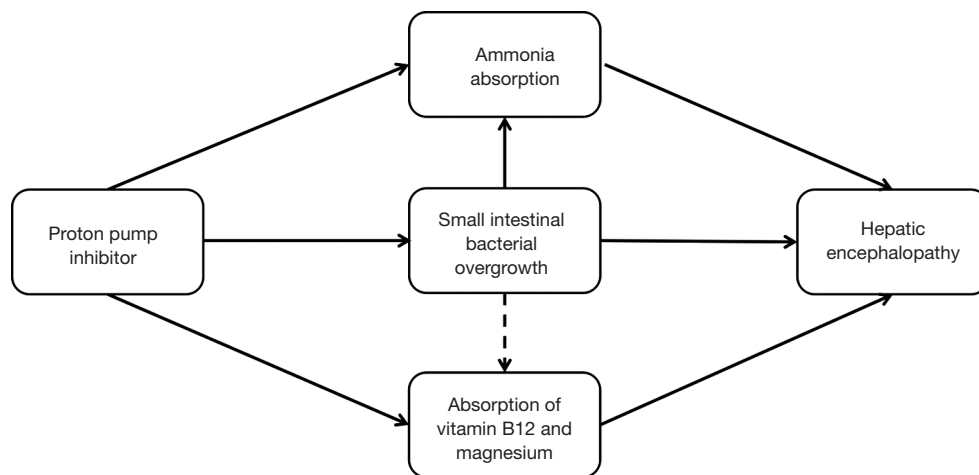


Figure 3 Possible relationship between proton pump inhibitor and increased risk of hepatic encephalopathy.

Second, PPIs therapy decreases the absorption of vitamin B₁₂ and magnesium (97,98), thereby impairing the cognitive ability (99). Some evidence found that the use of PPIs was associated with a high risk of dementia and Alzheimer's disease (100,101). Thus, PPIs may aggravate the risk of HE in cirrhotic patients (*Figure 3*).

Recently, some studies uniformly proved that the use of PPIs contributed to a higher risk of HE in liver cirrhosis. A small retrospective case-control study showed that the use of PPIs was an independent risk factor for HE occurrence (102). In a case-control study, using the Taiwan National Health Insurance beneficiaries database, Tsai *et al.* also found that the use of PPIs in patients with cirrhosis was prone to the occurrence of HE (22). Moreover, there was a dose-dependent relationship between PPIs and HE (22). Another retrospective study involving 865 cirrhotic patients with ascites demonstrated that PPIs therapy was a risk factor for the development of HE (aHR =1.36, 95% CI =1.01–1.84), particularly the occurrence of overt HE (aHR =1.88, 95% CI =1.21–1.91) (103). The cumulative risk of first-time HE is higher in patients with PPIs therapy than in those without PPIs therapy (31% *vs.* 25%) (103).

Conclusions

The widespread prescription of PPIs in patients with cirrhosis needs to be concerned. On the one hand, PPIs can effectively control the occurrence of complications after endoscopic treatment and reduce the risk of ulcers related to the helicobacter pylori infection in cirrhotic patients, which are the potential benefits. On the other

hand, the use of PPIs may increase the incidence of serious complications, such as bone fracture, CDI, SBP, and HE, which are the potential harms. However, the potential mechanisms regarding how PPIs increased the mortality remained uncertain. In future, more researches are needed to understand the impact of PPIs in liver cirrhosis.

Acknowledgements

Funding: None.

Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2017.03.04>). Andrea Mancuso serves as an unpaid editorial board member of AME Medical Journal. Xingshun Qi serves as an Editor-in-Chief of AME Medical Journal. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2017.03.04

Cite this article as: Zhu J, Yu H, Mancuso A, Qi X. Proton
pump inhibitors in liver cirrhosis: a review of benefits and
harms. AME Med J 2017;2:36.