

## LETTER to the EDITOR

# Experimental Strategies for Induction of Gastric Adenocarcinomas under Long-Term Proton Pump Inhibitor Administration and *Helicobacter Pylori* Infection

*Asian Pacific J Cancer Prev*, 13, 3005-3006

### Dear Editor

We read with interest the study by Tsukamoto et al. (2011) published in the recent issue of *Asian Pacific Journal of Cancer Prevention*. They examined the effect of the administration of long-term proton pump inhibitors (PPIs) to Mongolian gerbils (MGs) infected with *Helicobacter pylori* and observed the development of neuroendocrine tumors (NETs) and an increase in serum gastrin levels, but did not observe heterotopic proliferative glands (HPGs), gastritis, or any adenocarcinomas. In contrast, in our recent study, we observed atrophic corpus gastritis and the development of adenocarcinomas in an animal model (Hagiwara et al., 2011). Tsukamoto et al. cited our study and stated this difference may be due to differences in medicines or doses administered. However, we postulate that the differences between their experimental results and ours are caused by not only different medicines and doses administered but also the timing of initiation and duration of PPI administration.

We were surprised that they did not detect any HPGs or corpus atrophic gastritis in the *H. pylori*-infected plus PPI-administered group. Several researchers have reported observing HPGs in the glandular stomach of MGs infected with *H. pylori* (Tatematsu et al., 2005), and we also observed HPGs and corpus atrophic gastritis in not only the *H. pylori*-infected group but also the *H. pylori*-infected plus PPI-administered group in our recent study (Hagiwara et al., 2011). We speculate if *H. pylori* was eradicated or if their number was reduced significantly by lansoprazole administration in their study. Considering that PPIs are usually administered in adulthood, the timing of lansoprazole administration in their study, beginning one month after *H. pylori* infection, may be equivalent to that of lansoprazole administration in human infancy or childhood. The point of most concern in their study is that the authors have not evaluated the presence of infections. Moreover, they may have ignored another important fact that lansoprazole has stronger bacteriocidal activity against *H. pylori* than omeprazole; the MIC50 of lansoprazole is approximately 4-16 times lower than that of omeprazole (Midolo et al., 1996; Alarcon et al., 1998). These facts suggest that lansoprazole may have eradicated *H. pylori* in the early phase of their experiment before the establishment of *H. pylori* infection in the *H. pylori*-infected plus PPI-administered group in their study. Therefore, the timing of initiation of PPI administration may be important and should be set after considering

the stage in the life cycle of *H. pylori* present in human stomachs during infection. We maintain that the best timing of initiation of PPI administration is after the development of chronic atrophic gastritis, which in turn causes gastric adenocarcinomas. In our recent study, we considered this hypothesis and started to administer omeprazole six months after infection (Hagiwara et al., 2011).

Comparing doses between their study and ours is not easy. In 2007, we established an animal model in which the long-term administration of PPIs using food is possible. In addition, we reported the side effects associated with long-term use of PPIs (Hagiwara et al., 2007). The dose of omeprazole was based on body weight and serum gastrin levels at the end of six months of PPI administration, because mixing PPIs with food reduces activation of PPIs. The rates of inactivation of PPIs may differ between omeprazole and lansoprazole. Furthermore, long-term PPI administration leads to hypergastrinemia, which causes NETs (Larsson et al., 1988). No NETs were observed in our recent study in which omeprazole was administered for six months (Hagiwara et al., 2011). On the other hand, NETs were detected in their study in which lansoprazole was administered over 50 weeks. A period of PPI administration longer than six months may be needed for NETs to develop in MGs.

Considered together, when gastric carcinogenesis-related *H. pylori*-infection with long-term PPI administration is studied, the timing of initiation of PPI administration and types of PPIs are important factors. Additionally, hypergastrinemia also may be associated with gastric cancer development because hypergastrinemia is increased by *H. pylori*-infection as well as by PPI administration. However, our recent study demonstrated that hypergastrinemia, caused by long-term PPI administration without *H. pylori*-infection, did not induce any adenocarcinomas (Hagiwara et al., 2007; 2011). We concluded that the main cause of worsening corpus atrophy that leads to the development of adenocarcinoma was not long-term PPI administration but rather *H. pylori* infection (Hagiwara et al., 2011). Thus, we postulated that patients being considered for long-term PPI therapy should be tested for *H. pylori* infection, and if present, the pathogen should be eradicated.

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Tadashi Hagiwara et al

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