CORRESPONDENCE

The Indications, Applications, and Risks of Proton Pump Inhibitors

by Prof. Joachim Mössner in issue 27–28/2016

Laryngopharyngeal Reflux

The author is to be commended for his detailed presentation of the main gastro-esophageal diseases that are treated with proton-pump inhibitors (PPI) (1). Extra-esophageal conditions such as asthma and nonspecific cough also belong to the spectrum of indications but are only touched upon briefly. There is no mention at all of laryngopharyngeal reflux (LPR), a further extra-esophageal condition whose incidence is already high and still rising. Laryngeal mucosal irritation due to reflux is a common finding in otolaryngological practice, and the role of PPI in treating LPR should not be left out of any review of the subject. LPR can cause chronic laryngitis, laryngeal granulomas, and contact ulcers. The role of PPI in the treatment of chronic laryngitis and simultaneous reflux disease was discussed in *Deutsches Ärzteblatt International* in 2015 (2). PPI are probably an effective treatment for LPR (3); the apparent lack of efficacy in a number of studies is likely to have been caused by indiscriminate diagnosis of the condition (4).

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REFERENCES

1. Mössner J: The indications, applications, and risks of proton pump inhibitors—a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.
2. Reiter R, Hoffmann TK, Pickhard A, Brosch S: Hoarseness—causes and treatments. Dtsch Arztebl Int 2015; 112: 329–37.
3. Wei C: A meta-analysis for the role of proton pump inhibitor therapy in patients with laryngopharyngeal reflux. Eur Arch Otorhinolaryngol 2016; 273: 3795–801.
4. Campagnolo AM, Priston J, Thoen RH, Medeiros T, Assunção AR: Laryngopharyngeal reflux: diagnosis, treatment, and latest research. Int Arch Otorhinolaryngol 2014; 18: 184–91.

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Conflict of interest statement
The author states that he has no conflict of interest.

The Risk of Hypomagnesemia

Professor Mössner's article on proton-pump inhibitors (PPI) unfortunately contains no mention of the risk of hypomagnesemia (1). The literature contains a growing number of reports of severe magnesium deficiency caused by PPI intake (2, 3). As a result, in July 2012, the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) gave all manufacturers of approved PPI drugs three months to include mention of this risk in their summaries of product characteristics (4). The magnesium status should be borne in mind whenever a patient is taking PPI particularly over the long term or in parallel with other factors that can cause hypomagnesemia, such as diuretic use or diabetes mellitus. Magnesium may need to be given as treatment or as preventive supplementation.

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REFERENCES

1. Mössner J: The indications, applications, and risks of proton pump inhibitors—a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.
2. Famularo G, Gasbarrone L, Minisola G: Hypomagnesemia and proton-pump inhibitors. Expert Opin Drug Saf 2013; 12: 709–16
3. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al.: Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail 2015; 37: 1237–41.
4. Mitteilung des BfArM vom 25.07.2012 www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/textanpassung/TA_ppis_mitteilung.pdf?__blob=publicationFile&v=2) (last accessed on 5 September 2016).

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Dr. Kraus is an employee of Verla-Pharm.

Inpatient Overtreatment

During the discussion of infectious complications of long-term treatment with PPI (1), an increased incidence of C. difficile infection is mentioned. The cited meta-analysis (Kwok CS et al.) did indeed identify PPI as a risk factor for recurrent *C. difficile* infection but showed that the infection risk under PPI treatment is comparable to that under antibiotic therapy. Moreover, the estimated number needed to harm (NNH) among hospitalized patients is 67, i.e., for every 67 patients started on PPI treatment, one will suffer from recurrent *C. difficile* infection. A risk score has been developed for upper gastrointestinal bleeding among hospitalized patients outside the intensive care unit; only when this score reaches ≥10 points does the number needed to treat (NNT) drop to 95 (2). If a score of 10 points had been taken as a threshold for ordering a PPI – e.g. corresponding to a man aged 60 years or older on a general medical ward with acute renal failure and thrombocytopenia <50 000/µL – then PPI could have been saved in 82% of the total patient cohort (n=75 723). This overtreatment in the hospital setting persists when the drugs listed in the discharge summary are indiscriminately continued. A study in the German federal state of Mecklenburg-West Pomerania revealed that 263 (58%) of 506 patients discharged from 35 different hospitals had no clear indication for PPI, yet most of them were still inappropriately taking PPI after discharge (3). Finally, the recently published meta-analysis concerning acid suppression for stress ulcer prophylaxis in critically ill patients did not reveal an unequivocal superiority of PPI with respect to either overall survival or gastrointestinal hemorrhage (4). Although PPI have been in clinical use for more than 25 years, there is still a lack of evidence from clinical trials to justify their use in intensive care units around the world.

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REFERENCES

1. Mössner J: The indications, applications, and risks of proton pump inhibitors—a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.
2. Herzig SJ, Rothberg MB, Feinbloom DB et al.: Risk factors for nosocomial gastrointestinal bleeding and use of acid-suppressive medication in non-critically ill patients. J Gen Intern Med 2013; 28: 683–90.
3. Ahrens D, Behrens G, Himmel W, Kochen MM, Chenot JF: Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care. Int J Clin Pract 2012; 66: 767–73.
4. Krag M, Perner A, Wetterslev J, Wise MP, Hylander Møller M: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med 2014; 40: 11–22.

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In Reply:

I thank Professor Guntinas-Lichius for the important point that larnygopharyngitis due to reflux is also an indication for PPI. Many of these patients have typical reflux symptoms along with laryngitis and thus an uncontroversial indication for PPI. For those who have laryngitis without any typical symptoms of reflux esophagitis, the reflux finding score (RFS) has been developed and has been found to be well correlated with the laryngoscopic structural findings (1). There have been very few prospective, randomized, placebo-controlled trials of PPI for this indication. The indication was uncontroversial in the patients studied, all of whom had abnormal esophageal pH values; it is, therefore, surprising that laryngitis did not improve more than it actually did under PPI treatment (2). It seems that, for many patients with chronic hoarseness or irritative cough, acid reflux really is not the cause. There is certainly nothing to be said against trial treatment with PPI for a period of no longer than four weeks.

I cannot agree with Dr. Kraus' statement that there are many cases of severe magnesium deficiency under long-term treatment with PPI. A study published last year, based on a large number of patients, revealed that, in the absence other risk factors for hypomagnesemia, such as chronic renal failure, diarrhea, diuretics, or cancer, treatment with PPI alone hardly confers any risk (3). I would therefore not recommend routine serum magnesium measurement in patients taking PPI over the long term, unless they have other predisposing factors for hypomagnesemia.

Professor Steffen cites the important study by Ahrens et al. from Greifswald that confirms a statement I made in the article (4), to the effect that PPI are too often given without any clear-cut indication. He addresses a further important point as well: which patients should be given PPI to prevent so-called stress ulcers? Acid suppression with an H_2-blocker combined with the muscarinic receptor antagonist pirenzepine was a standard treatment in intensive care units for many years, until this was called into question when a study showed that intubated patients receiving H_2-blockers were at an elevated risk of pneumonia with Gram-negative bacteria (5). It was probably for this reason that the manufacturers of PPI drugs had no interest in conducting a placebo-controlled trial to determine whether even stronger acid suppression with PPI might be indicated to prevent ulcers in intubated patients. Even though the risk of pneumonia was later found to have been overestimated, there has still not been any trial that would definitively tell us which intensive-care patients should be treated with acid suppression—a matter that has taken on a different aspect in recent years, with the dropping prevalence of *Helicobacter pylori* and the shrinking percentage of patients with a history of ulcer. The available recommendations are based on low-level evidence, often derived merely from clinical observations rather than from trials that were designed to answer specific questions.

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REFERENCES

1. Belafsky PC, Postma GN, Koufman JA: The validity and reliability of the reflux finding score (RFS). Laryngoscope 2001; 111: 1313–7.
2. Lam PK, Ng ML, Cheung TK, Wong BY, Tan VP, Fong DY, Wei WI, Wong BC: Rabeprazole is effective in treating laryngopharyngeal reflux in a randomized placebo-controlled trial. Clin Gastroenterol Hepatol 2010; 8: 770–6.
3. Sharara AI, Chalhoub JM, Hammoud N, Harb AH, Sarkis FS, Hamadeh G: Low Prevalence of Hypomagnesemia in Long-term Recipients of Proton Pump Inhibitors in a Managed Care Cohort. Clin Gastroenterol Hepatol 2016; 14: 317–21.
4. Mössner J: The indications, applications, and risks of proton pump inhibitors—a review after 25 years. Dtsch Arztebl Int 2016; 113: 477–83.
5. Driks MR, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, Kunches LM, Farber HW, Wedel SA, McCabe WR: Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. N Engl J Med 1987; 317: 1376–82.

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Prof. Mössner directed and participated in clinical trials concerning the efficacy of lansoprazole, esomeprazole, pantoprazole, and omeprazole. Until 2009, he received financial support for clinical trials and honoraria for lectures at satellite symposia and continuing medical education events supported by the pharmaceutical industry, namely by the Altana Nycomed, AstraZeneca, Eisei, and Takeda companies. He has received reimbursement of meeting participation fees and travel expenses from AstraZeneca.