Proton Pump Inhibitors are not associated with Acute Kidney Injury in Critical Illness

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Abstract

Recent epidemiologic data linking proton pump inhibitor (PPI) use to acute and chronic kidney dysfunction is yet to be validated in other populations, and mechanisms have not been explored. Using a large, well phenotyped inception cohort of 15,063 critically ill patients, we examined the risk of acute kidney injury (AKI), as defined by the Kidney Disease Improving Global Outcomes criteria guidelines, according to prior use of a PPI, histamine-2 receptor antagonist (H_2RA), or neither. A total of 3,725(24.7%) patients reported PPI use prior to admission, while 905(6.0%) patients reported H_2RA use. AKI occurred in 747(20.0%) and 163(18.0%) of PPI and H_2RA users respectively, compared to 1,712(16.2%) of those not taking acid suppressive medications. In unadjusted analysis, PPI and H_2RA users had a 28% (95% CI 1.17–1.41, p<0.001) and 10% (95% CI 0.91–1.30, p=0.31) higher risk of AKI compared to those taking neither class of medication. However, in sequential models that included adjustment for demographics, cardiovascular comorbidities, indications for PPI use, and severity of illness, the effect of PPI on the risk of AKI was attenuated, and in the adjusted analysis, PPI was not associated with AKI (OR 1.02; 95% CI 0.91–1.13, p=0.73). The presence of sterile pyuria and hypomagnesemia did not modify the association between PPI use and AKI. In summary, after adjustment for demographics, illness severity and the indication for PPI use, PPI use prior to admission is not associated with critical illness AKI.

Keywords

Proton Pump Inhibitor; Histamine Receptor Antagonist Blocker; Acute Kidney Injury

Introduction

Recent epidemiologic data suggests that proton pump inhibitor (PPI) use may be associated with an increased risk of acute and chronic kidney disease, adding to a list of accumulating

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potential risks, including hypomagnesemia(1), infection(2), cardiovascular disease(3, 4), and mortality(5). Using the Atherosclerosis Risk in Communities study, a prospective observational study of representative communities, Lazarus et al. have linked self-reported PPI use to the development of chronic kidney disease (CKD), and then replicated the findings using a large hospital electronic medical record(6). PPI use has also been associated with an increased risk of acute kidney injury (AKI)(7, 8).

Mechanisms for this observed association have not previously been explored, but might occur through episodes of acute interstitial nephritis (AIN), a known PPI associated adverse effect (9–12). Although there are no standard diagnostic criteria for AIN, signs of non-infectious inflammation, such as sterile pyuria and white cell casts, along with eosinophiluria, are frequently used as clinical indicators. In addition, data has suggested that PPI exposure might lead to endothelial dysfunction and vasoconstriction, presumably through impaired lysosomal function(13) and decreased nitrogen oxide levels(14) respectively, and might explain the observed association between PPI use and myocardial infarction(15) and dementia(16). These findings might similarly link PPI use to AKI(17). And finally, hypomagnesemia, a potential consequence of chronic PPI use(1, 18), has been associated with an increased risk of chronic renal disease progression(19, 20).

Hypothesizing that PPI use might increase susceptibility to AKI, particularly in patients exposed to the physiologic stressors of critical illness, we examined whether PPI use prior to hospitalization was associated with an increased risk of AKI within the first seven days of critical illness. In addition, to explore potential mechanisms linking PPI use and AKI, we examined whether the presence of sterile pyuria, a clinical indicator of interstitial nephritis, and hypomagnesemia, modified the association of PPI use and AKI.

METHODS

Study Population

We used the MIMIC-II (Multiparameter Intelligent Monitoring in Intensive Care) research database, a joint venture managed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC). BIDMC is a large, urban academic medical center. The database contains lab results, electronic documentation, and bedside monitor trends and waveforms for all patients admitted to a BIDMC intensive care unit (ICU) between 2001 and 2008. Use of the MIMIC II database has been approved by the Institutional Review Boards of BIDMC and MIT. MIMIC-II contains data from 24,581 adult patients who were admitted to surgical or medical ICUs at BIDMC. Of the 16,192 with documented admission medication lists, and after excluding patients with End Stage Renal Disease and those missing documentation of renal function, a cohort analysis of 15,063 unique first hospitalizations remained.

Primary medication exposure

PPI or H_2RA exposure was defined as any PPI or H_2RA listed as a pre-admission medication. We developed a Natural Language Processing (NLP) algorithm that searched

discharge summaries for a discrete home medication section within the History and Physical examination performed on admission, as previously described(1).

Primary Outcome

The primary outcome was AKI during the first 7 days of ICU care, as defined by either a 0.3 mg/dL creatinine increase within 48 hours of admission or a 50 percent increase within 7 days of admission, or acute dialysis, in keeping with the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Admission creatinine was used to determine "baseline" renal function in keeping with best practice guidelines(21). In addition, we explored the association of PPI use with AKI as determined by a urine output of <0.5 mL/kg/hour for more than 6 hours during the first seven days of critical illness, in keeping with an alternative KDIGO definition.

Covariates

Demographic information included age, sex, and ethnicity, coded as White, African-American, Asian, Hispanic, Other, or Unknown, and ICU type (medical, surgical, or cardiac). We used oral diabetes medication or insulin usage as identified in admission medication lists, along with Elixhauser discharge coding, to identify diabetic patients(22). We identified heart failure patients through NLP searching of the past medical history section of the admission examination or Elixhauser discharge coding. A history of cardiac arrhythmia, pulmonary circulation disorder, hypertension, liver disease, peptic ulcer disease, alcohol abuse, weight loss, obesity and metastatic cancer were included according to Elixhauser discharge coding. Admission ICU vitals included systolic and diastolic blood pressure and heart rate. Age, sex, and race were used to impute missing vitals in 733 patients. Laboratory values obtained within 24 hours of ICU admission included white blood cell and platelet counts, and glucose and hemoglobin concentrations. We used a NLP algorithm of admission medication lists to document angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACE-I), diuretic and statin usage.

Statistical analysis

We present baseline characteristics according to use of PPI, H_2RA, or neither, with p values calculated for group differences between PPI and H_2RA users. We used logistic regression to describe the association of PPI use with AKI. To explore the potential effect of residual confounding, we performed sequential regressions with incremental adjustments, with variables chosen based on clinical judgment. We created indicator variables for PPI use and H_2RA use. Model 1 included age, sex, and race. Model 2 included model 1 plus admission intensive care unit type, history of diabetes, congestive heart failure, cardiac arrhythmia, hypertension or pulmonary circulation disorder. Model 3 included model 2 plus a history liver disease, peptic ulcer disease, alcohol abuse, weight loss, obesity and metastatic cancer. Model 4 included Model 3 plus admission systolic blood pressure, diastolic blood pressure, heart rate, glucose, white blood cell count, hemoglobin, and platelet count. Model 5 included Model 4 plus use of diuretics, ace inhibitor, angiotensin receptor blocker, and statins. All models included PPI and H_2RA, and the reference category was therefore patients not taking acid suppression medications. In addition, we included admission serum creatinine in Model

5, and used backwards stepwise regression to identify the significant (p values <0.001) predictors of AKI.

In absence of standard clinical criteria to identify sterile pyuria, we a priori considered the presence of urinary white cells, without either genitourinary contamination or infection, as indicative of potential renal tubulointerstitial inflammation. 6,174 patients had a urinalysis completed within 12 hours of ICU admission. We excluded patients with a positive urine culture (n=688), greater than two epithelial cells per high powered field (hpf)(n=551), bacteruria [few(n=803), rare (n=480), occasional (n=621), moderate (n=290), many (n=223) and loaded (n=1)] or with positive nitrate on urine dipstick (n=21), leaving 2,657 patients with documented urine dipstick analyses and 1,366 patients with documented urinary microscopy. Among these, sterile pyuria was defined as the presence of leukocyte esterase on urine dipstick, or greater than five white blood cells (WBC)s/hpf on urine microscopy, in keeping with our hospital laboratory's definition. We created indicator variables for those PPI users with sterile pyuria and PPI users without sterile pyuria, and were regressed into Model 5 above.

To examine whether hypomagnesemia modified the association between PPI use and risk of AKI, we examined a multiplicative interaction term between PPI and a serum magnesium concentration of <1.6 mg/dl, in keeping with our hospital laboratory definition of hypomagnesemia, in 10,868 patients with magnesium concentrations measured within 24 hours of ICU admission.

Finally, in order to explore whether PPI use was indicating general illness severity (model specificity), we examined the association of pre-morbid PPI use with the risk of sepsis, as determined by Martin criteria(23), in adjusted analysis (Model 5), an outcome seemingly unlikely to be physiologically linked to PPI use. All analyses were performed using JMP Pro 12 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Of 15,063 critically ill patients, 3,725(24.7%) and 905(6.0%) were using a PPI or H_2RA, respectively, prior to admission. PPI users tended to be older and generally sicker than those not taking acid suppression, with a higher prevalence of most comorbidities, including diabetes, heart disease, liver failure, and more frequent use of diuretics, ACE-Is, and ARB's (Table I). Compared to H_2RA users, those taking PPIs had a higher prevalence of liver disease, alcohol abuse, and diuretic use, a lower admission hemoglobin and a higher admission serum creatinine.

PPI use and AKI risk

AKI occurred in 747(20%) and 163(18%) of PPI and H_2RA users, respectively, compared to 1,712(16%) in those patients not taking an acid suppression medication. While the unadjusted risk of AKI with PPI use was significantly higher than those without acid suppression medication usage (Table II), adjustment for demographics (Model 1) and traditional cardiovascular comorbidities (Model 2) attenuated the association, although it

remained significant. However, the inclusion of standard clinical indications for PPI usage further attenuated the association (Model 3). In the final adjusted model (Model 5), PPI use was not significantly associated with a risk of AKI.

In Model 5, the significant predictors of AKI (p value <0.05) were age, sex, ICU type, history of diabetes, heart failure, hypertension, obesity, weight loss, liver disease, systolic blood pressure and heart rate, all four laboratory parameters, diuretic, statin, and ARB use. Inclusion of admission serum creatinine in Model 5 had little effect on the association of PPI and AKI(OR 1.02; 95% CI 0.91–1.28 p=0.77). In a model that used backwards stepwise regression to identify the significant predictors of AKI, PPI use was similarly not associated with AKI (OR 1.04; 95% CI 0.94–1.16, p=0.41).

In 11,312 patients with documented urinary output, PPI use was similarly not associated with an adjusted risk of AKI (p=0.41), as defined by urinary output.

PPI use, sterile pyuria, and AKI

There were 634(24%) and 148(6%) PPI and H_2RA users respectively in those with documented urine dipstick analyses within 12 hours of ICU admission, and 323(24%) and 89(7%) PPI and H_2RA users in those with documented urinary microanalyses. Compared to patients taking no acid suppression, PPI users with sterile pyuria, defined by either leukocyte esterase positivity or >5 WBC's/hpf, did not have a significantly higher risk of AKI in adjusted analysis (Table III).

PPI users with leukocyte positivity and >5 WBC's/hpf did not have a significantly higher adjusted risk of AKI compared to PPI users without sterile pyuria (OR 1.02; 95% CI 0.44–2.16, p=0.96 and OR 1.38; 0.52–3.42,p=0.49, respectively).

PPI use and AKI risk in hypomagnesemia

There were 1,704 (16%) patients with hypomagnesemia on ICU admission. A multiplicative interaction term between PPI use and hypomagnesemia was not significant (p=0.75). Amongst those with hypomagnesemia, PPI use was not associated with a significantly increased risk of AKI (OR 1.04, 95% CI 0.76–1.41, p=0.80).

Model control

There were 1,539 (10%) admissions for sepsis. Despite adjustment for demographics, multiple comorbidities and illness severity (Model 5), premorbid PPI use remained significantly associated with the risk of sepsis (OR 1.22 95% CI 1.07–1.39, p=0.003), suggesting that our model continued to lack specificity.

Discussion

Our data suggests that PPI use is not associated with an increased risk of AKI in critically ill patients, and highlights the potential challenge of residual confounding in observational studies.

Our negative findings might potentially be explained by study differences. Whereas the Lazarus study was conducted longitudinally in a community and an outpatient setting, our cross sectional analysis was restricted to the critically ill. Given the increased incidence of AKI in critical illness, with almost 17% of ICU admissions complicated by AKI within the first seven days, it is plausible that any potential effect of PPI use on the risk of kidney injury is dwarfed by the complex additional influences that might lead to renal injury in critical illness.

However, our analysis also raises important questions about the limitations of observational data in determining causality, and highlight potential sources of bias and residual confounding. Most previous studies, including our own, could not accurately identify the reason for PPI prescription. We used discharge coding to identify the comorbidities that might warrant PPI use, likely leading to significant misclassification. However, despite this limitation, inclusion of these comorbidities into our modelling (Model 4) attenuated the association of PPI use with AKI. For example, 8% of PPI users had liver disease by discharge coding, which was associated with a 33% increased risk of AKI. Since liver disease is an independent risk for kidney failure, yet its consequences, such as variceal bleeding, are an indication for PPI use(24), significant confounding by indication likely remains.

One approach to this has been to use H_2RA users as a model control. However, the decision of a physician to prescribe a PPI, which is generally more expensive, with a greater overall adverse risk profile, and typically used in the setting of H_2RA failure, does not equate the decision to prescribe a H_2RA. In our analysis, PPI users were clearly "sicker" than both H_2RA users and those using neither class of medicines, with a higher prevalence of comorbidities such as liver disease, lower admission serum hemoglobin concentrations, and more frequent use of medications that are associated with renal injury, such as diuretics. Although many of these factors can be entered into "adjusted analyses", accurately adjusting for the powerful and complex biologic effects of these conditions on an outcome is likely a statistical simplification than does not reflect the physiologic reality. Furthermore, despite our best efforts of "adjustment", including a wide range of patient characteristics, PPI use remained significantly associated with an admission for sepsis, an outcome that lack's obvious physiologic explanation, suggesting that PPI use might simply mark disease severity.

Since the proposed mechanism between PPI use and adverse renal outcomes could be through interstitial nephritis, we examined the effect of sterile pyuria on the association of PPI and AKI. But, we found that PPI users with sterile pyuria did not have a higher risk of AKI than those not taking acid suppression medicines nor than PPI users without sterile pyuria. In addition, we could not detect a significant association between PPI use and AKI in those with hypomagnesemia.

The strengths of our analysis lies in the granularity or the MIMIC dataset, providing access to discharge summaries, medications, laboratory parameters, as well as comorbidities, thereby allowing accurate determination of both the primary outcome and exposure. The use of sequential models illustrates the effect of residual confounding in our observational

analysis. There are several limitations of our analysis. Restricted to critically ill patients, our negative results cannot be extrapolated to a broader context without further study. In addition, we could not quantify the amount of PPI exposure, nor account for over-the-counter PPI use, and thus misclassification is possible. Furthermore, although we hypothesized that sterile pyuria is indicative of an interstitial nephritis, direct examination of a spun urine sediment for white cell casts is likely a superior diagnostic method, but was not available.

Conclusion

In summary, in adjusted analysis that includes some indication for PPI prescription, PPI use is not associated with AKI in critically ill patients. Despite recent suggestions otherwise, the association between PPI and renal outcomes remains hypothesis generating, and requires more rigorous analysis that limits residual confounding.

Acknowledgments

Abbreviations

PPI	Proton Pump Inhibitor
H$_2$RA	Histamine$_2$ Receptor Antagonist
CKD	Chronic Kidney Disease
AIN	Acute interstitial nephritis
MIMIC-II	Multiparameter Intelligent Monitoring in Intensive Care
ICU	Intensive Care Unit
hpf	High powered field
WBC	White blood cells
NLP	Natural Language Processing
ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker

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Table I

Baseline characteristics according to acid suppression use

	Proton-pump inhibitors (n=3,725)	H₂-receptor antagonists (n=905)	No acid-suppressive medications (n=10,528)	P value[1]
Age, mean (SD), y	67.9 (15.1)	67.4 (15.3)	61.8 (19.7)	.75
Male, no. (%)	2017 (54.1)	497 (55.1)	6143 (58.0)	0.23
Ethnicity, no. (%)				
White	2750 (73.4)	659 (72.8)	7455 (70.8)	
Black or African American	285 (7.6)	69 (7.6)	747 (7.1)	
Hispanic or Latino	101 (2.7)	24 (2.8)	343 (3.2)	0.68
Asian	64 (1.7)	17 (1.8)	258 (2.5)	
Other	68 (1.8)	15 (1.7)	287 (2.7)	
Unknown	457 (12.2)	121 (13.4)	1438 (13.7)	
Past Medical History, no. (%)				
Hypertension	1396 (37.5)	320 (35.3)	3593 (34.1)	0.16
Diabetes	1293 (34.7)	308 (34.0)	2576 (24.5)	0.86
Congestive Heart Failure	1103 (29.6)	253 (28.0)	2069 (19.7)	0.46
Cardiac arrhythmia	882 (23.7)	202 (22.3)	1893 (18.0)	0.48
Liver disease	307 (8.2)	47 (5.2)	417 (4.0)	0.003
Obesity	82 (2.2)	14 (1.5)	201 (1.9)	0.05
Metastatic cancer	196 (5.2)	47 (5.2)	465 (4.4)	0.91
Alcohol abuse	180 (4.8)	30 (3.3)	652 (6.2)	0.04
Weight loss	117 (3.1)	18 (2.0)	178 (1.7)	0.09
Peptic ulcer disease	40 (0.1)	8 (0.1)	54 (0.1)	0.37
Vital signs, mean (SD)				
Systolic blood pressure, mmHg	125.1 (25.3)	125.2 (25.9)	125.8 (24.2)	0.72
Diastolic blood pressure, mmHg	62.4 (15.6)	62.5 (15.6)	64.3 (15.5)	0.92
Heart rate, beats/min	88.0 (19.6)	86.7 (18.9)	87.7 (19.3)	0.08
Laboratory values on admission, mean (SD)				
Glucose, mg/dL	149.4 (84.3)	150.2 (88.1)	150.5 (91.9)	0.89
Hemoglobin, g/dL	11.4 (2.2)	11.8 (2.1)	12.2 (2.2)	<0.001
White blood cell count, K/uL	11.9 (7.4)	12.2 (8.0)	12.3 (9.5)	0.19
Platelets, K/uL	236.7 (125.7)	240.2 (113.6)	235.2 (111.1)	0.69
Albumin, g/dL[2]	3.3 (0.7)	3.4 (0.6)	3.5 (0.7)	0.27
Creatinine, mg/dL	1.5 (1.4)	1.3 (1.1)	1.2 (1.2)	0.002
Pre-illness medication usage no. (%)				
Angiotensin Conv. Enzyme Inhibitor	1044 (29.8)	253 (29.8)	2382 (22.6)	0.97
Angiotensin Receptor Blocker	309 (8.8)	76 (8.9)	647 (6.1)	0.99

	Proton-pump inhibitors (n=3,725)	H₂-receptor antagonists (n=905)	No acid-suppressive medications (n=10,528)	P value[1]
Statin	1403 (40.0)	328 (38.7)	3055 (29.0)	0.37
Diuretic	1390 (39.6)	282 (33.3)	2456 (23.3)	<0.001

95 individuals were taking both a PPI and H2RA

[1]p value represents group difference between PPI and H2RA users (excluding the 95 using both)

[2]Admission serum albumin concentration available in 5,828 patients.

Table II

Association of Proton Pump Inhibitor Use with subsequent Risk of Acute Kidney Injury

Model	Odds Ratio (95% confidence interval), p value		
	No acid suppressive medications	Proton Pump Inhibitors	Histamine Receptor Antagonists
Unadjusted			
	Ref.	1.28 1.17–1.41 p<0.001	1.10 0.91–1.30 p=0.31
Adjusted			
Model 1. Demographics	Ref.	1.20 1.08–1.31 p<0.001	1.03 0.85–1.22 p=0.78
Model 2. Model 1+ cardiovascular comorbidities	Ref.	1.14 1.03–1.25 p=0.01	0.98 0.82–1.17 p=0.86
Model 3. Model 2 + possible clinical indications for PPI use	Ref.	1.10 1.00–1.21 p=0.05	0.98 0.81–1.17 p=0.80
Model 4. Model 3 + severity of illness	Ref.	1.04 0.94–1.15 p=0.46	0.94 0.78–1.14 p=0.57
Model 5. Model 4 + outpatient medication use	Ref.	1.02 0.91–1.13 p=0.73	0.94 0.78–1.15 p=0.59

Model 1. Adjusted for age, sex, race (n=15,044)

Model 2 Adjusted for mode 1 plus admission intensive care unit type, history of diabetes, congestive heart failure, cardiac arrhythmia, hypertension or pulmonary circulation. (n=15,024)

Model 3. Adjusted for model 2 plus history liver disease, peptic ulcer disease, alcohol abuse, weight loss, obesity and metastatic cancer (n=15,024)

Model 4. Adjusted for model 3 plus admission systolic blood pressure, diastolic blood pressure, heart rate, glucose, white blood cell count, hemoglobin, and platelet count. (n=13,305)

Model 5. Adjusted for model 4 plus use of diuretics, ace inhibitor, angiotensin receptor blocker, and statins. (n=13,209)

Table III

Proton Pump Inhibitor Users with and without sterile pyuria and risk of AKI

	Odds Ratio (95% confidence interval), p value			
	No acid suppressive medications	Proton Pump Inhibitor Use and sterile pyuria	Proton Pump Inhibitor Use without sterile pyuria	Histamine Receptor Antagonist
Pyuria defined by leukocyte esterase positivity				
Unadjusted	Ref	1.80 0.90–3.311 p=0.09	1.52 1.17–1.97 p<0.001	1.47 0.92–2.27 p=0.10
Adjusted[1]	Ref.	1.16 0.54–2.27 p=0.69	1.10 0.82–1.47 p=0.51	1.21 0.73–1.92 p=0.44
Pyuria defined by > 5 WBC's/hpf				
Unadjusted	Ref.	2.66 1.20–5.47 p=0.02	1.52 1.06–2.16 p=0.02	1.72 1.20–5.47 p=0.06
Adjusted[2]	Ref.	1.64 0.70–3.62 p=0.24	1.05 0.69–1.57 p=0.80	1.58 0.85–2.83 p=0.14

Both analyses adjusted per model 5.

[1] N=2,360 in adjusted analysis

[2] N=1,173 in adjusted analysis