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Acid-Suppressive Medication Use in Acute Stroke and Hospital-Acquired Pneumonia

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Abstract

Objective—Pneumonia is a morbid complication of stroke, but evidence-based strategies for its prevention are lacking. Acid-suppressive medications have been associated with increased risk for nosocomial pneumonia in hospitalized patients. It is unclear whether these results can be extrapolated to stroke patients, where other factors strongly modulate pneumonia risk. We investigated the association between acid-suppressive medication and hospital-acquired pneumonia in patients with acute stroke.

Methods—All patients hospitalized with acute ischemic stroke or intracerebral hemorrhage in a large, urban academic medical center in Boston, Massachusetts from 6/2000 – 6/2010, ≥ 18 years of age and hospitalized for ≥ 2 days were eligible for inclusion. Acid-suppressive medication use was defined as any pharmacy charge for a proton-pump inhibitor or histamine-2 receptor antagonist. Multivariable logistic regression was used to control for confounders. The main outcome measure was hospital-acquired pneumonia, defined via ICD-9-CM codes.

Results—The cohort comprised 1,676 admissions. Acid-suppressive medication was ordered in 1,340 (80%) and hospital-acquired pneumonia occurred in 289 (17.2%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication compared to unexposed (20.7% versus 3.6%, OR=7.0, 95% CI 3.9–12.7). After adjustment, the

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OR of hospital-acquired pneumonia in the exposed group was 2.3 (95% CI 1.2–4.6). The association was significant for proton-pump inhibitors (OR=2.7, 95% CI 1.4–5.4), but not for histamine-2 receptor antagonists (OR=1.6, 95% CI 0.8–3.4).

Interpretation—In this large hospital-based cohort of patients presenting with acute stroke, acid-suppressive medication use was associated with increased odds of hospital-acquired pneumonia.

INTRODUCTION

Pneumonia is the most common serious medical complication and a leading cause of death in stroke patients.[1–5] Occurrence of pneumonia in the early phases after a stroke may also lead to poorer functional outcome and promote long-term disability.[6] Identification of modifiable risk factors for pneumonia after stroke is important as a prelude to developing effective prevention strategies that could help reduce the morbidity, mortality and healthcare costs from stroke.

Stroke patients are known to harbor several risk factors that favor development of pneumonia.[2, 3, 7, 8] Broadly these include factors related to the incident stroke itself (stroke severity or stroke associated deficits such as somnolence, dysphagia), age, comorbidities, and certain interventions like mechanical ventilation.[2, 3, 7, 8] However, the role of certain classes of medications in promoting pneumonia in these patients has not been well investigated.

Recently, acid-suppressive medications have been associated with hospital-acquired pneumonia in several different hospitalized patient populations.[9–11] It is unknown whether these results can be generalized to the stroke population. Four small studies have examined the relationship between acid-suppressive medication and nosocomial pneumonia in stroke patients.[3, 12–14] While 2 of the studies, both performed in Chinese cohorts, found higher unadjusted rates of nosocomial pneumonia in patients receiving acid-suppressive medication, neither study performed any confounder adjustment.[13, 14] The remaining 2 studies both identified an elevated risk of pneumonia in stroke patients on acid-suppressive medication. However, one focused on patients in an acute stroke rehabilitation facility, the other focused exclusively on ventilator-associated pneumonia, and both were small and underpowered to demonstrate statistical significance.[3, 12] We therefore sought to determine the association between acid-suppressive medication use and hospital-acquired pneumonia in a large cohort of patients presenting with acute stroke.

METHODS

Setting and Data Collection

A cohort of all patients admitted with acute stroke to a large academic medical center in Boston, Massachusetts from June 1, 2000 through June 1, 2010 was investigated. The study was approved by the institutional review board at the medical center and granted a waiver of informed consent. Data were collected from both in-depth medical record review and electronic medical information databases maintained at the medical center, as indicated below. These databases, collected prospectively for clinical purposes, contain patient-specific information related to each admission during the study time period.

Inclusion and Exclusion Criteria

We used the following discharge International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, based on published studies,[15, 16] to define acute ischemic stroke and intracerebral hemorrhage: 431, 433.11, 433.21, 433.31, 434.01, 434.11. All adult admissions (at least 18 years of age) with at least one ICD-9-CM code for stroke in any position were eligible for inclusion. We reviewed the charts of all patients identified in this manner to confirm the presence of an acute stroke and excluded those admissions where acute stroke did not occur. We additionally excluded admissions where stroke occurred after hospitalization, those where pneumonia was present on admission, those with brain or lung neoplasms, and those with incomplete medical data. Lastly, we excluded admissions less than 48 hours in duration. This cutoff was chosen based on the rationale that it would take at least 48 hours of inpatient hospitalization to classify the pneumonia as hospital-acquired, consistent with current criteria of the American Thoracic Society and the Infectious Diseases Society of America.[17]

Acid-Suppressive Medication Exposure

Acid-suppressive medication exposure was ascertained using pharmacy charges and defined as at least one pharmacy-charge for a proton-pump inhibitor or histamine-2 receptor antagonist during the hospitalization.

Hospital-Acquired Pneumonia Outcome

We defined hospital-acquired pneumonia as any discharge ICD-9-CM code for bacterial pneumonia listed as a secondary discharge diagnosis (i.e. not listed as the primary discharge diagnosis). ICD-9-CM codes used in this analysis are listed in the Appendix. This definition has been used and validated in a prior analysis.[10]

Covariates

Covariates were included that were thought to predict use of acid-suppressive medications, as well as variables thought to increase the risk of hospital-acquired pneumonia based on prior literature. Data collected from electronic databases included age; sex; race; length of hospitalization; whether the patient spent time in the intensive care unit, and use of specific classes of medications, including any drug with sedating effects (benzodiazepines, barbiturates, hypnotics, anti-psychotics, opiates), systemic steroids, and commonly used anti-platelet medications (aspirin, clopidogrel). All of the comorbidities included in the Charlson Comorbidity Index,[18] as operationalized from administrative data by Quan et al.,[19] were controlled for, with the exception of HIV/AIDS owing to insufficient numbers of patients with this comorbidity. Rather than using a summary index score, each comorbidity was incorporated into the model as a separate, independent measure, as advocated by Elixhauser et al.[20] Several ICD-9-CM codes were added to the diagnostic categories of dementia and peptic ulcer disease already present in the Charlson Comorbidity list to increase the capture rate of these conditions, both hypothesized to have important associations with both acid-suppressive medication exposure and hospital acquired pneumonia (see Appendix). We additionally controlled for any ICD-9-CM code for

gastrointestinal hemorrhage and alcohol and/or drug abuse due to hypothesized associations with both acid-suppressive medication use and hospital acquired pneumonia (see Appendix).

Data collected via in-depth medical record review by investigators blinded to exposure status included the National Institutes of Health Stroke Scale (NIHSS) score, presence or absence of dysphagia, history of pneumonia, smoking status (ever versus never), and whether the patient was intubated during the hospitalization. NIHSS scores were estimated retrospectively using validated algorithms where they were missing.[21]

Race/ethnicity data were obtained by patient self-report at the time of registration by employees who have received specific training in obtaining and coding this information into fixed categories.

Statistical Analysis

The Fisher exact test or Chi-square test were used to compare categorical variables and a nonparametric median test was used for continuous variables. Unadjusted incidence rates of the primary and secondary outcomes in exposed and unexposed patients were compared using the Fisher exact test or bivariable logistic regression, where appropriate.

We used a multivariable logistic regression model to adjust for possible confounders, where hospital-acquired pneumonia was the dependent variable and acid-suppressive medication (exposure to either a histamine-2 receptor antagonist or proton-pump inhibitor) and all covariates were independent variables.

A 2-sided type-I error of < 0.05 was used to indicate statistical significance for all comparisons. Assuming a rate of 15 hospital-acquired pneumonia per 100 unexposed admissions in our cohort, we estimated that a sample size of 1,120 admissions would be necessary to achieve 90% power to detect a relative risk of 1.5 in exposed versus unexposed patients. All analyses were carried out using SAS software, V9.2 (Cary, NC).

Exposure Subgroup and Sensitivity Analysis

We assessed the independent associations between proton-pump inhibitors and histamine-2 receptor antagonists and the primary outcome using a second multivariable logistic regression model of pneumonia that included a 4 category exposure variable (no acid-suppressive medication, histamine-2 receptor antagonist alone, proton-pump inhibitor alone, and both), along with all covariates as independent variables.

Because we did not have information on the date of the occurrence of the hospital-acquired pneumonia, we could not be sure of the correct temporal sequence between exposure and outcome, raising the possibility of exposure misclassification. To address this threat, we performed a sensitivity analysis wherein we repeated our main analysis after reclassifying all admissions in which acid-suppressive medication was not started within the first 2 full days of admission as unexposed.

RESULTS

Patient Admission Characteristics

There were 2,993 adult admissions with an ICD-9-CM code for stroke from June 1, 2000 through June 1, 2010. After excluding admissions with a length of stay less than 2 days (n = 453), admissions with missing medication data (n = 420), admissions where stroke occurred after hospitalization or was an incorrect diagnosis (n=410), records where pneumonia was present at admission (n=4), those with incomplete data (n=15), or patients with a primary brain or lung neoplasm (n=15), 1,676 admissions comprised the final cohort. Out of these 1,676 admissions there were 1,635 unique patients, indicating repeated admissions ranging from 1 to 3 admissions per patient during the time frame. The median age of the cohort was 74 years (range 19 – 104 years) and 845 (50%) were men.

Exposure to Acid-Suppressive Medication

Overall, acid-suppressive medication was ordered in 1,340 (80%) admissions and 1,276 (95%) of these orders occurred within the first 2 full days of hospitalization. Of the group exposed to acid-suppressive medications, 971 (72%) received proton-pump inhibitors and 683 (51%) received histamine-2 receptor antagonists, with 314 (23%) exposed to both. There were significant differences in baseline characteristics between those exposed and unexposed to acid-suppressive medication (Table 1).

Relationship of Acid-Suppressive Medication to Hospital-Acquired Pneumonia

Table 2 shows the unadjusted incidence rates of hospital-acquired pneumonia relative to acid-suppressive medication status. The primary outcome of hospital-acquired pneumonia occurred in 289 admissions (17.2%). The mortality rate was higher in admissions with hospital-acquired pneumonia, compared to those without this complication (23.9% versus 10.0%; OR 2.8, 95% confidence interval [CI] 2.0 to 3.9). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication relative to the unexposed group (20.7% versus 3.6%; OR 7.0, 95% CI 3.9 to 12.7). After adjusting for potential confounders using a multivariable logistic regression model, the odds ratio of hospital-acquired pneumonia in the group exposed to acid-suppressive medication was 2.3 (95% CI 1.2 to 4.6; Table 2). Among the variables in our model, acid-suppressive medication exposure was the strongest risk factor for hospital-acquired pneumonia after history of pneumonia (OR 7.1, 95% CI 4.4 to 11.4) and dysphagia (OR 3.8, 95% CI 2.6 to 5.7).

Exposure Subgroup and Sensitivity Analysis

When examining the independent associations between subclasses of acid-suppressive medication and hospital-acquired pneumonia, we found a significant association for proton-pump inhibitors (OR 2.7, 95% CI 1.4–5.4) but not for histamine-2 receptor antagonists (OR 1.6, 95% CI 0.8–3.4); see Table 2. For those exposed to both medication subclasses there was no increase in risk beyond that seen with proton-pump inhibitors alone (OR 2.0, 95% CI 0.96–4.2).

After reclassifying admissions in which acid-suppressive medication was ordered after the first 2 full days of hospitalization as unexposed (n = 64), the adjusted OR of hospital-acquired pneumonia was 2.0 (95%CI 1.2–3.4).

DISCUSSION

In this large hospital-based cohort of adult patients with acute stroke, acid-suppressive medications were used in 80% and use was associated with more than double the odds of hospital-acquired pneumonia. In a pre-specified subgroup analysis, the association was stronger for proton-pump inhibitors than for histamine-2 receptor antagonists. To our knowledge, this is the first adequately powered large cohort study identifying an association between acid-suppressive medication and hospital-acquired pneumonia in patients presenting with acute ischemic stroke or intracerebral hemorrhage. Our results demonstrate that the risks from acid suppressive medications are considerable in the hospitalized stroke population even after accounting for several other influential covariates.

Current guidelines lack evidence based recommendations for pneumonia prevention in stroke patients.[22, 23] Identifying swallowing impairments, implementing dietary modification, head elevation and shortened use of ventilator support have, however, been emphasized.[23] Other investigators have developed tools for identifying patients at high risk for pneumonia after a stroke, though it is unclear how this informs patient care at present.[7, 24] Our results suggest that acid-suppressive medications are an independent risk factor for pneumonia in stroke patients and more restrictive use of these medications, especially in high risk patients such as those who are elderly or with aspiration, could be an important part of an effective prevention strategy.

Our finding of an 80% exposure rate is higher than exposure rates in the general hospitalized patient population, where acid-suppressive medications are used in 40 to 70 percent of admissions.[10, 25, 26] The most widely cited guidelines on stress ulcer prophylaxis do not include acute stroke as a risk factor for gastrointestinal bleeding in and of itself, and recommend stress ulcer prophylaxis with acid-suppressive medication only in hospitalized patients admitted to the ICU with either coagulopathy or mechanical ventilation.[27] While we are unable to assess coagulopathy in this study as laboratory values were not available, 57% of patients spent time in the ICU, and only 29% of patients in our study received mechanical ventilation. Thus, an exposure rate of 80% seems quite high, particularly given that gastrointestinal bleeding is thought to be a relatively infrequent complication after acute stroke.[28–30] Data on the overall exposure to these medications in the stroke population is not previously described. If exposure in the larger stroke population parallels that of our cohort, then the attributable risk of pneumonia from these medications in stroke patients is considerable. Future studies should assess the indications for use in this patient population and whether use is consistent with current guidelines.

There are several proposed mechanisms by which acid-suppressive medications and proton-pump inhibitors in particular may contribute to pneumonia risk. First, studies have demonstrated modification of the upper gastrointestinal flora and, resultantly, respiratory flora in the setting of a less acidic gastric medium. This may predispose patients to

pneumonia in the setting of aspiration, a common complication of acute stroke.[31–34] We demonstrated an association between acid-suppressive medication and hospital-acquired pneumonia even after adjusting for dysphagia, however, suggesting additional mechanisms may be involved. There is some evidence that human lung cells contain proton pumps which may be inhibited by proton pump inhibitors, altering the pH of respiratory secretions and further promoting bacterial growth.[35] Additionally, several studies have demonstrated that proton-pump inhibitors impair white blood cell function, which could also contribute to increased rates of pneumonia in exposed patients.[36, 37] This effect may further exacerbate the immunosuppressive effects of an acute stroke and requires further examination.[38, 39]

Our finding of statistically significant increased risk for pneumonia in patients on proton-pump inhibitors but not histamine-2 receptor antagonists, despite an odds ratio of 1.6 for the latter, likely reflects lack of power for this subgroup comparison. Our power to detect such a difference was less than 40% via post-hoc power calculation. While we cannot, therefore, conclude lack of risk from histamine-2 receptor antagonists, the data do suggest that the risk from proton-pump inhibitors is greater than that from histamine-2 receptor antagonists. This finding parallels the findings of other studies, which consistently demonstrate greater risk for infectious complications with proton-pump inhibitors compared to histamine-2 receptor antagonists.[9–11]

There are several strengths to our study, including the large sample size with detailed data on several influential covariates, independent confirmation of all stroke cases by a separate review of medical records, robust statistical methods, and consistency of findings on sensitivity analysis. There are also some limitations. First, because we did not know the indication for use we cannot comment on appropriateness of use in this analysis. Furthermore, lack of outpatient medication history rendered us unable to focus on new initiations. Since prior literature has demonstrated increased risk of pneumonia in the first week of initiation of acid-suppressive medication, our findings may therefore underestimate the true association between acid-suppressive medication and pneumonia. Another limitation relates to use of administrative data to identify cases of hospital-acquired pneumonia. Although a prior validation exercise using data from the same hospital demonstrated high levels of capture using this definition,[10] there still could be false positive cases of pneumonia which could bias our observed associations. However, there is no reason to think such misclassification would be non-differential with respect to exposure, making bias from this type of misclassification seem unlikely.

The lack of information on the temporal association between acid-suppressive medication exposure and date of diagnosis of hospital-acquired pneumonia is another study limitation. The fact that exposure occurred within the first 2 full days of hospitalization in 95% of patients prescribed acid-suppressive medication suggests that bias from exposure misclassification is unlikely to have affected our results. Nonetheless, we performed a sensitivity analysis in which all patients who received their first dose of acid-suppressive medication more than 2 full days into their hospitalization were reclassified as unexposed. Although the OR for the main effect decreased from 2.3 to 2.0, the result was still statistically significant, and some attenuation was expected because this approach biases toward the null.

Additionally, as with any observational study, we cannot know the counterfactual ideal, and the possibility of unmeasured confounders exists despite controlling for 30 variables in our models. It seems unlikely, however, that residual confounding could completely explain an odds ratio of 2.3 in exposed patients. Furthermore, because this analysis did not take into account the potential benefits of acid-suppressive medication with respect to prevention of gastrointestinal bleeding, further studies are necessary to better understand the net clinical effect. Lastly, although we studied 1,676 admissions over a 10 year period, the single-center nature of our study limits generalizability; our findings should be validated by other institutions.

In conclusion, in this large cohort of patients presenting with acute ischemic or hemorrhagic stroke, acid-suppressive medication was associated with more than doubling of the odds of hospital-acquired pneumonia. The association was stronger for proton-pump inhibitors than for histamine-2 receptor antagonists. These medications represent a potentially modifiable risk factor for pneumonia in acute stroke patients. Our results suggest more restrictive use of these medications is warranted in stroke patients, especially those considered to be at high risk for pneumonia.

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APPENDIX

ICD-9-CM codes used for outcome and comorbidities.

I. Outcome:

Pneumonia: 481, 482, 483, 485, 486, 507

II. Comorbidities: The Charlson Comorbidities,[18] as operationalized by Quan et al.,[19] were used for the analysis. Below are just the comorbidities that either were added (not already present in the Charlson Comorbidity List) or enhanced, as described in the text.

Comorbidities not already included in the Charlson Comorbidity Index:

Gastrointestinal hemorrhage: 578

Alcohol/drug use: 291, 292, 303, 304, 305

Enhanced comorbidities (includes ICD-9-CM codes recommended by Quan et al.,[19] as well as added ICD-9-CM codes as described in the text):

Delirium/Dementia: 290, 2941, 3312, 293, 294, 331, 797

Peptic Ulcer Disease: 530, 531, 532, 533, 534, 535, 536, 7871, 3064

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Table 1

Demographic and clinical characteristics of study population (n=1,676).

Variable	Acid-suppressive medication (n = 1340)	No acid-suppressive medication (n = 336)	p-value
Median age – years (range)	74 (19 – 104)	76 (21 – 97)	0.30
Male – no. (%)	675 (50)	170 (51)	0.95
Race or ethnic group – no. (%)			0.47
White	1042 (78)	270 (80)	
Black	109 (8)	31 (9)	
Hispanic	53 (4)	9 (3)	
Asian	36 (3)	6 (2)	
Other or unknown	100 (7)	20 (6)	
NIH Stroke Scale – median (range)	8.0 (0–37)	2.5 (0–35)	<0.001
Myocardial infarction – no. (%)	146 (11)	29 (9)	0.27
Congestive heart failure – no. (%)	225 (17)	42 (13)	0.06
Peripheral vascular disease – no. (%)	106 (8)	35 (10)	0.15
Delirium/Dementia – no. (%)	57 (4)	12 (4)	0.65
Chronic pulmonary disease – no. (%)	206 (15)	43 (13)	0.26
Connective tissue disease – no. (%)	31 (2)	5 (1)	0.53
Peptic ulcer disease/reflux – no. (%)	163 (12)	11 (3)	<0.001
Mild liver disease – no (%)	38 (3)	6 (2)	0.34
Moderate or severe liver disease – no (%)	5 (0)	1 (0)	1.0
Diabetes without complications – no. (%)	264 (20)	73 (22)	0.40
Diabetes with complications – no (%)	48 (4)	13 (4)	0.75
Paraplegia/hemiplegia – no. (%)	245 (18)	48 (14)	0.09
Renal disease – no (%)	120 (9)	31 (9)	0.92
Cancer – no (%)	65 (5)	10 (3)	0.18
Metastatic carcinoma – no. (%)	47 (4)	6 (2)	0.12
Alcohol/drug abuse – no. (%)	127 (9)	36 (11)	0.47
Gastrointestinal hemorrhage – no. (%)	32 (2)	2 (1)	0.05
Dysphagia – no. (%)	662 (49)	70 (21)	<0.001
History of pneumonia – no. (%)	108 (8)	8 (2)	<0.001
Smoking – no. (%)	514 (38)	136 (40)	0.49
Intensive Care Unit stay – no. (%)	921 (69)	42 (13)	<0.001
Length of hospitalization (days) – median (IQR)	7 (4–12)	4 (3–6)	<0.001
Intubation – no. (%)	464 (35)	20 (6)	<0.001
In-hospital medications – no. (%)			
Sedative	987 (74)	166 (49)	<0.001
Steroid	208 (16)	10 (3)	<0.001
Antiplatelet	650 (49)	224 (67)	<0.001

Abbreviations: NIH = National Institutes of Health; IQR = interquartile range (25 – 75%)

Table 2

Rates of hospital-acquired pneumonia according to acid-suppressive medication status (n=1,676).

Medication	Hospital-Acquired Pneumonia n (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Acid-suppressive medication (H2B or PPI)			
Unexposed	12 (3.6)	Ref.	Ref.
Exposed	277 (20.7)	7.0 (3.9–12.7)	2.3 (1.2–4.6)
Multi-category exposure variable			
No acid-suppressive medication	12 (3.6)	Ref.	Ref.
H2B alone	71 (19.2)	6.4 (3.4–12.1)	1.6 (0.8–3.4)
PPI alone	123 (18.7)	6.2 (3.4–11.4)	2.7 (1.4–5.4)
Both (H2B and PPI)	83 (26.4)	9.7 (5.2–18.2)	2.0 (0.96–4.2)

Abbreviations: OR = odds ratio; CI = confidence interval; H2B = histamine-2 receptor blocker; PPI = proton-pump inhibitor.

*Adjusted for all variables in Table 1 using a multivariable logistic regression model.