

Proton Pump Inhibitor Prescription in Patients with Liver Cirrhosis: Indications in Theory and the Real World

Editorial

Volume 1 Issue 1 - 2015

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Received: June 26, 2015 | **Published:** July 10, 2015

Abstract

In a climate of spending review and pharmaeconomics any prescription should be made according to recognized indications, also to limit exposure of fragile patients to possible secondary effects and complications. In this editorial we comment on the case of PPIs in patients with cirrhosis or with polyopathy.

Keywords: Proton Pump Inhibitors; Polypharmacy; Polypathology; Chronic Liver disease; Cirrhosis; Appropriateness

Editorial

Population aging is leading to the emergence in recent years of a new "clinical phenotype" characterized by the summation of several diseases (polyopathologies) [1] with the subsequent accumulation of therapies (polypharmacy) [2] often on the advices received from different specialists and, every now and then, with a lack of harmonization or continuity [2-4]. Among the drugs most frequently prescribed in absolute nowadays, a prominent place is occupied by the proton pump inhibitors (PPIs) which are drugs very effective in controlling gastric acid secretion and well tolerated, with a side effect profile very favorable [5].

Even so, favorable profile of tolerance does not mean the lack of side or secondary effects, especially when prescribing such drugs involves a chronic use or administration for an indefinite time [5]. Furthermore, many prescriptions are frequently made only for the sake of controlling symptoms, rather than for a definite diagnostic orientation [5-11].

Actually, evidences are accumulating on a range of possible side effects of PPIs [12-25] that vary from syndromes of malabsorption causing deficiencies - for example of iron, magnesium or copper [26], to osteoporosis or susceptibility to infections of the gastrointestinal tract or the respiratory system. Regarding the predisposition to infections, various are the hypotheses advanced to explain such susceptibility: by one side, the reduction of the dampening effect of gastric acid on the pathogenic intestinal flora and the consequent variations in the composition of the intestinal micro biota, and on the other maybe some direct effect on the modulation of the immune response, due to functional interference on the cells responsible for the innate immunity [27-29].

A chronic condition frequent in the age group over 50 - especially in men is liver cirrhosis, regardless of the different possible etiologies: viral, exotoxic, metabolic and often combined etiologies [30,31]. The clinical picture of cirrhosis is

itself highly variable and depends on the degree of evolution of the disease: from completely asymptomatic in the early stages, until catastrophic syndromes in more advanced forms with portal hypertension and all its secondary manifestations. Among the most serious manifestations of portal hypertension, some are specific to the upper gastrointestinal tract as the portal hypertensive gastropathy and the appearance of esophageal varices at high risk of bleeding. Upper gastrointestinal bleeding is considered among the most feared complications of cirrhosis, being burdened with high mortality and probability of recurrence in the short term [31].

The reference to the upper digestive tract and to lesions of continuity of the gastrointestinal mucosal lining (i.e. erosions or ulcers) or submucosal vascular ectasias (as ruptures of esophageal or gastric varices) among the possible complications of chronic liver diseases, immediately generates a mental association with gastric acid secretion as a possible causal agent or trigger. Consequently, the availability of powerful drugs capable of efficiently blocking the gastric acid secretion determines an uncritical appeal to PPIs for the prevention of bleeding of upper gastrointestinal tract [32,33]. Undoubtedly, if we check the recognized indications for the use of PPIs, they are classically

- 1) A limited course (4-6 weeks) for the treatment of peptic ulcer - the PPIs have historically had the role of changing the natural course of peptic ulcer disease subtracting land to surgery;
- 2) A maybe longer course for the treatment of erosive esophagitis or in general the pathology secondary to gastroesophageal reflux acid, and, finally
- 3) The prophylaxis of bleeding from chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin or steroids [7,34].

However, the indications of use for PPIs remain exactly the same also in the setting of the very particular patient with cirrhosis of the liver, in which the efficient prevention of bleeding from esophageal and gastric varices rests on the administration of unselective beta-blockers and / or endoscopic band ligation. Not even the prophylaxis of bleeding from portal hypertensive gastropathy is included among the official indications of use of these agents [31,35]. Regarding the use of NSAIDs and a possible long term use of PPIs in the prevention of bleeding, surely in the case of a patient with advanced liver cirrhosis, NSAIDs are contraindicated for substantial reasons, therefore also this indication decedes to the origin [36].

The case of current variceal bleeding- then differently from the setting of prophylaxis-is the only indication accepted for the use of PPIs in acute and across the period from varices band ligation or sclerotherapy and up to the few weeks following the procedure. In that interval, PPIs seem to hasten recovery as they reduce the size of the ulcers caused by the procedure itself, and the fall of eschars [37]. Indeed, medical treatment of acute bleeding, a real medical emergency, especially if associated with hemorrhagic shock, contemplates the use of PPIs although the backbone of treatment is the administration of vasoactive agents - such as vasopressin or somatostatin - and the local control of bleeding, - through endoscopic varices band ligation or sclerotherapy - associated with the prevention of infections with antibiotics [31,35]. If that is the theory regarding PPIs' indications, what is the practice in the real world? If we look at the prescription pattern in the general population, we already made large reference to the excess prescription of PPIs also linked to the summation of therapies in the elderlies.

Regarding specifically patients with liver cirrhosis, in published series on drug prescriptions in that setting from different geographical locations, [32,33] over sixty percent of patients received the prescription of PPIs compared with a prevalence of peptic pathology not exceeding 20%, a figure comparable to the prevalence in the general population. Moreover, often the reasons for prescription of PPIs in patients with cirrhosis are not reported, or are very indefinite or are based on vague not specific dyspeptic symptoms.

Indeed, patients with liver cirrhosis - especially if in advanced stages - are to be considered very fragile and prone to "over-complication" for their unstable equilibrium. What means that we have to avoid any possible harm derived from the misuse of any drug included the generally well-tolerated PPIs. It is not merely a question of spending review or of pharma-economics, it is a question of appropriateness and accuracy in making prescriptions always following the golden rule of Medicine that is "primum non nocere" (first, do no harm!).

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