Potential Costs of Inappropriate Use of Proton Pump Inhibitors

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Abstract: *Background:* Proton pump inhibitors (PPIs) are commonly overused in hospitalized patients. The objectives of this study were to determine the extent of their inappropriate initiation in patients with low risk for gastrointestinal hemorrhage, factors associated with their continuation on discharge and potential cost of this trend. *Methods:* Retrospective examination of patients with low risk for gastrointestinal hemorrhage admitted to a tertiary-care teaching hospital over a 3-month period who received esomeprazole. The following information was collected: age, gender, PPI status (*de novo* or continued) and admitting diagnoses. Additional information collected from the *de novo* subgroup included indication for PPI, number of days on PPI and continuation of the drug on discharge. The cost of the medication was obtained from pharmacy records. *Results:* Four hundred nine patients were admitted during the study period and 204 (49.9%) received PPI *de novo*. Among these, 155 patients (76%) had an inappropriate indication for PPI. Of these, 62 (40%) patients were continued on PPI on discharge. Older age was a significant predictor of continuation of PPI at discharge. The estimated cost of the inpatient and outpatient inappropriate use of PPI was $12,272 and $59,272, respectively. *Conclusions:* PPIs are overused in the majority of hospitalized patients with low risk for gastrointestinal bleeding and this practice gets perpetuated at discharge, especially in older patients. The cost of this phenomenon is alarming.

Key Indexing Terms: Proton pump inhibitors; Costs; Low-risk patients. **[Am J Med Sci 2014;347(6):446–451.]**

Since their introduction in the late 1980s, proton pump inhibitors (PPIs) have proven to be effective drugs in the treatment of gastric acid secretion disorders. Their effectiveness and superiority to histamine receptor (H2) blockers have made them the drugs of choice in the management of such conditions.[1–3] For many years, PPIs were perceived as medications with a relatively safe side effect profile. However, multiple recent studies have reported an increased incidence of serious complications associated with their use such as *Clostridium difficile* infection, interstitial nephritis, hypomagnesemia, community-acquired pneumonia, increased risk of fractures and even an increased mortality risk.[4–9]

Given their proven effectiveness, a widespread advertizing strategy has been applied to these medications, resulting in a progressive increase in the number of dispensed prescriptions in recent years.[10] In a recent report, approximately 113 million prescriptions for PPIs were written in the United States in 2008, making them the 2nd highest sold prescription drug class.[11] Furthermore, this report stated that esomeprazole (Nexium) has been the 2nd single best-selling drug in the country since 2005 and that the revenues generated by this trend peaked at 13.6 billion dollars in 2010.

Despite well-defined FDA-approved indications,[12–20] multiple articles have reported the frequent inappropriate use of PPIs.[21–25] Although the bulk of these studies have focused on the patterns of inappropriate PPI prescription behaviors and the reasons behind their use, scarce data exist regarding the cost of this recent trend. In an effort to further characterize this phenomenon, this study aimed to determine the extent of inappropriate initiation of PPIs among hospitalized patients, determine any factors associated with the continuation of these medications on discharge and estimate the potential costs for both institutions and patients.

MATERIALS AND METHODS

A retrospective medical record review of all patients admitted to a teaching internal medicine service at a tertiary-care urban hospital between January 1 and March 31, 2010, was performed. Patients of either gender, with an age range of 20 to 99 years, who received 40 mg of oral esomeprazole once a day within 24 hours of admission, were selected for the study if they were deemed to have a low risk for gastrointestinal (GI) bleeding. For the purpose of the study, "low risk" for GI bleeding was defined as the absence of any of the following at the time of admission: history or presence of upper and/or lower GI bleeding, gastritis, peptic ulcer disease, gastroesophageal reflux disease (GERD), respiratory distress requiring intubation and abdominal pain of unexplained causative factors. Patients were excluded from the study if they were admitted for <48 hours, readmitted within 2 weeks of discharge or required intensive care therapy at the time of admission or at any point throughout the hospitalization. A total of 409 patients were included in the study.

The following information was collected from the medical record by 3 physicians using a standardized data abstraction protocol: age, gender, PPI status ("*de novo*" if the medication was started at admission or "continued" if the patient was already taking it before the admission), PPI dose and admitting diagnosis. All the admission diagnoses were grouped into 6 major categories (cancer, infectious diseases, GI, pulmonary, cardiac and neurological). The patients in the continued group were excluded from the final analysis because corroboration of the indications for PPI was not obtained from the prescribing physician. Analysis of the *de novo* group was the main focus of the study; therefore, specific additional information collected from this group included indication for PPI use, number of days on PPI during admission and continuation or discontinuation of the drug on discharge. Accepted indications for PPI were obtained from the FDA recommendations and are listed in Figure 1.[12–20] Because of formulary regulations, the PPI used in this study was esomeprazole. The cost of this medication at the aforementioned dose was obtained from the hospital pharmacy records. The monthly cost of the same dose of esomeprazole for the general public is listed

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FDA APPROVED INDICATIONS
Healing of erosive esophagitis
Maintenance of Healing of erosive esophagitis
NSAID induced dyspepsia
Treatment of *H. pylori* in combination with antibiotics
Short term treatment of active PUD
Maintenance of healed duodenal ulcer
Healing of NSAID associated gastric ulcer
Risk reduction of NSAID associated gastric ulcer
Critically ill patients on prolonged mechanical ventilation
Pathologic hypersecretory conditions (Zollinger-Ellison syndrome)
GERD

FIGURE 1. FDA-approved indications for proton pump inhibitors.

in Figure 2.[11] The study was approved by the hospital's institutional review board.

Statistical Analysis

Continuous normally distributed data are presented as mean ± SD and were compared with the unpaired *t* test. Data not normally distributed are presented as median and interquartile range (IQR) and were compared with the Mann-Whitney's *U* test. Categorical data are presented as frequencies (%). In the *de novo* group, the univariable relationship between dichotomous (gender and diagnostic category) or continuous variables (age and number of days on PPI) and the prescription of PPI on discharge was evaluated using a Fisher's exact test or the Spearman's ρ correlation coefficient, respectively. Logistic regression was used to determine whether any of the previously mentioned variables were significant independent predictors of prescription of PPI on discharge in the multivariable analysis. Because of sample size limitations, we evaluated each diagnosis separately by adding it as a last step to a stepwise model, which included age, gender and number of days on PPI as potential predictors. Statistical analysis was performed using SPSS statistical software program (version 20; SPSS, Chicago, IL). A $P < 0.05$ was considered *a priori* to indicate statistical significance.

RESULTS

A total of 2,094 patients were admitted to this institution during the study period. Of these, 629 (30%) patients were started on PPI within 24 hours of admission. Two hundred twenty patients were excluded from the study as follows: 168 had GI-related admitting diagnoses including 91 with upper GI hemorrhage, 39 with lower GI hemorrhage, 9 with peptic ulcer disease and 29 with abdominal pain of uncertain causative factors. Another 52 patients were excluded because they required intensive care monitoring either at admission or during their hospitalization. Four hundred nine patients met all the inclusion and exclusion criteria. Figure 3 illustrates the selection process. In the final sample, 204 patients (49.9%, 95% confidence interval [CI]: 45%–55%) received PPI *de novo* and the remaining 205 (50.1%, 95% CI: 45%–55%) received continued treatment. The demographic characteristics of the *de novo* group are listed in Table 1, and a list of all the indications for PPI in this subgroup is found in Table 2. In the *de novo*

Generic Name	Average Monthly Cost ($)
Esomeprazole 40 mg	239
Lansoprazole 30 mg	253
Dexlansoprazole 60 mg	170
Omeprazole 40 mg	172
Rabeprazole 20 mg	274
Pantoprazole 40 mg	192

FIGURE 2. Average cost of different proton pump inhibitors available.