Use of proton pump inhibitors is associated with increased mortality due to nosocomial pneumonia in bedridden patients receiving tube feeding

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Aim: To investigate the association between the use of proton pump inhibitors (PPI) and nosocomial pneumonia and gastrointestinal bleeding in bedridden patients receiving tube feeding.

Methods: A total of 116 bedridden hospitalized patients receiving tube feeding, of which 80 were supported by percutaneous endoscopic gastrostomy and 36 by nasogastric tube, were included in the present study. The patients were divided into two groups: 62 patients treated with PPI (PPI group) and 54 patients without PPI (non-PPI group). Mortality due to nosocomial pneumonia was evaluated using the Kaplan–Meier approach and the log-rank test.

Results: A total of 36 patients (31%) died of nosocomial pneumonia during the observation period; the mortality rate due to nosocomial pneumonia was significantly higher in the PPI group than in the non-PPI group (P = 0.0395). Cox proportional hazard analysis showed that the use of PPI and lower levels of serum albumin were independent predictors of 2-year mortality due to nosocomial pneumonia. Gastrointestinal bleeding was observed in four patients in the non-PPI group (7.7%) and in one patient in the PPI group (1.6%); there was no significant difference between the two groups.

Conclusion: The use of PPI in bedridden tube-fed patients was independently associated with mortality due to nosocomial pneumonia, and the PPI group had a non-significant lower incidence of gastrointestinal bleeding than the non-PPI group. Geriatr Gerontol Int 2018; 18: 1215–1218.

Keywords: bedridden, mortality, nosocomial pneumonia, proton pump inhibitors, tube feeding.

Introduction
Proton pump inhibitors (PPI) are known to be highly effective in the treatment of peptic disease and are often used for a long period to prevent gastrointestinal bleeding, especially in hospitalized patients.1,2 However, recent observational studies have shown that the use of acid-suppressive medications, especially PPI, was associated with an increased risk of nosocomial pneumonia.3–6 Therefore, risk-benefit considerations might be important to determine the indication and discontinuation of acid-suppressive medications.

Nasogastric tube (NGT) and gastrostomy tube placement are useful to maintain enteral access for nutrition, hydration and medication for patients with dysphagia due to stroke, brain injury, neurodegenerative diseases and obstruction due to cancer. However, previous studies reported a poor prognosis in elderly patients with tube feeding, mainly due to complications of aspiration pneumonia.7–9 Furthermore, elderly tube-fed patients might have several risk factors for gastrointestinal bleeding, such as aging, history of esophagitis and peptic ulcer, antplatelet and anticoagulant therapy, and gastrostomy tube placement,10,11 and are often treated with acid-suppressive medications. Thus, the aim of the present study was to investigate the association between the use of PPI and the incidence and mortality of nosocomial pneumonia in bedridden patients receiving tube feeding. Additionally, the...
incidence of gastrointestinal bleeding was compared between elderly tube-fed patients with and without PPI treatment.

Methods

The present study included 116 hospitalized, bedridden patients receiving tube feeding who were admitted to the Rikita Hospital, Hiroshima, Japan, from January 2011 to December 2015; the patients were unable to move by themselves or communicate with each other. A total of 80 were supported by percutaneous endoscopic gastrostomy and 36 by NGT. Patients who had continued tube feeding without early complications for at least 1 month were included in the analysis. The diagnosis of pneumonia was based on radiological shadows on chest X-ray or computed tomography, blood examination and clinical symptoms. Causes of death were determined by reviewing the clinical documents of the attending physicians. All percutaneous endoscopic gastrostomy placements had been carried out before admission. The patients were categorized into two groups: patients treated with PPI (PPI group) and those without PPI (non-PPI group). The baseline characteristics of the PPI group and the non-PPI group were compared using the Mann–Whitney U-test or Fisher’s exact test. Durations from hospital admission to the onset of or death from nosocomial pneumonia were evaluated using the Kaplan–Meier approach and the log-rank test. Patients for whom tube feeding was discontinued and substituted with total parenteral nutrition or peripheral infusion, or patients who died from other causes were censored. Furthermore, those who stopped PPI or changed PPI to histamine type-2 receptor antagonists in the PPI group and those who started PPI in the non-PPI group were compared using the Cox proportional hazards model. The baseline characteristics of the patients and the incidence of nosocomial pneumonia in the two groups were compared using the statistical software R version 3.2.2 (R Foundation, Vienna, Austria). The log-rank test and Cox proportional hazards model were carried out using the “survival” package of the R software.

Results

The mean observation period of 116 patients was 251 days (95% confidence interval 205–296 days). A total of 73 patients (62.9%) had cerebrovascular diseases, and 27 patients (23.3%) had cerebral degenerative disorders (Table 1). PPI were prescribed in 80 patients in the PPI group and 20 patients in the non-PPI group received anticoagulant and/or antiplatelet therapy, two of the 20 patients treated with PPI in the non-PPI group were compared using the Mann–Whitney U-test and Cox’s exact test. The baseline characteristics of the two groups were compared using the statistical software R version 3.2.2 (R Foundation, Vienna, Austria). The log-rank test and Cox proportional hazards model were carried out using the “survival” package of the R software.

Table 1  Primary diagnosis of inpatients enrolled in this study

| Cerebrovascular diseases                      | PPI     | Non-PPI  | P-value |
|---------------------------------------------|---------|----------|---------|
| Cerebral stroke                             | 45 (38.8%) |          |         |
| Cerebral hemorrhage                         | 19 (16.3%) |          |         |
| Subdural hematoma                           | 5 (4.3%) |          |         |
| Traumatic brain injury                      | 3 (2.6%) |          |         |
| Subarachnoid hemorrhage                     | 1 (0.9%) |          |         |
| Cerebral degenerative disorders             |         |          |         |
| Alzheimer’s disease                         | 23 (19.8%) |          |         |
| Parkinson’s disease                         | 2 (1.7%) |          |         |
| Progressive supranuclear palsy              | 1 (0.9%) |          |         |
| Multiple system atrophy                     | 1 (0.9%) |          |         |
| Diuse atrophy                               | 11 (9.5%) |          |         |
| Hypoxic brain damage                        | 3 (2.6%) |          |         |
| Brain tumor                                 | 2 (1.7%) |          |         |
| Total                                       | 116     |          |         |

Table 2  Patient characteristics in the proton pump inhibitor and the non-proton pump inhibitor groups

| Medications         | PPI     | Non-PPI  | P-value |
|---------------------|---------|----------|---------|
| ACEI                | 7 (11.3%) | 2 (3.7%) | 0.172   |
| Mosapride           | 14 (22.6%) | 4 (7.4%) | 0.038   |
| Corticosteroids     | 3 (4.8%) | 2 (3.7%) | 1.000   |
| NSAIDs              | 0 (0%) | 0 (0%) | 1.000 |
| Antiplatelet agents/ | 31 (50%) | 20 (37%) | 0.191 |
| anticoagulants      |         |          |         |

Data presented as the mean ± SD. Significant differences were evaluated using the Mann–Whitney U-test or Fisher’s exact test. ACEI, angiotensin-converting enzyme inhibitors; Alb, albumin; ChE, cholinesterase; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GNT, nasogastric tube; NSAIDs, non-steroidal anti-inflammatory drugs; PEG, percutaneous endoscopic gastrostomy; PPI, proton pump inhibitors; TC, total cholesterol; TG, triglyceride; TP, total protein.

A total of 73 patients suffered from nosocomial pneumonia, and the incidence of the nosocomial pneumonia in the PPI group was significantly higher than that in the non-PPI group (P = 0.0394; Fig. 1a). Furthermore, 58 patients died during the observation period, of which 36 patients died of pneumonia. There was no significant difference in the all-cause mortality rate between the two groups (P = 0.5040; Fig. 1b). However, the mortality rate due to nosocomial pneumonia within 2 years in the PPI group was significantly higher than that in the non-PPI group (39% ± 22%, P = 0.0395; Fig. 1c). Cox proportional hazard analysis showed that the use of PPI and the lower levels of serum albumin were independent predictors of 2-year mortality due to nosocomial pneumonia (Table 3). The use of mosapride or angiotensin-converting enzyme inhibitors (ACEI) was not associated with lower mortality due to pneumonia.

Clinically significant gastrointestinal bleeding was observed in four of 52 patients in the non-PPI group (7.7%) and in one of 62 patients in the PPI group (1.6%), and there was no significant difference between the two groups (P = 0.182). Among those with anticoagulant and/or antiplatelet therapy, two of the 20 patients (10%) in the non-PPI group developed upper gastrointestinal bleeding, and none of the 32 patients in the PPI group (P = 0.143).

Discussion

In the present study, we have investigated the risks and benefits of PPI in elderly patients receiving tube feeding with special focus on pneumonia and gastrointestinal bleeding. During the observation period, 31% of the patients died of nosocomial pneumonia, and the use of PPI was an independent risk factor for mortality due to pneumonia. Additionally, 85% of the patients used PPI, and the
incidence of gastrointestinal bleeding was non-significantly lower in the PPI group than in the non-PPI group.

This is the first study to show that the use of PPI is an independent predictor of mortality due to nosocomial pneumonia in elderly bedridden patients receiving tube feeding. Recent meta-analysis of observational studies and randomized controlled trials reported that the use of acid-suppressive medications, especially PPI, is associated with increased incidence of both community- and hospital-acquired pneumonia.15 Herzg et al. reported that acid-suppressive medications were used in 52% of 63,878 hospitalized patients, and the incidence of hospital-acquired pneumonia was significantly higher in those treated with acid-suppressive medications than in those without (4.9% vs 2.0%, respectively).3

Increased risk of pneumonia due to the use of PPI can be explained by gastric alkalization and bacterial overgrowth in gastric contents.13 In vitro studies suggested an alternative mechanism of diminished neutrophil bactericidal activity by omeprazole.14 15 Elderly bedridden patients receiving tube feeding were shown to have high mortality due to pneumonia,6,9 and the present study shows that PPI can increase the risk of mortality and pneumonia in this high-risk patient population.

In the present study, the use of PPI was associated with a non-significant lower incidence of gastrointestinal bleeding within the mean observation period of 251 days. PPI might be used to prevent gastrointestinal bleeding in critically ill patients.16 They were also shown to be effective in non-critically ill patients who had risk factors, such as age >60 years, male sex, liver disease, acute renal failure, sepsis, using an internal medicine service, and using anticoagulants and antplatelets.17–19 Furthermore, patients with percutaneous endoscopic gastrostomy tube might have a relatively high risk of esophagitis, duodenal ulcers, gastric erosions and gastritis.15 Therefore, elderly patients receiving tube feeding often have several risks of gastrointestinal bleeding, which makes it difficult to discontinue antacid medications. However, when considering the increased pneumonia mortality in the PPI group observed in the present study, discontinuation of PPI might be considered after thorough evaluation of the risk for gastrointestinal bleeding. Future prospective studies might be warranted to evaluate the benefit and harm by discontinuation of PPI in this patient population.

In the present study, the use of ACEI or mosapride citrate was not associated with a reduced risk of pneumonia. Mosapride citrate is a prokinetic drug that promotes upper gastrointestinal motility and prevents gastroesophageal reflux, and was also shown to reduce the incidence of aspiration pneumonia.20–22 ACEI also have been shown to be effective in reducing the risk of aspiration.22 However, just nine patients were treated with ACEI, and 18 patients were using mosapride citrate. Therefore, it is possible that the present study could not detect a significant effect of these medications because of the small sample size of each subgroup.

The present study had several limitations. First, it was a retrospective review from one long-term care hospital. Second, a routine checkup of the gastrointestinal fiberscope was not usually carried out. The enrolled patients could not communicate; thus, asymptomatic gastrointestinal diseases, gastroesophageal reflux or complications from hiatal hernias were not evaluated. Third, mosapride and ACEI, which were shown to be effective in reducing the risk of aspiration pneumonia, were not found to be effective in the present study.
Disclosure statement

The authors declare no conflict of interest.

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