

# THE DOUBLE EDGED SWORD OF PPIs

The **proton pump inhibitors** (PPIs) have been used for almost thirty years, as the first clinical trial about the effect of **omeprazole** on gastric secretion was published by *The Lancet* in 1983 (Muller et al., 1983). Since, the popularity of those drugs has been constantly increasing to the point that they have become the most prescribed drugs in gastroenterology. The major shift that we have observed during all those years concerns the duration of treatments, initially focusing on the healing of gastric and duodenal ulcers for one or two months. Today, we see many patients being prescribed PPIs (or taking over the counter PPIs by themselves) long term, not to say "for life", with the goal of addressing heartburn and other symptoms related to gastro-esophageal reflux disease.

However, these drugs are not void of side effects and taking them continuously for so many years has started to raise concerns as shown by this article published in the *American Journal of Medicine* in 2009: "*The collective body of information overwhelmingly suggests an increased risk of infectious complications and nutritional deficiencies*" (Ali et al., 2009). Also in 2009, the famous Danish epidemiologist Poulsen published worrying data about the links between PPI use and gastric cancer, underlining the fact that PPIs increase the secretion of gastrin, knowing the relationship between hypergastrinaemia and gastrointestinal neoplasia (Poulsen et al., 2009). He also observed an "*increased incidence among PPI users with most prescriptions and longest follow-up*" (Poulsen et al., 2009), which implies that problems will develop from length of intake as well as with increased dosages (this seems to represent another strong trend in recent prescriptions, as anyone can observe).

Long-term acid inhibition will necessarily trigger hypochlorhydria and hypergastrinaemia (Tepes, 2011), two physiological shifts at the root of most complications. Of course, we would need more prospective randomized trials rather than epidemiological data (Tepes, 2011) and we should probably reconsider the indications for anti-reflux surgery (Venkataraman and Krishnan, 2012), especially as "*PPIs do not reduce the number of reflux events and do not provide long-term cure for gastro-esophageal reflux disease or GERD*" (Hershcovici and Fass, 2011). More recently, several publications raise awareness about long-term PPI intake, as shown by a title that appeared early 2012 in *Drugs*: "*Prescribing proton pump inhibitors: is it time to pause and rethink?*" (Vakil, 2012). At this stage of knowledge, our conclusion cannot differ from this quote: "*The risk-benefit ratio of PPIs is increasingly recognized as being less favourable. This leads to a more critical viewpoint and raises the question whether the side-effects of PPIs may outweigh the benefits, especially with long-term use*" (von Rahden et al., 2012).

While hypergastrinaemia can cause gastric carcinoids made of enterochromaffin-like cells (Jianu et al., 2012), most of the side effects develop due to hypochlorhydria. It affects both the capacity to digest proteins (offering more undigested peptides to the appetite of intestinal bacteria) and to protect our digestive tract against invasive pathogens such as yeast or protozoan, normally killed by the stomach acidity. Besides, a higher stomach pH implies a higher pH in the small intestine, the typical trigger for small intestinal bacterial overgrowth or SIBO (Paiva et al., 1998). These profound changes compared to normal physiology certainly explain the multiple observations linking PPI intake with infectious conditions: bacterial gastroenteritis (Garcia Rodriguez et al., 2007), *Clostridium difficile* diarrhea (Koretz, 2012), pneumonia (Giuliano et al., 2012), interstitial nephritis (Harmark et al., 2007), and serious infections in general, especially among patients with compromised immune defenses (Bajaj et al., 2012). We will therefore share this conclusion from the above-mentioned article by Giuliano: "*Practitioners need to be vigilant about adverse effects of PPIs and consider alternative therapies*".

Increased pH will also alter the absorption capacity by modifying the ionic status of many minerals, such as calcium, magnesium, and iron, whereas physiological changes in the small intestine upset the absorption of hard to absorb vitamins, typically vitamin B12. No wonder that PPI intake has been associated with anemia (Sarzynski et al., 2011) and above all with iron-deficient anemia that is even harder to treat (Ajmera et al., 2012). Many recent articles underline the severity and the persistence of hypomagnesaemia as result of PPIs (Furlanetto and Faulhaber, 2011; Hess et al., 2012). Osteoporosis and increased risk of bone fracture represent other obvious side effects (Fraser et al., 2012) that cannot be ignored among elderly patients... and among all the others!

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