Proton Pump Inhibitors for Prophylaxis of Nosocomial Upper Gastrointestinal Tract Bleeding

Effect of Standardized Guidelines on Prescribing Practice

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Background: Proton pump inhibitors (PPIs) are frequently prescribed for prophylaxis of nosocomial upper gastrointestinal tract bleeding. Some inpatients receiving PPIs may have no risk factors for nosocomial upper gastrointestinal tract bleeding, and PPIs may be continued unnecessarily at hospital discharge. We aimed to assess the effect of standardized guidelines on PPI prescribing practices.

Methods: Guidelines for PPI use were implemented on the medical service at a tertiary center. We reviewed PPI use among inpatient admissions during the month before implementation of guidelines and then prospectively evaluated PPI use among admissions during the month after implementation of guidelines.

Results: Among an overall cohort of 942 patients, 48% were prescribed PPIs while inpatients, and 41% were prescribed PPIs at hospital discharge. Univariate predictors of inpatient PPI use included age, length of hospital stay, history of gastroesophageal reflux disease or upper gastrointestinal tract bleeding, and outpatient PPI, aspirin, or glucocorticoid use. Among patients not on an outpatient regimen of PPIs at admission, implementation of guidelines resulted in lower rates of inpatient PPI use (27% before vs 16% after, *P* = .001) and PPI prescription at discharge (16% before vs 10% after, *P* = .03).

Conclusion: Introduction of standardized guidelines resulted in lower rates of PPI use among a subset of inpatients and reduced the rate of PPI prescriptions at discharge.

Arch Intern Med. 2010;170(9):779-783

NOSOCOMIAL UPPER GASTROINTESTINAL TRACT BLEEDING (UGIB) IS ASSOCIATED WITH CONSIDERABLE MORTALITY. GASTRIC MUCOSAL “STRESS ULCERS” ARE FREQUENTLY IMPLICATED AS AN UNDERLYING CAUSE OF NOSOCOMIAL UGIB, AND RISK FACTORS (INCLUDING COAGULOPATHY AND MECHANICAL VENTILATION) HAVE BEEN IDENTIFIED AMONG PATIENTS IN THE INTENSIVE CARE UNIT (ICU) (HEREAFTER REFERRED TO AS ICU PATIENTS). Pharmacologic gastric acid suppression can provide effective prophylaxis against UGIB in at-risk ICU patients.

Proton pump inhibitors (PPIs) suppress gastric acid production at the level of the hydrogen/potassium–adenosine triphosphatase pathway and are widely prescribed for nosocomial UGIB prophylaxis. Proton pump inhibitors may be overused among non-ICU inpatients without risk factors for UGIB. Moreover, PPIs prescribed for prophylactic purposes to inpatients may be continued unnecessarily at the time of hospital discharge.

Long-term PPI use may have an effect on mineral absorption and metabolism, including calcium malabsorption, resulting in an increased risk of hip fracture. In addition, PPI use may increase the risk of enteric infections such as *Clostridium difficile* and nonenteric infections, including community-acquired and nosocomial pneumonia. Proton pump inhibitors may influence the action of certain other prescription medications, including diminishing the antiplatelet effects of clopidogrel bisulfate in patients receiving both medications after hospitalization for acute coronary syndrome.

This study aimed to assess the use of PPIs for UGIB prophylaxis among inpatients on a non-ICU general medicine service and to measure the effect of standardized guidelines on PPI prescribing practices. We hypothesized that PPIs are overused in the non-ICU medical inpatient population and that the introduction of standardized guide-
lines would result in lower rates of inpatient PPI use and fewer PPI prescriptions at discharge.

**METHODS**

The study was conducted at a single tertiary academic medical center—Massachusetts General Hospital, Boston. We drafted guidelines for PPI use among inpatients, including guidelines pertaining specifically to the use of PPIs for nosocomial UGIB prophylaxis.

To draft guidelines, a PubMed search was performed to identify relevant English-language studies from the medical and scientific literature. Search terms included the following: nosocomial gastrointestinal bleeding, gastrointestinal bleeding prophylaxis, stress ulcer prophylaxis, gastric acid suppression, proton pump inhibitor, proton pump inhibitor prophylaxis, and combinations thereof. Studies reporting retrospective or controlled prospective data were eligible for review. In studies reporting an intervention consisting of pharmacologic gastric acid suppression, the outcome and magnitude of the intervention were reviewed. A formal level of evidence grade was not assigned to individual studies; however, relevant findings were used to draft guidelines, which were then reviewed, edited, and endorsed by the collective faculty of the gastrointestinal unit. A consensus set of guidelines was subsequently approved by the hospital pharmacy administration before implementation. The eAppendix (http://www.archinternmed.com) contains a full version of the guidelines.

We introduced the guidelines to the medical house staff via oral presentation at a scheduled didactic conference. The guidelines were described in detail, and the house staff were notified that the guidelines would be implemented on the medical service on a 1-month trial basis. We asked the house staff to refer to the guidelines when considering the use of PPIs for nosocomial UGIB prophylaxis but to realize that the use of PPIs on a patient-by-patient basis should ultimately be left to individual clinical judgment. We informed the house staff that PPI use at admission, during admission, and at discharge for all admissions to the medical service over the ensuing calendar month would be measured but that individual provider prescribing practices would not be audited. All medical house staff subsequently received a copy of the guidelines (eAppendix) by e-mail. No further dissemination of the guidelines or reminders occurred during the 1-month period.

The institutional review board approved retrospective review of the medical record for all admissions to the medical service during 1 calendar month before introduction of the guidelines, as well as all admissions during 1 calendar month after introduction of the guidelines. Patients eligible for inclusion in this study included all outpatients admitted to and discharged from the inpatient medical service; most of these patients were admitted from the emergency department. The study excluded inpatients transferred to the medical service from an inpatient nonmedical service within Massachusetts General Hospital, patients transferred from another inpatient medical facility, and patients transferred to the medical service from an ICU or medical step-down unit. The study also excluded patients admitted with a primary or secondary diagnosis of gastrointestinal tract bleeding, patients who underwent upper gastrointestinal tract endoscopy during the course of their hospital stay, and patients who did not survive to discharge. For patients admitted and discharged more than once during the study period, each discharge was counted as a separate study enrollment.

Massachusetts General Hospital uses an electronic medical record, and provider order entry is computer based. We extracted demographic data, including age and sex, from the electronic medical record. Medical history, including history of gastroesophageal reflux disease, peptic ulcer disease, or UGIB, and outpatient medication use were defined as documented by the house staff in the history and physical at admission. The study defined inpatient PPI use as the presence of a physician’s order for formulary PPIs at any point during a patient’s hospital admission, retrievable through a search of computerized provider order entry. Proton pump inhibitor use at discharge was defined as the inclusion of a prescription for PPIs among the patient’s discharge medications in the electronic discharge summary.

Statistical analysis was performed using available software (JMP 7.0; SAS Institute, Cary, North Carolina). Univariate analysis was performed by testing of significance using the t test for comparison of continuous variables and the χ² test for comparison of nominal or binary variables. Logistic regression analysis was performed using candidate predictors chosen on the basis of univariate analysis results and a priori hypotheses. A variable selection algorithm was not used for logistic regression analysis. All reported P values are 2-sided, with P < .05 as the threshold for statistical significance.

**RESULTS**

The final overall cohort consisted of 942 patients. Among these, 458 patients were admitted and discharged during the month before implementation of PPI guidelines (preguidelines cohort), and 484 patients were admitted and discharged during the month after implementation of PPI guidelines (postguidelines cohort).

In the overall cohort, outpatient PPI use was documented in 36% of patients at the time of admission, which exceeded the combined documented rates of gastroesophageal reflux disease (14% of patients) and peptic ulcer disease or UGIB (7% of patients). Forty-nine percent of all patients in the cohort were prescribed PPIs while inpatients, and 41% were prescribed PPIs at discharge. Full demographic data are summarized in Table 1 and Table 2.

In comparing the preguidelines and postguidelines cohorts, no significant difference was noted in the proportion of patients who were prescribed PPIs during admission (52% vs 46%, P = .36) or at discharge (42% vs 40%, P = .97) (Table 3). However, in the subset of patients without documented outpatient PPI use at the time of admission, fewer patients were prescribed PPIs while inpatients (27% vs 16%, P = .001) and at discharge (16% vs 10%, P = .03) after implementation of PPI guidelines (Table 3).

**UNIVARIATE ANALYSIS**

In univariate analysis, inpatient PPI use was associated with older age, longer length of hospital stay (LOS), and reported history of gastroesophageal reflux disease, peptic ulcer disease, or UGIB. In addition, outpatient use of PPIs, aspirin, clopidogrel, and glucocorticoids each predicted inpatient use of PPIs (Table 4).

**LOGISTIC REGRESSION ANALYSIS**

We constructed a logistic regression model to determine predictors of inpatient PPI use, controlling for confounding and covariate factors. Model inputs included age; LOS;
history of gastroesophageal reflux disease, peptic ulcer disease, or UGIB; and outpatient PPI, aspirin, clopidogrel, nonsteroidal anti-inflammatory drug, or glucocorticoid use. In the overall cohort, outpatient PPI use at the time of admission was the strongest predictor of whether a patient would be prescribed PPIs while an inpatient (odds ratio, 69.1; \( P < .001 \)). The only other significant predictor in multivariate analysis was length of stay (odds ratio, 1.04 for each unit increase in LOS; \( P = .04 \)). The model results and significance of predictors did not differ when comparing the 2 study periods—before and after implementation of standardized PPI guidelines.

The model was rerun with inclusion of only the cohort of patients not receiving an outpatient regimen of PPIs at the time of admission. Among this cohort, individual PPI use was independently predicted by LOS and by outpatient glucocorticoid use.

Prior studies have demonstrated overuse of PPIs in the non-ICU inpatient setting as well as on medical subspecialty services and in long-term nursing facilities. This study demonstrates that PPI use is prevalent among non-ICU medical inpatients at a tertiary teaching hospital, that almost half of all medical inpatients over the course of the 2-month study period received PPIs during their inpatient stay, and that implementation of standardized guidelines may have a measurable effect on rates of PPI use.

In the overall cohort, rates of outpatient PPI use and PPI prescriptions at discharge did not diminish after implementation of guidelines, suggesting (at face value) a negligible effect of the intervention. However, the effect of the intervention may be masked by the high rate of outpatient PPI use and by the fact that a greater percentage of patients reported outpatient PPI use at admission in the postguideline study period compared with the preguideline study period (37% vs 35%). Among the cohort of patients not taking PPIs at the time of admission, the rate of outpatient PPI use declined from 27% to 16% after imple-
mentation of guidelines ($P= .001$), and the percentage of these patients receiving PPI prescriptions at discharge declined from 16% at baseline to 10% after implementation of guidelines ($P= .03$). While this resulted in only 38 fewer inpatient PPI prescriptions and 21 fewer outpatient prescriptions over the course of a 1-month trial period among a selected inpatient population, the volume and effect of such a decline would be substantial when considered for hospitalwide implementation.

The strongest predictor of inpatient PPI use in our cohort was whether a patient reported PPI use at the time of admission. More than one-third of patients (36%) reported PPI use at the time of admission. This is consistent with the findings of a prior study\(^5\) from an academic teaching hospital medical service in which 29% of patients reported taking acid suppression medication before admission. It is uncertain whether the strong effect of outpatient PPI use on inpatient PPI use represents continuation of appropriate outpatient PPI therapy for an accepted indication, continuation of outpatient PPI therapy (irrespective of indication) for inpatient prophylactic purposes, or rote continuation of an outpatient regimen without reevaluation at the time of admission. Our study was not specifically designed to assess whether PPI therapy was appropriate on a patient-by-patient basis, and in our protocol, providers were not asked to specify indications for PPI therapy. However, the study intervention (implementation of PPI guidelines) was designed to discourage the use of PPIs for prophylaxis of nosocomial UGIB in patients without clear risk factors for nosocomial UGIB.

LOS also predicted inpatient PPI therapy in our cohort, a finding consistent with prior published data.\(^6\) It is uncertain whether this is a function of increased inpatient exposure providing increased opportunity for initiation of inpatient PPI therapy, represents the development of an appropriate indication for PPI therapy, or is a nonspecific marker of severity of illness.

The goal of this study was to assess PPI use for prophylactic purposes in a non-ICU setting. By design, the study cohort excluded patients with an alternative indication for PPI therapy, specifically patients with an admitting diagnosis of gastrointestinal tract bleeding. In addition, the cohort excluded patients admitted to the general medical service from the ICU or medical step-down unit, as PPI therapy in these patients might reflect inadvertent continuation of stress ulcer prophylaxis initiated in the ICU among at-risk patients rather than de novo PPI prophylaxis in average-risk inpatients. While these exclusion criteria eliminate some potential confounders from our cohort, they may also limit the external validity of the study.

The study design posed several additional limitations. Much of the data was retrieved from medical record review. Patient recall bias may have resulted in underreporting or overreporting of outpatient medication use, including the use of prescription or nonprescription PPIs and prescription or nonprescription aspirin or nonsteroidal anti-inflammatory drugs. Additional factors not included in the univariate or logistic regression analyses may have influenced inpatient PPI use. For instance, our analysis does not include measures of severity of illness or specific admitting diagnoses, which may be predictive of inpatient PPI therapy. In addition, we did not measure initiation of new inpatient antiplatelet or anticoagulant therapy and are unable to assess the influence of these medication regimens on inpatient PPI use. We also did not measure rates of inpatient or outpatient use of histamine\(_2\), receptor antagonists and cannot assess whether prescribers simply substituted these medications for PPIs after implementation of guidelines. Finally, this study was not designed to assess whether PPI use rates translate into any (beneficial or adverse) meaningful clinical outcome.

The developed set of guidelines is designed as a general framework for prescribing practices, does not address every clinical circumstance in which prophylactic PPI therapy might be considered, and is subject to individual interpretation, which may vary by provider. This reflects in part the relative lack of controlled published data demonstrating specific risk factors for nosocomial UGIB in a non-ICU population, as well as our desire to implement practical easy-to-use guidelines that posed neither excessive restrictions nor a cumbersome algorithm. Therefore, one can argue that the introduction of guidelines and the subsequent measured decline in PPI use do not represent a true cause-and-effect relationship. There may be some natural variability in PPI use rates on a month-to-month basis depending on the prescribing practices of individual providers rotating through the inpatient medical service. It is also conceivable that mere awareness that PPI use rates were being measured as part of this study, rather than an understanding of the guidelines, may have influenced provider prescribing practices. Therefore, while the results of this study should be considered hypothesis generating, the potential financial and health-related effects of such an intervention may be substantial, and our results should provide impetus for a more comprehensive longer study to determine the effect of PPI guidelines on inpatient and outpatient PPI prescribing practices, rate of inpatient UGIB, and cost.

An important question is whether the observed decline in PPI use rates among a subset of inpatients will be durable and sustained after completion of this study. Our study was not designed to answer this question. Prior data have questioned the sustained effectiveness and cost-effectiveness of interventions aimed at reducing prescriptions of acid-suppressive drugs in the outpatient or general practitioner setting.\(^21\) One option available in the inpatient setting, and which we are considering, is embedding a clinical decision support module in the provider order entry system: when a physician attempts to order an inpatient PPI, the physician is prompted with a review of guidelines for appropriate PPI use and is then offered the option to continue with or abandon the PPI prescription. Data suggest that such prescribing computerized decision support systems have the potential to alter physician behavior\(^22\) and might significantly enhance the effect of PPI prescribing guidelines among house staff.

In summary, inpatient PPI therapy was prevalent among our cohort, with almost half of all medical inpatients receiving an inpatient PPI and more than 40% of patients prescribed PPIs at discharge. These figures seem to be driven by high outpatient rates of PPI use. Factors associated with inpatient PPI therapy include outpatient PPI use and LOS. Implementation of standardized
guidelines regarding appropriateness of inpatient PPI use results in decreased inpatient and discharge PPI therapy among patients not receiving outpatient PPI therapy at the time of admission.

Accepted for Publication: December 9, 2009.
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Author Contributions: Dr Yachimski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yachimski, Farrell, Hunt, and Reid. Acquisition of data: Yachimski and Reid. Analysis and interpretation of data: Yachimski and Reid. Drafting of the manuscript: Yachimski. Critical revision of the manuscript for important intellectual content: Yachimski, Farrell, Hunt, and Reid. Statistical analysis: Yachimski. Obtained funding: Yachimski. Administrative, technical, and material support: Reid. Study supervision: Hunt and Reid. Financial Disclosure: None reported.
Funding/Support: This research was supported by grant T32 DK007191 from the National Institutes of Health (Dr Yachimski).
Previous Presentation: This study was presented as an abstract at Digestive Disease Week 2009, May 30-June 4, 2009; Chicago, Illinois.
Additional Contributions: The Massachusetts General Hospital medical house staff participated in this study.

REFERENCES