LESS IS MORE

Failing the Acid Test

Benefits of Proton Pump Inhibitors May Not Justify the Risks for Many Users

A staggering 113.4 million prescriptions for proton pump inhibitors (PPIs) are filled each year, making this class of drugs, at $13.9 billion in sales, the third highest seller in the United States. These medications are effective for treatment of erosive and ulcerative esophagitis, Barrett esophagus, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GERD), as well as for short-term treatment of ulcer disease, as part of a combination regimen for Helicobacter pylori eradication and for prevention of ulcers due to non-steroidal anti-inflammatory drugs. However, these indications do not account for more than a hundred million prescriptions. So it should come as no surprise that PPIs have been shown to be overprescribed; between 53% and 69% of PPI prescriptions are for inappropriate indications.2,4,5

See also pages 749, 751, 765, 772, 779, and 784

With so much talk of the seemingly unsustainable increases in the cost of health care in the United States, readers may be anticipating an editorial on how decreasing inappropriate PPI use would result in substantial savings and help “bend the curve” of American health care expenditures. Indeed, the financial costs of these medications are astounding. I am also tempted to preach about how much “health” $14 billion could buy if spent on prevention and early intervention. However, in the spirit of the Archives’ new series “Less is More,”6 I wish to put aside all financial arguments and instead consider only the harm of the inappropriate use of these medications.

All drugs have adverse effects, but that alone is not a reason to avoid them. Rather, prior to prescribing medications, good clinicians must weigh the benefits vs the risks and the seriousness of the disease vs the seriousness of the adverse effects. For example, antiretroviral medications for human immunodeficiency virus have many serious and even life-threatening adverse effects, but multiple studies have shown that they extend life and prevent devastating infections. In comparison, PPIs are often prescribed for dyspepsia, in the absence of ulcer disease, esophagitis, or severe GERD. That PPIs relieve dyspepsia is without question, but at what cost (and I do not mean financial)? Five studies in this issue of the Archives help to answer this question.

Gray and colleagues’ assessed the impact of PPIs on fractures in the Women’s Health Study. With a sample of 130,487 postmenopausal women and extensive follow-up (7.8 years), they found that PPIs were associated with an increased rate of spine, lower arm, and total fractures. The increases in risk were modest (eg, the hazard ratio for total fractures was 1.25 [95% confidence interval], 1.15-1.36), but increases of common conditions due to commonly used medications add up to a lot of morbidity on a population level.

The increases in the risk of Clostridium difficile infection with PPIs are not at all modest, reflecting the likely importance of gastric acid in protecting against infection from this pathogen.8-10 A pharmacoepidemiologic study of more than 1,000,000 hospital discharges in this issue of the Archives demonstrates a dose-response curve between level of acid suppression and C difficile infection.11 Compared with patients receiving no acid suppression therapy, the risk of C difficile infection increased an estimated 53% for those receiving histamine-2 receptor antagonists, 74% for those receiving daily PPI, and more than doubled for those receiving more frequent PPI dosing. Another article in this issue extends this association by demonstrating that the use of PPIs during treatment for C difficile infection was associated with a 42% increase in the rate of C difficile recurrence.12

Besides increasing the risk of fractures and C difficile infection, PPIs are also known to increase the risk of both hospital and community-acquired pneumonia.13-15 As with the data on C difficile infection, there is a suggestion of a dose-response relationship between degree of acid suppression and risk. The risk of pneumonia is higher in patients receiving PPIs than in those receiving histamine-2 receptor antagonists.14,15

Even in patients for whom PPIs are indicated, are higher degrees of acid suppression necessary to achieve higher efficacy? Although this question has not been studied for the majority of indications, the answer is no in the case of patients with bleeding due to peptic ulcers. A meta-analysis in this issue of the Archives shows that higher-dose PPIs (defined as a dose equivalent to an 80-mg bolus followed by 8 mg/h for 72 hours or similar dose) were not more effective in decreasing the rates of rebleeding, surgical intervention, or mortality than lower doses.16 If higher doses are not more effective, why are they used? One possibility is that in the absence of evidence, medical practice tends to follow the philosophy that if some is good, more must be better—a philosophy reinforced by drug sales representatives and direct-to-consumer advertising.

In the drive to decrease harm due to PPI use, we can take some comfort in the study by Yachimski and col-
leagues. They found that introduction of a standardized guideline on prescribing practice decreased inpatient use of PPI prescriptions, but only among patients not receiving PPIs at the time of hospital admission. This makes sense because the bulk of PPI prescribing occurs among outpatients.

Why are so many people treated with PPIs? One reason is that dyspepsia, a condition that leads to its use, is very common (25% of adults report dyspepsia), and PPIs are very effective at reducing the symptoms and have no immediate adverse effects that would dissuade patients from their use. Equally important, prescribing PPIs fits our medical model. The patient has a symptom; we give it a fancy name. We call persistent indigestion (without evidence of ulcer disease or esophagitis) “functional dyspepsia.” We call heartburn “gastroesophageal reflux.” Next, we treat the symptom with a medication, ideally one in pill form.

The problem with this paradigm is that for most patients the adverse effects of PPIs outweigh the benefits. Reducing the unnecessary use of these medications will require action by both physicians and patients. As physicians, we should offer treatments other than PPIs for functional dyspepsia, prescribe short courses of PPI treatment (after disclosure of possible risks and benefits), and consider a trial of discontinuing PPI therapy in patients who are asymptomatic. Once our patients fully appreciate the adverse effects of PPIs, they themselves may prefer other treatments, including tincture of time (eg, eating smaller meals [especially before bed], weight loss, smoking cessation, stress reduction), and other nonmedical interventions (eg, raising the head of their bed).

On a broader level, the over prescription of PPIs should also remind us to critically evaluate our own treatment paradigms: “more is better” or “do no harm”?

Mitchell H. Katz, MD

Author Affiliation: San Francisco Department of Public Health, San Francisco, California.

Correspondence: Dr Katz, San Francisco Department of Public Health, 101 Grove St, San Francisco, CA 94102 (mitch.Katz@sfdph.org).

Financial Disclosure: Dr Katz is an independent consultant for Health Management Associates.

REFERENCES