Potential problems of long-term use of proton pump inhibitors

Duan Chen, Chun-Mei Zhao, Timothy C Wang

1Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Norway, 2Department of Digestive and Liver Diseases and Herbert Iring Comprehensive Cancer Center, Columbia University Medical Center, New York, USA

Proton pump inhibitors (PPIs) was developed from thiocarboxamides derivatives in 70s. Currently, various PPIs are similar in chemical structure and thus are highly effective and relatively safe. PPIs are used in 60% of inpatients with little benefit in half, resulting in long-term use as outpatients. Recent clinical data have indicated various potential problems associated with long-term use of PPIs, including pneumonia, Clostridium difficile infection, bone fracture, malabsorption, cognitive impairment and dementia, fundic gland polys, hyperplasia of ECL cells and gastric carcinoids (ECLoma) and even gastric cancer. Possible underlying mechanisms involve PPI-induced hypochlorhydria, hypergastrinemia, PPI per se and its metabolites. Animal experimental data showed that the ECL cell hyperplasia reflected the transiently elevated ECL cell proliferation rate during the early phase but was not associated with an accelerated rate of mitosis during the late phase of PPI treatment (52 weeks), suggesting that there are additional factors than hypergastrinemia that involve in the tumorigenesis of ECLoma. In addition to histamine and pancreastatin, the ECL cells produce a blood calcium-lowing peptide which involve in bone mineralization. Long-term use of PPI was associated with an impaired function of the ECL cells as indicated by formations of large vacuoles and lipofuscin bodies and absence of secretory vesicles in the cytoplasm. Thus, hypochlorhydria-induced bone loss may be partly due to the so-called ”ECL-cell disease”. Hypergastrinemia acts on CCK-2 receptor to stimulate the gastric stem cells and to induce apoptosis in gastric epithelial cells, which might contribute to the development of gastric cancer in mice. Thus, we recommend to limit use of PPIs to those patients who benefit most and to develop new class of drugs targeting the CCK-2 receptor.