INVITED COMMENTARY

Risks of Proton Pump Inhibitors in Patients with Cirrhosis: Please Peruse the Indications

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Abstract

The use of proton pump inhibitor (PPI) in cirrhotic patients can be associated with increased risks of long-term mortality, decompensation, hepatic encephalopathy, spontaneous bacterial peritonitis, and infection, but not with short-term mortality. Ensure clear indications at lowest effective dose of is mandatory for the use of PPI among cirrhotic patients.

Keywords Cirrhosis · Proton pump inhibitors · Hepatocellular carcinoma · Hepatic decompensation · Spontaneous bacterial peritonitis

Commentary

Although proton pump inhibitors (PPIs) are commonly prescribed for cirrhotic patients with gastroesophageal reflux or dyspeptic symptoms as well as to treat gastrointestinal bleeding (GIB), PPI use may induce dysbiosis from decreased production of gastric acid. Possible consequences of hypochlorhydria include small intestinal bacterial overgrowth, intestinal mucosal inflammation, and intestinal paracellular permeability, and possibly directed translocation of luminal bacteria into submucosal lymphoid tissue [1]. Indeed, the use of PPIs in cirrhotics are repeatedly reported, though actively disputed, to be associated with an increased risk of spontaneous bacterial peritonitis (SBP) [2], hepatic encephalopathy [3] (HE) [3], and mortality [4]. Nevertheless, many of the previous studies were cross-sectional, potentially reflecting the biases associated with this type of study design. Indeed, in the one multicenter and prospectively designed study available, no significant association was reported between SBP and PPI use in cirrhotics [5].

To address the actual impact of PPIs in cirrhotic patients, Wong et al. [6] in this issue of *Digestive Diseases and Sciences* conducted a meta-analysis restricted to longitudinal studies. A total of 28 studies with 260,854 cirrhotic patients (18 retrospective cohort studies, 9 prospective studies, and 1 post hoc analysis of a randomized controlled trial) were included. The study was rigorously designed and analyzed, with time-dependent analysis and risk assessment of longitudinal events using pooled adjusted hazard ratios. The authors also included prospective studies, employing sensitivity analysis to establish causality links with Bradford Hill's Criteria.

The authors found that a high percentage of cirrhotic patients (55.93%) used PPIs. PPI usage was associated with significantly increased risks of hepatic decompensation, HE, SBP, infection, and long-term, but not short-term (< 90 days), mortality (Fig. 1). Such findings were confirmed using subgroup analysis of prospective studies alone, likely the principal strength of this meta-analysis.

Besides the increased risk of adverse outcomes in cirrhotics with PPI exposure, prior retrospective cross-sectional studies [3, 4, 7, 8] have identified a dose-dependent effect relation of PPIs with hepatic decompensation, HE and mortality. Despite the findings of current meta-analysis, Wong et al. were not able to evaluate the impact of cumulative dosage of PPI with dose-dependent meta regression analysis due to the very few longitudinal studies that addressed this issue. In fact, results from two prospective studies [9, 10] demonstrated inconclusive results for the dose–response effect of PPIs and decompensation/infection. More large-scale

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Fig. 1 Increased risks of adverse outcomes in cirrhotics with PPI usage

randomized trials are necessary to address this gap in knowledge.

Regarding PPI use and mortality in cirrhotics, there are conflicting results according to recent meta-analyses and prospective studies. As stated, Wong et al. showed that long-term, but not short-term mortality, was associated with PPI use. A recent study from the US Veterans Health Administration database demonstrated that PPI use was associated with reduced all-cause mortality in cirrhotics with prior GIB, but had no significant association among all others [7]. In another study, a real world *post hoc* analysis of the ATTIRE trial, PPI use at baseline in hospitalized patients with decompensated cirrhosis did not increase incidence of infection or mortality for up to 6 months, but was associated with a significantly increased incidence of grade III/IV HE during their hospital stay [11]. The authors suggested that the association with HE appeared to be related to patients with GIB (variceal bleeding or endoscopic variceal treatment under sedation or anesthetic) where there was increased use of PPI, introducing the bias of confounding by indication; and that the harm was not actually attributable to the PPIs itself. These controversial results suggest that the presence of GIB should be an imperative confounding factor to be controlled for in future studies, as this group of cirrhotic patients may represent a fundamentally different phenotype. Furthermore, the interval between starting PPIs

and occurrence of adverse outcomes were not available in all studies. Only one previous study demonstrated that the median time from initiating PPI to development of first SBP episode was about 1 year [2]. This information will be useful in application to clinical practice and requires further research as well.

In conclusion, the authors of the current study have demonstrated robust evidence from longitudinal studies to suggest the potential harm of PPIs in patients with cirrhosis. We agree with the authors that PPIs should be appropriately used at the lowest effective dose in cirrhotic patients for clearly defined indications. Despite potential confounders in patients with GIB, it is good practice for us to adhere to the latest Baveno VII consensus stating: "PPIs, when started before endoscopy, should be stopped immediately after the procedure unless there is a strict indication to continue them" [12]. The use of PPIs should be actively reviewed at regular intervals and discontinued as appropriate.

Declarations

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