F1000 FACULTY CRITIQUE

Histamine-2 receptor antagonists versus proton pump inhibitors for stress ulcer prophylaxis in the ICU [version 1; referees: not peer reviewed]

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Abstract

An evaluation of a recent study by MacLaren R, Reynolds PM, Allen RR *et al*: **Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit.** *JAMA Intern Med* 2014, **174:**564-574.

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Critique of:

Citation

MacLaren R, Reynolds PM, Allen RR: **Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit.** *JAMA Intern Med* 2014, **174**:564–574.

Background

Histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) are commonly used to prevent gastrointestinal tract (GI) hemorrhage in critically ill patients. The stronger acid suppression of PPIs may reduce the rate of bleeding but enhance infectious complications, specifically pneumonia and *Clostridium difficile* infection (CDI).

Methods

Objective

To evaluate the occurrence and risk factors for GI hemorrhage, pneumonia, and CDI in critically ill patients.

Design

Retrospective, pharmacoepidemiologic, cohort study evaluating patient data voluntarily submitted to the Premier Perspective database (Premier Inc).

Setting. ICUs in 71 US hospitals.

Subjects. Patients 18 years or older, admitted to an ICU between January 1, 2003, and December 31, 2008, requiring more than 24 hours of invasive mechanical ventilation and receiving either an H_2RA or PPI for 48 hours or more while intubated.

Outcomes. Primary outcomes were secondary diagnoses of International Classification of Diseases, Ninth Revision (ICD-9)–coded GI hemorrhage, pneumonia, and CDI occurring 48 hours or more after initiating invasive ventilation.

Data analysis. Propensity score was determined where the use of H_2RAs or PPIs was the dependent variable and the covariates of age, sex, admission year, primary diagnosis, ICD-9–coded disease states occurring within 48 hours of ICU admission, and use of corticosteroids, anticoagulants, platelet inhibitors, or total parenteral nutrition were the independent variables. Propensity score-adjusted and propensity-matched multivariate regression models were used to control for confounders.

Results

Of 35 312 patients, 13 439 (38.1%) received H_2RAs and 21 873 (61.9%) received PPIs. Gastrointestinal hemorrhage (2.1% vs 5.9%; $P < .001$), pneumonia (27% vs 38.6%; $P < .001$), and CDI (2.2% vs 3.8%; $P < .001$) occurred less frequently in the H_2RA group. After adjusting for propensity score and covariates, odds ratios of GI hemorrhage (2.24; 95%CI, 1.81-2.76), pneumonia (1.2; 95%CI, 1.03-1.41), and CDI (1.29; 95%CI, 1.04-1.64) were greater with PPIs. Similar results were obtained in the propensity-matched models of 8799 patients in each cohort.

Conclusions

Proton pump inhibitors are associated with greater risks of GI hemorrhage, pneumonia, and CDI than H_2RAs in mechanically ventilated patients. Numerous other risk factors are apparent. These data warrant confirmation in comparative prospective studies.

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Commentary

First reported 40 years ago, stress ulceration of the gastric mucosa is a common complication of critical illnesss[1,2]. Endoscopic evidence of gastrointestinal (GI) mucosal damage occurs in 60–100% of intensive care unit (ICU) patients and occult bleeding occurs in 15–50% of those with ulcerations[3]. Clinically overt bleeding is seen in 5–25% of patients not receiving prophylaxis and is associated with increased mortality and higher costs[4]. As a consequence, acid blockade to prevent stress ulceration has become a mainstay of preventive care in the ICU[3].

The most frequently used agents for this purpose are histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs). Yet which of these two agents is preferable remains an unanswered question. A higher pH, as can typically be achieved with PPIs, is associated with less gastric erosion and more effective topical clotting[3,5,6]. However a high pH is also associated with bacterial overgrowth in the GI tract, potentially leading to increased infectious risk, particularly for pneumonia and *Clostridium difficile* infection (CDI)[7,8]. This tension creates a tradeoff between the two agents, whereby PPIs may be more effective at preventing GI bleeding but also more likely to cause nosocomial infections[9].

Several randomized controlled trials (RCTs) tried to resolve this tension by directly comparing PPIs to H_2RAs, but were underpowered for differences in patient centered outcomes. Meta-analyses of these RCTs generally showed that PPIs are associated with lower bleeding risk, but did not demonstrate an overall mortality reduction and were unable to examine CDI risk[10–13]. Differences in bleeding were also much smaller in higher quality studies[10]. Despite these inconclusive data, the Surviving Sepsis Campaign Guidelines published in 2012 and endorsed by 29 professional societies recommended the use of PPIs rather than H_2RAs for stress ulcer prophylaxis[14].

The recent study by Maclaren and colleagues[15] attempts to illuminate this issue using the tools of pharmacoepidemiology, an emerging science that exploits large observational datasets to determine the effectiveness and safety of drugs. Since pharmacoepidemiological studies are observational rather than experimental, they are prone to confounding and indication biases. However, they are typically large, making them powered to detect even small treatment effects and represent "real world" scenarios, making them more generalizable than most randomized trials.

In the Maclaren study the authors used the Premier Perspective Database, the largest inpatient drug utilization database in the U.S., to compare the effectiveness of H_2RAs and PPIs among mechanically ventilated patients[16]. Eligible patients included adult ICU patients who were mechanically ventilated for at least 24 hours and received either an H_2RA or PPI for more than 48 hours. The investigators excluded patients admitted with GI bleeding or who received both types of acid suppression, and performed propensity score-adjusted and matched multivariate regression models to control for confounders. The primary outcomes were diagnoses of GI hemorrhage, pneumonia and CDI occurring at least 48 hours after the institution of mechanical ventilation. The key study findings were higher risks for GI hemorrhage, pneumonia and CDI in the PPI group as compared to the H_2RA group.

The increased risk of GI bleeding in patients receiving PPIs is perhaps the most surprising study result. One potential mechanism offered by the authors is that H_2RAs may ameliorate the oxidative stress after mucosal injury. This explanation is probably unlikely given that PPIs also mitigate ischemia-reperfusion in gastric ulcers[17,18], and the bulk of clinical evidence demonstrates decreased acid production with PPIs[3,10]. A perhaps more plausible explanation is misclassification bias. Inaccuracies in data coding might have led to the inclusion of patients receiving PPIs as treatment for bleeding rather than prevention. Additionally, it is possible that among the 4,000 patients excluded from the study because they received both agents, some began on H_2RAs and then were switched to PPIs after a bleed, thus artificially lowering the observed incidence of bleeding in the H_2RA group. More consistent with the previous literature is that PPIs were associated with increased risk of pneumonia and CDI[19,20].

This study has several limitations that are common to all observational studies. In particular there is potential for unmeasured confounding by severity of illness, as might occur if PPI users were sicker and thus more prone to bleeding and infections unrelated to PPI use. The authors attempted to overcome this problem using a propensity score for the use of PPI. Although propensity scores can create balanced groups, it is still possible that the groups differed in systematic ways, since propensity scores can only account for measured variables[21].

Despite these limitations, this study challenges the dogma that PPIs are associated with a lower risk of GI hemorrhage in mechanical ventilation. This study also supports previous investigations demonstrating a link between PPIs and increased risk of pneumonia, and for the first time convincingly demonstrates an association with higher *Clostridium difficile* infection risk in critically ill patients.

Recommendation

Given the limitations of current meta-analyses and the lack of high-quality RCT data, it is time for an appropriately powered randomized study comparing these two classes of acid-suppression agents for stress ulcer prophylaxis. Such a study should be powered not only for GI bleeding and infection but also for overall mortality, since data on GI bleeding and infection alone would not allow us to weigh those two competing risks. This trial might also include a group that would receive no prophylaxis at all if the patient tolerates enteral feeding. In the meantime, clinicians opting to provide stress ulcer prophylaxis should consider their own beliefs about the risks and attributable mortality of both bleeding and infections, as either drug can be justified as the agent of choice given the available literature. Yet at the same time, guidelines' recommendations endorsing PPIs are probably premature.

Abbreviations

GI: gastrointestinal; H_2RAs: histamine-2 receptor antagonists; PPIs: proton pump inhibitors; PS: propensity score.

Competing interests

The authors declare that they have no competing interests.

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