Editorial

Proton pump inhibitors and hepatic encephalopathy: fly quiet in the eye of the storm

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Portal hypertension (PHT) is the ominous root of the most demanding manifestations of end stage liver disease or cirrhosis, mostly independent from the etiology of chronic liver disease. The multiform clinical manifestations of PHT include upper digestive tract bleeding, ascites, and hepatic encephalopathy (HE) (1).

The diagnostic hallmark of PHT is the increase of the hepatic vein portal gradient (HVPG) measured by jugular catheterism: a gradient >5 mmHg is indicative of PHT; 10 mmHg is the threshold for esophageal varices formation, and when HVPG reaches a value of 12 mmHg it is predictive of imminent varices rupture and of the other complications of PHT (1).

Nevertheless, HVPG determination is an invasive diagnostic technique and cannot be used routinely in all patients with liver cirrhosis. Consequently, the diagnosis of PHT is primarily based on other non-invasive or less invasive diagnostic tools (ultrasound and/or endoscopy), or on the whole array of clinical manifestations of PHT (i.e., any form of cirrhosis decompensation) (1,2).

Ascites is most frequently the first clinical sign of decompensation in cirrhosis and, generally, the onset of ascites (like any first episode of decompensation) significantly affects the over-all prognosis of the patient with liver cirrhosis, as it is well known (1).

HE is another clinical manifestation of PHT and of cirrhosis decompensation. Basically, residual liver function plays the key role in the onset of HE. However, many factors may act as precipitating causes: diuretics use or excess, infections, constipation, disproportionate dietary protein ingestion, gastrointestinal bleeding, hemodynamic derangements, hypovolemia, electrolyte disturbances, acid-base imbalance (namely alkalosis), portosystemic shunts—spontaneous or surgical or TIPS (transjugular intrahepatic portosystemic shunt) mediated—the use of psychotropic medications (especially benzodiazepines), intoxications and alcohol abuse, etc. (3).

Even if large, the list is not complete, but keeping in mind all the possible causes of HE is important, because the occurrence of overt HE requires the identification of the cause(s) to guide treatment in the most efficacious way. In facts, HE is usually a completely reversible syndrome if we succeed to remove—or at least counterbalance—the cause(s) or precipitating factors (3).

To make the picture more complete, a key factor of the worsening of cirrhosis and of the clinical manifestations of PHT has been recently identified in the derangements of the gastro-enteric flora, the microbiota, which could determine a shift toward a pro-inflammatory and pro-fibrotic inner environment (4).

In their original epidemiological study, newly published on Gastroenterology, Tsai *et al.* suggest we could add proton pump inhibitors (PPIs) to the list of factors favoring HE (5).

Indeed, PPIs are among the most frequently prescribed class of drugs all over the world, and specifically in patients with liver cirrhosis (6). Even so, PPIs are in the middle of a "conceptual storm" as they have been directly or indirectly associated to a number of different clinical disorders ranging from infections (pneumonia, *Clostridium difficile* colitis, spontaneous bacterial peritonitis in cirrhosis, etc.),

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to osteoporosis, gastric cancer, dementia, etc. (7).

Namely, the infective complications of PPIs are specifically thought to be linked to the loss of the acid barrier effect with the secondary modifications of the gut microbiota and small intestinal bacterial overgrowth. All factors that also contribute to HE incidence in liver cirrhosis (8,9).

Data appearing in recent years tend to set doubts on the concept that PPIs are drugs with virtually null side effects, obviously in front of an unquestionable efficacy. PPIs are a class of drugs too often "automatically" prescribed in any patient affected by any kind of chronic disease, or in patients who simply need to assume drugs chronically, regardless of the "potential" gastro detrimental effects (7,10).

As a matter of facts, we must agree that PPIs play an essential role in the treatment and prevention of definite peptic or erosive gastroesophageal pathologies. We must also say that historically PPIs—as epigones of anti-H2 receptor agonists—can be listed among the drugs that have changed the natural history of peptic disease, sparing a great number of surgical interventions, saving lives, and moving patients with acid mediated pathologies from the surgical to the medical wards and fields of interest (10).

With these premises, most studies in Literature addressing the point of possible clinically significant side effects of the chronic and indefinite assumption of PPIs are retrospective or cross-sectional in nature, and those study designs limit the level of evidence. The study of Tsai *et al.* is a prospective nested 1:1 case control study with a follow-up period of 5 years, and can rely on data from a registry of 1,000,000 patients that represent the general population of Taiwan. On that ground, the authors found a significant predisposing effect of PPIs on the occurrence of HE in patients with cirrhosis in a dose dependent manner. This predisposing effect was related to all tested molecules, with the exception of rabeprazole, indicating a class effect, opposed to a molecule-restricted effect. Furthermore, the exception of rabeprazole was eventually determined by the smaller population exposed to that drug (57 patients), compared with the number of patients who assumed the other four molecules (varying from 120 patients for pantoprazole, to 193 patients for lansoprazole) (5).

Another important observation in the study of Tsai *et al.* is precisely the direct time-dependent effect of PPIs on HE occurrence. That we could resume, PPIs are efficacious and safe when assumed for a definite time, and for the proper indications of use according to the label. Problems arise when prescriptions are prolonged, and at the limits of or off-label (5,10).

In conclusion, to optimize efficacy and safety PPIs should be prescribed for the recognized indications and for the best time duration. Notwithstanding the accumulating evidences of possible important side effects of PPIs long term or indefinite treatment, they remain one of the most prescribed class of drugs (11), forcing indications to the limits (and behind…) of the label.

That is, you can fly quiet if you are "in the eye of the storm", even when surrounded by turmoil.

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