Postoperative pneumonia in elderly patients receiving acid suppressants: a retrospective cohort analysis

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ABSTRACT

Objective To test whether gastric acid suppressants are associated with an increased risk of postoperative pneumonia in patients undergoing elective surgery.

Design Population-wide retrospective cohort analysis.

Setting Canadian acute care hospitals between 1 April 1992 and 31 March 2008.

Patients Consecutive patients aged >65 years admitted for an elective operation.

Outcome measure Postoperative pneumonia recorded in inpatient postoperative notes.

Results A total of 593 265 patients were included, of whom about 21% were taking an acid suppressant. Overall, 6389 patients developed postoperative pneumonia, with a rate significantly higher for those taking acid suppressants (13 per 1000) than controls (10 per 1000), equivalent to a 30% increase in frequency. Gastric acid suppressants are not associated with an increased risk of postoperative pneumonia. We examined the safety of acid suppressants extended to those patients prescribed proton pump inhibitors, experiencing long term treatment, receiving high doses, and undergoing high risk procedures.

Conclusion After adjustment for patient and surgical characteristics, acid suppressants are not associated with an increased risk of postoperative pneumonia among elderly patients admitted for elective surgery.

INTRODUCTION

Pneumonia is a common, serious, and potentially lethal complication following elective surgery. The incidence varies between 2% and 20% (depending on the patient population and the strategy used to diagnose pneumonia), is more common than cardiac complications in most settings, and collectively affects about a million surgical patients each year in North America. Multi-drug resistant bacteria, hospitalisation in an intensive care unit, and previous antibiotic use are among the world’s most commonly used medications and are sometimes available without prescription. The purpose of this study was to test whether acid suppressants are associated with an increased risk of postoperative pneumonia. We examined acid suppressants as an entire group as well as distinguished by class (proton pump inhibitors, H₂ antihistamines, and miscellaneous agents). We focused on older patients because this group accounts for most major operative procedures, cases of postoperative pneumonia, and surgical deaths.

METHODS

Patient selection

We identified consecutive patients older than 65 years admitted for elective surgery in all Ontario hospitals between 1 April 1992 and 31 March 2008 through the Canadian Institutes for Health Information databases. These databases have been validated previously, and we used all 16 years available for analysis. We did not include outpatients, those who had day surgery, or younger patients because of the low rate of pneumonia in these groups and the lack of available prescribing data. Patients who underwent multiple procedures were analysed according to first presentation so that each patient counted only once in each analysis. Our focus was on elective operations to ensure a cohort free of active pneumonia at the time of operation.
of inception. The study design was approved by the Sunnybrook Research Ethics Committee.

Acid suppressants
For each patient, we searched prescription records from the universal drug database for the year before admission, reasoning that these drugs would customarily be continued perioperatively. This assumption is in line with standard practices that recommend continuing acid suppressants (for those already receiving them) but not initiating acid suppressants prophylactically (for those not already receiving them). We classified patients who received two or more prescriptions for an acid suppressant in the year before surgery (including at least one prescription in the 90 days before surgery) as receiving this drug on a chronic basis. Otherwise, we classified the patient as a control. This strategy assured that ascertainment was blinded, free of reverse causality bias, conservative in design, and congruent with prior research.23

Specific medications
We distinguished prescriptions according to drug, dose, and duration. The specific drugs were lansoprazole, omeprazole, pantoprazole, rabeprazole (proton pump inhibitors); cimetidine, famotidine, nizatidine, ranitidine (H2 antihistamines); and aluminium hydroxide, misoprostol, and sucralfate (miscellaneous group). The dose was classified by separating those prescribed the median amount or less of each drug (such as omeprazole 20 mg) from those prescribed higher doses (such as omeprazole 40 mg). The duration of therapy was calculated from the date of the initial prescription and allowing up to a 120 day supply (based on prescribing practices in this region and uncertain patient adherence).23 These methods were similar to those in recent studies linking acid suppressants to community acquired pneumonia.

Validating medications—Acid suppressants were generally available only by prescription in Canada during the study interval (oral antacids being the main exception). A prior validation study indicated that the prescription drug database has an accuracy rate of 99% when compared with pharmacy records.26 Additionally, we tested for misclassification by using more expansive and restrictive definitions of medication exposure. The expansive definition included patients who had any prescription for an acid suppressant in the year before surgery. The restricted definition required four or more prescriptions for an acid suppressant in the year before surgery (with at least one in the 90 days before surgery). We also developed a “clearest case” analysis by analysing patients who stayed consistent with both expansive and restrictive definitions of medication use.

Pneumonia outcomes
The primary outcome was the development of pneumonia during a patient’s hospital stay based on the full inpatient record and coded according to the international classification of diseases (ICD-9 codes 480.0 to 487.9 for years 1992 to 2002, and ICD-10 codes J10.0 to J18.9 for years 2002 to 2008). Surgical complications such as pneumonia are not always identified by clinicians, rigorously recorded in a patient’s chart, or entered into databases. Hence, the codes are specific (about 98%) but not sensitive (about 35%).27-30 We also conducted alternative analyses with wider and narrower codes for pneumonia. To validate our results and examine the more severe spectrum, we also considered complex combinations of outcomes—namely, patients who experienced postoperative pneumonia and had a prolonged stay in hospital (≥7 days), required admission to an intensive care unit, or died in hospital after surgery.

Risk factors
We measured the major predictors of postoperative pneumonia established in systematic reviews—namely, patient age, chronic obstructive lung disease, surgical site, duration of anaesthesia, ASA (American Society of Anesthesia) score, and use of a nasogastric tube. We estimated the duration of surgery from anaesthesia billing logs reported in 15 minute intervals using methods validated elsewhere.23 Estimates of ASA scores that classify patients before surgery reflected anaesthesia billing and diagnoses in the year before surgery in accord with past research.23 Use of a nasogastric tube was based on physician fee codes (G322, G355, G356, G357). The available databases did not contain reliable information on obesity, spirometry, radiology, current smoking status, or functional dependence.

Additional risk factors—We also gathered data on other factors associated with postoperative pneumonia in some studies.33-34 We derived the patients’ age, sex, and income quintile from the Ontario Registered Persons Database.35 We identified drug therapy for lung disease at baseline by assessing prescriptions for an inhaled bronchodilator in the year before admission. We determined the use of other chronic treatments by searching for prescriptions for systemic corticosteroids, benzodiazepines, opioid analgesics, antipsychotics, antidepressants, and gastric motility agents in accord with prior research.30 Comorbidities were based on the Charlson index.31 Global counts of prior outpatient and inpatient care were based on measures under universal insurance.30 We did not account for geographical location or characteristics of the hospital.

Statistical analysis
For the crude comparison, we used the χ2 test to compare the frequency of postoperative pneumonia in those patients taking acid suppressants with those who were not taking acid suppressants. In the primary analysis we used multivariable logistic regression to adjust this comparison for patient and procedure factors, since the time of onset of pneumonia was not recorded. Propensity score matched analyses yielded nearly identical results to regression analysis and are not reported. We tested for selection bias through a secondary analysis of patients who had received an
Table 1 | Characteristics of patients aged >65 years admitted for elective surgery categorised by treatment with gastric acid suppressants (cases). Values are percentages unless specified otherwise

| Characteristic                          | Cases (n=121 850) | Controls (n=471 415) |
|-----------------------------------------|-------------------|----------------------|
| Mean (SD) age (years)                   | 74.7 (6.1)        | 74.0 (6.0)           |
| Female                                  | 55.0              | 47.4                 |
| Social status*                          |                   |                      |
| Lower                                   | 62.8              | 59.6                 |
| Higher                                  | 35.8              | 39.3                 |
| Missing                                 | 1.4               | 1.1                  |
| Past diagnoses:                         |                   |                      |
| COPD                                    | 27.8              | 20.2                 |
| Asthma                                  | 12.6              | 8.6                  |
| Heart failure                           | 14.9              | 9.9                  |
| Parkinson’s disease                     | 1.7               | 1.4                  |
| Pneumonia                               | 13.1              | 9.0                  |
| Stroke                                  | 12.8              | 10.2                 |
| Chronic treatments:                     |                   |                      |
| Systemic corticosteroid                 | 5.3               | 2.1                  |
| Inhaled β agonist                       | 8.2               | 4.4                  |
| Inhaled anticholinergic                 | 4.1               | 2.1                  |
| Inhaled corticosteroid                  | 8.5               | 4.6                  |
| Opioid analgesic                        | 21.9              | 11.5                 |
| Benzodiazepine                          | 25.8              | 13.2                 |
| Antipsychotic                           | 2.2               | 1.4                  |
| Antidepressant                          | 12.3              | 5.8                  |
| Gastric motility agent                  | 8.2               | 1.2                  |
| Mean (SD) No of hospital visits in past 3 years: |       |                      |
| Outpatient visits                       | 49.3 (33.4)       | 38.0 (26.7)          |
| Inpatient admissions                    | 1.0 (2.1)         | 0.6 (1.3)            |
| Mean (SD) Charlson score                | 0.7 (1.4)         | 0.6 (1.4)            |
| Type of surgery:                        |                   |                      |
| Cardiac                                 | 9.7               | 9.2                  |
| Thoracic                                | 2.6               | 2.5                  |
| Neurosurgical                           | 1.8               | 1.6                  |
| Vascular                                | 5.9               | 6.2                  |
| Musculoskeletal                         | 22.7              | 19.1                 |
| Abdominal                               | 26.0              | 23.8                 |
| Retroperitoneal                         | 1.2               | 1.4                  |
| Lower urogenital                         | 17.6              | 22.8                 |
| Breast and skin                         | 4.7               | 5.5                  |
| External head and neck                  | 2.8               | 3.3                  |
| Ophthalmological                        | 4.7               | 4.4                  |
| Unclassified                            | 0.3               | 0.3                  |
| Postoperative care‡                     |                   |                      |
| Nasogastric tube                        | 3.1               | 2.6                  |
| Hypoalbuminaemia                        | 0.2               | 0.1                  |
| Mean (SD) ASA score‡                    | 2.0 (0.7)         | 1.9 (0.7)            |
| Mean (SD) duration of surgery (hours)   | 2.2 (1.5)         | 2.2 (1.5)            |

*Based on income quintile derived from the Ontario Registered Persons Database, dichotomised as the three lowest fifths and the two highest fifths.
†Derived from Ontario Health Insurance (OHIP) billing codes: codes G322, G355, G356, G357 for nasogastric tube; code 263 for hypoalbuminaemia.
‡ASA (American Society of Anesthesiology) score ranges from 1 to 5, higher values indicating sicker patients.

acid suppressant in the past year but not in the 90 days before surgery. We tested further for hidden confounders in stratified analyses accounting for duration of use, specific medication, and relative dose.

RESULTS

During the 16 year interval a total of 955 914 elective operations were conducted on 593 265 patients involving 269 hospitals and 4195 surgeons. We observed no major trends over the years. The typical patient was 74 years old; underwent an abdominal, musculoskeletal, or lower urogenital operation; and had an average duration of anaesthesia of 132 minutes. Neurosurgical and retroperitoneal operations were the least common surgeries, yet still amounted to thousands of patients (9754 and 7911, respectively). The median length of stay was four days, about a quarter of patients (n=152 998) stayed in hospital more than a week, and 13% (n=74 222) were admitted to a critical care unit. Relatively few patients were hospitalised for pneumonia during the year before surgery (n=4812).

About 21% of patients (n=121 850) were taking an acid suppressant, and 79% (n=471 415) were not taking an acid suppressant before surgery. The two groups were similar in mean age, duration of surgery, and ASA scores (table 1). Multiple other risk factors for postoperative pneumonia were imbalanced against the acid suppressant group, including a history of chronic lung disease and prior pneumonia. Acute gastrointestinal bleeding was rarely diagnosed in the postoperative setting (n=226), particularly among patients receiving acid suppressants (odds ratio 0.73 (95% confidence interval 0.51 to 1.05)). The most commonly used acid suppressants were omeprazole (n=25 948) and ranitidine (n=45 531), and most patients (74%) had received treatment for several years before surgery.

Postoperative pneumonia was diagnosed in 6389 patients after surgery (roughly 11 per 1000). The frequency of this outcome was about a third higher among patients taking acid suppressants before surgery (13 per 1000) than among controls (10 per 1000) (odds ratio 1.30 (1.23 to 1.38), P<0.001). Accounting for age, sex, type of surgery, and duration of anaesthesia yielded a smaller increase in risk (odds ratio 1.20 (1.13 to 1.28)). Accounting for age, chronic lung disease, prior pneumonia, and hypoalbuminaemia yielded further attenuation (odds ratio 1.12 (1.05 to 1.19)). The final multivariable model, which adjusted for all baseline characteristics, showed no significant increase in the risk of postoperative pneumonia associated with acid suppressants (adjusted odds ratio 1.02 (0.96 to 1.09)).

The apparent safety of acid suppressants was evident across a variety of patient and procedure factors. Each analysis yielded no major increase in the risk of postoperative pneumonia, although the confidence intervals were broad in a few subgroups (figure). Overall, 11 of the 29 prespecified subgroups indicated a point estimate below 1.00, and 27 of the 29 prespecified subgroups showed a nominal P value >0.05. The findings were highly consistent among patients with different...
ages, durations of surgery, and ASA scores, as well as those with a history of lung disease or prior pneumonia. All of the prespecified subgroups overlapped the 95% confidence interval of the main analysis, as did a post hoc subgroup analysis restricted to patients undergoing thoracic surgery (odds ratio 1.06 (0.88 to 1.28)).

Our findings were consistent across different drug classes and doses of acid suppressants. Proton pump inhibitors (the most potent acid suppressants) were associated with no significant risk of postoperative pneumonia (adjusted odds ratio 0.97 (0.88 to 1.06)). Similarly, H₂ antihistamines also appeared safe (adjusted odds ratio 1.07 (0.98 to 1.17)), as did miscellaneous acid suppressants (adjusted odds ratio 1.13 (0.93 to 1.37)). Patients prescribed doses at or below the median showed no increase in the risk of postoperative pneumonia (adjusted odds ratio 1.03 (0.94 to 1.13)), nor did patients prescribed higher doses (adjusted odds ratio 1.01 (0.93 to 1.10)).

We found no major anomalies related to duration of treatment. Patients treated for multiple years showed no significant increase in risk (adjusted odds ratio 1.01 (0.93 to 1.08)). Similarly, patients treated for a single year showed no significant increase in any of these severe forms of pneumonia (table 2). Overall, we observed a 12 day absolute increase in median length of stay for all patients who developed postoperative pneumonia (odds ratio 1.08 (0.97 to 1.20)).

We explored whether pneumonia was any more severe for patients receiving acid suppressants compared with those patients not receiving acid suppressants. For example, patients who developed pneumonia were about four times more likely than those who did not develop pneumonia to be admitted to an intensive care unit after surgery (54% v 12%, P<0.001). Similarly, patients who developed pneumonia were more likely than patients who did not develop pneumonia to stay in hospital more than a week (89% v 32%, P<0.001) or die during hospitalisation (18% v 1%, P<0.001). Acid suppressants were not associated with a significant increase in any of these severe forms of pneumonia (table 2).

As expected, other factors were significant predictors of postoperative pneumonia. The type of surgery was extremely important (table 3), with the highest relative increase in risk for each 2 minutes of time. Age, sex, insertion of a nasogastric tube, postoperative hypoaalbuminaemia, and various comorbidities were each independent predictors (in accord with past research). The overall predictive accuracy of the 10 factors was strong (C statistic 0.81). All other baseline characteristics (listed in table 1) were not associated with a significant independent increase in risk, including gastric motility agents (adjusted odds ratio 1.07 (0.92 to 1.25)).

### Table 1: Odds ratios of postoperative pneumonia associated with acid suppressants

| Subgroup                  | No of events | Sample size | Odds ratio (95% CI) |
|---------------------------|--------------|-------------|---------------------|
| Total cohort              | 6389         | 593 265     |                     |
| Age (years)               |              |             |                     |
| <75                       | 3171         | 342 561     |                     |
| ≥75                       | 3218         | 250 704     |                     |
| Female                    | 2532         | 190 416     |                     |
| Male                      | 3857         | 302 849     |                     |
| Social status             |              |             |                     |
| Lower                     | 4040         | 229 045     |                     |
| Higher                    | 2295         | 357 473     |                     |
| Past diagnoses            |              |             |                     |
| COPD                      | 2467         | 129 118     |                     |
| Asthma                    | 828          | 55 924      |                     |
| Heart failure             | 1303         | 64 733      |                     |
| Parkinson's disease       | 140          | 8888        |                     |
| Pneumonia                 | 1500         | 58 448      |                     |
| Stroke                    | 948          | 63 602      |                     |
| No of clinic visits in past 3 years |       |             |                     |
| <30                       | 2035         | 243 273     |                     |
| ≥30                       | 4354         | 349 992     |                     |
| No of hospitalisations in past 3 years |       |             |                     |
| 0                         | 2932         | 364 231     |                     |
| ≥1                        | 3457         | 229 034     |                     |
| Charlson score            |              |             |                     |
| 0                         | 2545         | 430 723     |                     |
| 1                         | 1648         | 91 377      |                     |
| ≥2                        | 2196         | 71 165      |                     |
| Type of surgery           |              |             |                     |
| Cardiac                   | 1077         | 55 225      |                     |
| Non-cardiac               |              |             |                     |
| High risk                 | 2608         | 178 496     |                     |
| Medium risk               | 1919         | 153 169     |                     |
| Low risk                  | 785          | 206 375     |                     |
| ASA score                 |              |             |                     |
| 1                         | 794          | 164 545     |                     |
| 2                         | 3998         | 343 417     |                     |
| ≥3                        | 1597         | 85 303      |                     |
| Duration of surgery (hours) |            |             |                     |
| <3                        | 2407         | 411 525     |                     |
| ≥3                        | 3096         | 123 477     |                     |

**Association of postoperative pneumonia with taking acid suppressants in patients aged ≥65 years admitted for elective surgery, analyses for total cohort and subgroups. Odds ratios from adjusted multivariable analysis using logarithmic scale: result for total cohort is 1.02 (95% CI 0.96 to 1.09). (COPD=chronic obstructive pulmonary disease, ASA=American Society of Anesthesia)**
Table 2 | Association of pneumonia with taking gastric acid suppressants among patients aged >65 years admitted for elective surgery

| Characteristic | Adjusted odds ratio (95% CI)* |
|---------------|-----------------------------|
| Age, per decade increase | 1.54 (1.47 to 1.61) |
| Sex, men relative to women | 1.29 (1.22 to 1.37) |
| Past diagnoses: | |
| COPD | 1.48 (1.38 to 1.59) |
| Asthma | 0.76 (0.69 to 0.83) |
| Heart failure | 1.25 (1.16 to 1.35) |
| Parkinson’s disease | 1.36 (1.12 to 1.66) |
| Pneumonia | 1.67 (1.55 to 1.79) |
| Chronic treatments: | |
| Systemic corticosteroid | 1.16 (1.01 to 1.33) |
| Inhaled β agonist | 1.18 (1.05 to 1.33) |
| Inhaled anticholinergic | 1.21 (1.06 to 1.38) |
| Inhaled corticosteroid | 1.24 (1.11 to 1.38) |
| Benzodiazepine | 1.14 (1.06 to 1.30) |
| Antipsychotic | 1.61 (1.34 to 1.92) |
| Antidepressant | 1.18 (1.07 to 1.30) |
| Inpatient admissions, ≥1 in past 3 years | 1.02 (1.01 to 1.03) |
| Charlson score, per unit increase | 1.18 (1.16 to 1.19) |
| Type of surgery, relative to abdominal surgery: | |
| Cardiac | 1.26 (1.14 to 1.38) |
| Thoracic | 2.72 (2.46 to 3.00) |
| Vascular | 1.38 (1.25 to 1.52) |
| Musculoskeletal | 0.75 (0.69 to 0.82) |
| Lower urogenital | 0.30 (0.26 to 0.34) |
| Breast and skin | 0.21 (0.16 to 0.28) |
| Ophthalmological | 0.07 (0.04 to 0.12) |

Indirectly, our study also contrasts with recent research on the association between acid suppressants and pneumonia observed in non-surgical settings.39-41

Main limitation
The most important limitation of our study is that it is not a randomised trial that eliminates all confounding. However, the controlled nature of inpatient elective surgical services argues against major confounding from active smoking, ongoing alcohol consumption, reverse causality, or other confounders relevant to community acquired pneumonia.42 The analyses, in addition, provided data on almost all major clinical predictors, and the results (tables 2 and 3) yield a pattern that is difficult to attribute to misclassification of pneumonia outcomes or medication exposures.43 The main advantage of a randomised trial would be in prospective data collection to obtain more information about microbiology, radiology, medication compliance, clinical course, long term outcomes, milder...
Postoperative pneumonia is a common and serious complication after major surgery in elderly patients. Several randomised trials have reported that gastric acid suppressants sometimes increase the risk of ventilator associated pneumonia in critical care unit patients. Some of the most important risk factors for postoperative pneumonia include a history of chronic obstructive pulmonary disease, heart failure, Parkinson’s disease, or pneumonia; nasogastric tubes; and prescriptions of antipsychotics. Accounting for such differences in other risk factors reveals no direct association between gastric acid suppressants and a patient’s risk of postoperative pneumonia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Postoperative pneumonia is a common and serious complication after major surgery in elderly patients. Several randomised trials have reported that gastric acid suppressants sometimes increase the risk of ventilator associated pneumonia in critical care unit patients. Some of the most important risk factors for postoperative pneumonia include a history of chronic obstructive pulmonary disease, heart failure, Parkinson’s disease, or pneumonia; nasogastric tubes; and prescriptions of antipsychotics. Accounting for such differences in other risk factors reveals no direct association between gastric acid suppressants and a patient’s risk of postoperative pneumonia.

WHAT THIS STUDY ADDS

Patients who received gastric acid suppressants were predisposed to postoperative pneumonia but were also prone to independent risk factors for postoperative pneumonia. Some of the most important risk factors for postoperative pneumonia include a history of chronic obstructive pulmonary disease, heart failure, Parkinson’s disease, or pneumonia; nasogastric tubes; and prescriptions of antipsychotics. Accounting for such differences in other risk factors reveals no direct association between gastric acid suppressants and a patient’s risk of postoperative pneumonia.

Further limitations

Negative studies are sometimes prone to biases that differ from those in studies that report significant differences. Over-adjustment bias, for example, sometimes causes adjusted analyses to be less valid than crude analyses. This bias occurs if an event downstream in the course of a disease is mistakenly considered a baseline characteristic. Outcome heterogeneity can be a second potential bias if, for example, acid suppressants were to increase the risk of Gram positive bacterial pneumonia and decrease the risk of Gram negative pneumonia. In such circumstances, a comprehensive analysis might fail to detect either finding. Similarly, patient diversity can be a third bias if the same exposure is helpful to some patients and harmful to other patients, and the patient groups are hard to distinguish. We do not believe these three issues biased our results.

Relative advantages

One strength of our research relates to its statistical power, with a sample size almost double that of the US National Veterans Affairs Surgical Quality Improvement Program. The design allows the analyses to address the vagaries of ascertaining patient compliance since acid suppressants are not usually changed around elective surgical procedures. The multicentred sampling provides a rigorous test free of referral bias or selection bias. The data also show that postoperative pneumonia diagnostic codes are specific (but not sensitive) given that our crude analysis yielded significant increase in risk similar to recent reports (and a base rate lower than surveillance reports). In addition, the statistical power corroborates other predictors of pneumonia reported in other studies, including use of benzodiazepines and nasogastric tubes.

Clinical relevance

The implication of our research is that the bacterial colonisation induced by gastric acid suppressants may be a major finding in laboratory experiments but may have little clinical importance for postoperative pneumonia, so that concerns over the safety of acid suppressant therapy in the perioperative setting are perhaps misplaced. Minimising a patient’s risk of postoperative pneumonia might be better prioritised through focusing on smoking cessation, optimising nutrition, reducing any psychoactive medications, prompt discontinuation of nasogastric tubes, chest expansion manoeuvres, and other opportunities for protecting the respiratory tract around the time of an operation.

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Data sharing: No additional data available.

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