RESEARCH ARTICLE

Proton Pump Inhibitors and Primary Liver Cancer

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Abstract

During the last years proton pump inhibitors (PPIs), previously regarded as very safe drugs and allowed to be sold over the counter, have been reported to give side effects in many organ systems. However, most of these negative reports probably are due to residual confounding factors. In general, the side effects of PPIs are due to their biological effect in removing the biological effect of gastric juice that is killing microorganisms, and the secondary hypergastrinemia in an unsuccessful attempt to restore normal gastric acidity. Whereas the possibility that hypergastrinemia could predispose to gastric cancer has been permanently on the agenda since the introduction of PPIs, the removal of the important protective effect towards microbes has surprisingly only been focused on during the later years as a consequence of increased interest on the gut microbiome. PPI treatment affects the microbiome, and it exists one report describing increased risk of primary liver cancer due to PPI use. Changes in the gut microbiome have been shown to participate in the pathogenesis of chronic liver diseases caused by ethanol as well as obesity. In general, chronic liver diseases predispose to liver cancer. There are also rodent studies incriminating inhibition of gastric acid secretion in the pathogenesis of primary liver cancer. However, it must be concluded that presently the role of PPIs in the development of primary liver cancer seems weak.

Introduction.

Acid related diseases (peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD)) together with non-ulcer dyspepsia (NUD), a condition where symptoms by many are perceived to be due to gastric acidity, are all prevalent. Thus, drugs reducing gastric acidity have a large potential. Indeed, the until now the most efficient of these drugs, the PPIs, are used regularly by a large proportion of the adult population in the Western countries[1]. Previously, the PPIs were claimed to be among the safest drugs with a very low incidence of side effects [2]. However, during the last years there have appeared reports describing association between PPI use and serious diseases in many organ systems [3 4]. However, due to liberal use of PPIs, particularly in seriously ill patients, confounding factors most probably gave rise to these apparent side effects. Moreover, these side effects have not been described in animal long-term studies using high doses of PPIs.

On the other hand, since the introduction of PPIs there has been concern related to their biological effect due to their efficacy in reducing gastric acid secretion which made them the preferred drug with respect to treatment , but at the same time induced hypergastrinemia which led to ECL cell derived tumours in rodents [5]. The removal of the biological main function of gastric juice, that is killing of swallowed microorganisms [6] was initially of little concern, but more recently their effect on gut microbiome has been focused [7 8]. The PPIs themselves seem to be very safe compounds, but their side-effects are due to their efficacy in removing an important biological defense function and the feed-back mechanisms involved in an in vain attempt to restore normal function. A few years ago, there was a report describing an association between PPI use and liver cancer [9]. My immediate thought that this connection was one of the many associations due to confounding factors, but when I searched the literature, I realized that effects on the gut microbiome could be a plausible factor [10]. The present review will give a short overview on the role of intestinal permeability, bacterial transfection, the microbiome, and the effect of PPI treatment on the microbiome and possible consequences for liver diseases in general and liver cancer in special.

Primary liver cancer

In this review I will use hepatocellular carcinoma synonymously with primary liver cancer (PLC) and accordingly not cover cholangiocarcinoma and rare primary liver malignancies. PLC occurs mainly in a cirrhotic liver[11] and often after long latency between the start of a chronic liver disease and development of cancer . A chronic loss of liver cells due to chronic inflammation will obviously lead to increase proliferation of the hepatocytes which will by chance increase the risk of mutations finally leading to development of malignant growth. Hepatitis B and C viruses probably have themselves a tumourigenic effect on the hepatocytes besides causing inflammation related death of hepatocytes. Moreover, iron has a toxic effect on the liver stimulating fibrosis as well as development of PLC [12] Thus, infection with hepatitis B perinatally predisposes to PLC in spite of often rather low inflammation and fibrosis [13]. Nevertheless, chronic loss of hepatocytes due to inflammation itself is becoming the major cause of PLC since

treatment and prophylaxis of hepatitis B and C have improved during the last decades, whereas alcohol-related liver disease as well as non-alcohol steatohepatitis (NASH), both predisposing to PLC, have increased in prevalence[14]. Moreover, bacterial translocation due to altered intestinal permeability probably has a pathogenic role in both these conditions [15 16]. The importance of the intestinal microbiome increases when the barrier of the gut wall is reduced allowing transfection more easily. The intestinal microbiome thus becomes important for chronic liver diseases including cirrhosis and PLC [17].

Intestinal Microbiome

There are a great variety of intestinal commensal microbes that participate in the maintenance of the intestinal barrier by direct and indirect mechanisms. The role of the different microbial species in this process cannot be separated from each other. Small bowel bacterial overgrowth seems to be particularly important for the development of bacterial translocation [18]. Changes in the intestinal microbiome are particularly prevalent in patients with cirrhosis [19], indicating that dysbiosis can contribute to as well as be a result of cirrhosis. Both in rodents and man lipopolysaccharide (LPS) in blood which is an indirect parameter for the tightness of the intestinal wall, is increased in liver diseases/failure [20]. LPS binds to toll-like receptor (TLR) 4 probably having an important function in further inflammation, fibrosis, and carcinogenesis [21]. Interestingly, treatment of antibiotics to reduce the growth of gram-negative bacteria in ethanol-fed rats reduced liver injury, indirectly showing the important role of microorganisms in alcohol-induced liver disease [22]. Moreover, animal experiments have shown that LPS-TLR4 axis plays an important role in hepatic fibrosis [23], a condition predisposing to PLC [24]. Accordingly, intestinal microbiome seems to play a role in all phases in the development of liver disease including PLC in conditions like ethanol-induced liver disease and NASH, but also in the final carcinogenesis in hepatitis B and C. There are drugs that affect the intestinal microbiome, and among them, the PPIs are the most prevalently used.

Primary Liver Cancer and Proton Pump Inhibitors

A few years ago, Tran and co-workers described an increased risk of PLC in patients taking PPIs[9]. In another study, however, patients having taken PPI for more than 2 years, were not found to have an increased risk of liver cancer [25]. Neither was PPI use in patients with PLC treated with sorafenib found to have negative consequences [26]. On the other hand, PPI use in patients with liver cirrhosis increases the risk for bacterial peritonitis [27]. It is, however, firmly established that PPI treatment changes the gut microbiome [8 28] including giving rise to small intestine bacterial overgrowth [29 30]. The most convincing study connecting PPI dosing/treatment to liver diseases and thus the final step of chronic liver diseases, PLC, is the study by Llorente et al.[31].They showed that PPI dosing as well as genetic knock-out of the proton pump induced progression of alcoholic liver disease as well as non-alcoholic liver steatosis and steatohepatitis via provoking increased amount of Enterococcus species. They also in parallel made a follow-up study on alcohol dependent persons with respect to liver disease during a ten years period and found that those using or having used PPIs had increased prevalence of liver disease and also increased faecal Enterococcus[31]. However,

it should be recalled that Håkanson et al. did not report any liver changes in rats otherwise normal, dosed with omeprazole in high dose and giving marked trophic effects on the stomach [32]. Although they did not do a detailed examination of the liver, their finding do not suggest that PPIs alone have any major effect on the liver. Therefore there are some clinical and animal studies indicating the PPI treatment in combination with other hepatotoxic agents could play a role in hepatocarcinogenesis [10].

Conclusion

Chronic liver diseases predispose to fibrosis, cirrhosis and ultimately to primary liver cancer. It seems to be established that changes in the gut microbiome including in the small intestine, may increase the risk and intensity of all these phases. Moreover, there is no doubt that profound acid inhibition changes the gut microbiome and then particularly in the small intestine. However, studies indicating that PPI treatment may induce primary liver cancer are very scarce, and only one rat study where PPI was combined with ethanol has described induction of liver disease. PPI alone was apparently without negative consequences for the liver. Therefore, the risk of PPI treatment with respect to primary liver cancer seems presently to be very low. More animal studies combining PPIs with clinically relevant hepatotoxic agents are required.

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