

## EDITORIAL

### **PPIs: Between overuse and underprescription when really necessary**

Hydrochloric acid gastric secretion plays, among its primary physiological foundations, a role as protective barrier against infection with external agents from the diet and also contributes to the digestion of ingested food (1). However, this secretion is a critical factor shared by a number of highly prevalent diseases involving the upper gastrointestinal tract. Paradigms of such conditions include gastroduodenal peptic ulcer and gastroesophageal reflux disease.

From late 19<sup>th</sup> century to middle 20<sup>th</sup> century a significant research race took place in an attempt to find drugs potentially effective for the management of conditions related to gastric acid secretion. It was not until the mid-1970s, with the synthesis of the first H<sub>2</sub> antagonist (cimetidine), that a substantial shift occurred in the management of these disorders. However, despite the higher efficacy of this drug as compared to previously available compounds, the block of gastric acid secretion was only partial, and neither effective symptom relief nor complete esophageal and/or gastric lesion healing could be achieved. The real revolution in the management of acid secretion-related conditions came during the late 1970s with the discovery of omeprazole, which represented a historical milestone in this field of medicine and rapidly opened up a number of research areas that eventually led to the synthesis of newer compounds with differential characteristics, all of them presently classed as proton-pump inhibitors (PPIs) (2). These drugs share a benzimidazole group with great affinity and inhibitory activity for the enzyme H<sup>+</sup>/K<sup>+</sup>-ATPase in gastric parietal cells, thus blocking their activity and the hydrochloric acid production chain at its final link regardless of the activation of muscarinic, histamine and/or gastrin receptors (3).

PPIs represent the most powerful gastric anti-secretory drugs currently available. This characteristic, together with the high prevalence of diseases associated with high acid secretion in the stomach, has led to their being the most widely prescribed drugs worldwide (4). The first generic PPI introduced in our country was omeprazole back in 2001; ever since, prescriptions have exponentially increased. In 2010, omeprazole became the most commonly consumed active compound in Spain, in number of packages sold. Specifically, 51.87 million packages were sold, which represents 5.51% of all medicinal product packages turned over that year (5). In comparison to other European countries, Spain leads gastric anti-secretory drug consumption with prescriptions soaring 70% over the European average (6).

Although PPI indications are well defined (7-10), they are frequently ignored in daily practice, leading to an overuse that has been exposed by numerous studies (11). Besides the significant financial and healthcare impact of PPI overuse, and despite their being considered safe drugs in the long term, their use is not exempt from risks and multiple studies still discuss the potential adverse effects of these medicinal products (12).

Considering all the above, Villamañán and colleagues report, in the present issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)*, an interesting descriptive, observational study that was performed in a Spanish third-level hospital; in it they carried out a cross-sectional analysis to find out the proportion of patients put on PPIs during a hospital stay, and the appropriateness or inappropriateness of such prescriptions; they also examined the extent to which in-hospital prescriptions subsequently induce sustained prescription at the outpatient clinic (13). They considered approved PPI indications those authorized by Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); off-label though recommended indications those found in various clinical practice guidelines, both Spanish and otherwise; and off-label and not recommended those not endorsed by any of the above-mentioned publications.

The study included a total of 379 patients, of which 294 had been prescribed a PPI (77.6%). This therapy was initiated during a hospital stay for 143 patients (48.6%; 95% CI: 42.8-54.5); the rest had had it prescribed previously and the drug was now a part of their standard regimen. Amongst the group where PPIs were prescribed at admission, in 91 patients (63.6%; 95% CI: 55.2-71.5) the indication was deemed inappropriate, mostly because of their unnecessary inclusion in surgical, diagnostic and therapeutic protocols. The remaining indications were considered appropriate, 26 (18.2%; 95% CI: 12.2-25.5) corresponded to approved indications and 26 (18.2%; 95% CI: 12.2-25.5) corresponded to off-label though recommended indications according to clinical practice guidelines. Most common inappropriate PPI indications included the surgical prophylaxis of gastrointestinal stress ulcers in the absence of bleeding risk factors (18 patients, 19.8%) and “gastroprotection” in polymedicated patients not receiving stomach-damaging compounds (17 patients; 19.8%). Inappropriate prescriptions were more common in surgical than in medical wards (73.6% vs. 26.4%; respectively), particularly in traumatology and general surgery departments. Of all 232 patients where PPI prescription could be followed up following hospitalization, its ongoing use was recommended to 153 (65.9%; 95% CI: 59.5-72.0), and 53% of these had been taking a PPI prior to their admission.

Several interesting aspects deserve highlighting in the reported manuscript. First, it confirms a high level of unwarranted PPI use in patients admitted to hospital. A number of studies in different countries, including Spain, show similar PPI overuse rates in the inpatient setting (58% and 74%, respectively) (10,13-17). Findings are also consistent with those of other reported studies (7,18-20) as regards the primary causes of inappropriate PPI prescription – stress ulcer prophylaxis in patients with a low risk for GI bleeding, and “gastroprotection” in polymedicated individuals off drugs with gastroerosive potential. The belief that stress ulcer prophylaxis with PPIs is necessary for all inpatients is widespread despite specific guidelines against it (21). It is currently admitted that prophylaxis for stress ulcers using gastric antisecretory drugs should not be administered to all patients in critical care, but rather restricted to subjects at risk for said ulcers, particularly individuals on ventilators and/or with a coagulopathy (9,22,23). Also striking is the excessive use of PPIs for “gastroprotection” in polymedicated patients not on gastrolesive drugs. Such use is very common both in inpatients and in outpatients; however, a commonly ascertained absence of PPI gastroprotection for patients at risk and on clearly gastroerosive drugs (NSAIDs and/or aspirin) is also puzzling (24-27).

PPI overuse variability according to inpatient ward as unveiled by this study is very interesting, with a higher proportion of inappropriate prescriptions in surgical as compared to medical services (73.6% vs. 26.4%). From the data provided by authors the actual causes of overprescription in these wards remains unclear; the authors report the inclusion of PPIs in surgical protocols. The widespread use of pre-established protocols in electronic prescription programs may be time-saving for practitioners and provide safety against oversight regarding specific therapeutic measures for a number of conditions; however, indiscriminate use by overlooking individual patient characteristics may result in an increased number of inappropriate prescriptions. Sadly, the study did not include an analysis of data from the gastroenterology department, since increased awareness for gastroprotection and familiarity with PPI use among these specialists would have provided highly interesting data and conclusions.

Finally, the study reveals that PPIs initiated during hospital admission did not lead to an important PPI overuse in primary care. Similar studies do claim that in-hospital PPI use results in increased outpatient prescriptions, with PPI use remaining very high in this setting in the absence of appropriate indications (16,28,29).

Because of both medical and –most importantly– healthcare-economic criteria there is little doubt that health professionals should make all efforts to achieve a rational use of drugs. Appropriate PPI use is important for this healthcare approach because of widespread use and overuse, and in view of the potential complications sustained use may end in, particularly when inappropriate. Awareness only through papers reporting PPI overuse is likely insufficient, and more proactive actions via training programs on appropriate drug prescription are needed. Physician involvement is required to this end; but proactive, effective measures by health agencies (both national and regional) are key to provide resources and promote collaboration between primary and specialist care, as well as with medical societies. It is only from this perspective that excellence in health care and an appropriate use of the extensive, effective –indeed finite though increasingly costly– resources it encompasses may be achieved.

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