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Do proton-pump inhibitors increase the risk for nosocomial pneumonia in a medical intensive care unit?

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Abstract

Purpose: The aim of this study was to determine whether the use of gastric acid-suppressive agents increases the risk of nosocomial pneumonia (NP) in a medical intensive care unit population.

Materials and Methods: Retrospective cohort study in a medical intensive care unit of a 554-bed, university-affiliated, academic medical center.

Results: A total of 924 medical records were included in the database during the study period of which 787 patients were included in the study. Out of this cohort,104 patients (13.2%) eventually developed a NP. The risk for patients who received proton-pump inhibitors (adjusted hazard ratio [AHR] 0.63; 95% CI 0.39-1.01) was not significantly different than in non exposed patients. Variables most strongly associated with NP were the administration of sedatives or neuromuscular blockers for at least 2 consecutive days (AHR 3.39;95% CI 1.99-5.75), an Acute Physiology and Chronic Health Evaluation II (APACHE II) severity score greater than 15 (AHR, 3.34; 95% CI 1.82-6.50), and presence of a central venous catheter (AHR, 1.76; 95% CI 1.12-2.76).

Conclusions: Prior use of a proton-pump inhibitor did not correlate with a significant increase in the risk of developing NP. This risk was higher with the administration of sedatives or neuromuscular blockers, increased disease severity, and placement of a central venous catheter.

1. Introduction

Nosocomial pneumonia (NP) is the most frequent hospital acquired infection and is associated with considerable morbidity and mortality, accounting for 25% of all infections in the intensive care unit (ICU) [1]. Patients receiving mechanical ventilation are particularly prone to developing this complication as ventilator associated pneumonia develops in 9% to 27% of all intubated patients [2]. The main mechanism for acquisition is through the aspiration of oropharyngeal secretions into the lower bronchial tree [3]. Many risk factors have been identified including male sex, age, admission for burns, trauma or central nervous diseases, history of respiratory or cardiac diseases, immunosuppression, supine patient positioning, presence of an artificial airway, enteral and parenteral nutrition, sedatives and analgesics, blood transfusions, and hyperglycemia [4]. Stress ulcer prophylaxis with both antacids and histamine type 2 (H_2) blockers has also been identified as a risk factor for ICU

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acquired pneumonia [5]. Increase in gastric colonization secondary to pH modification has been shown and may cause retrograde colonization of the pharynx [6]. In a landmark trial comparing ranitidine to sucralfate, there was a trend towards an increase in the incidence of pneumonia in the ranitidine group [7].

Proton-pump inhibitors (PPIs) are increasingly used in the ICU for both stress ulcer prophylaxis and gastrointestinal (GI) bleeding [8]. As these agents are more efficacious in elevating gastric pH, the risk of gastric colonization and subsequent pharyngeal colonization may be higher. In one study, bacterial overgrowth, which was defined as more than 10^5 cfu/ml, was significantly more present in patients treated with omeprazole than with cimetidine (53% vs 17%; $P < .05$) [9]. Recently, observational studies in the community setting have associated the use of PPIs with a significant increase in the risk of community-acquired pneumonia in both adults and children [10,11]. In the hospital setting, one small prospective observational study failed to show an increase in the risk of NP with PPIs compared to H_2 blockers [12]. One randomized trial has shown a trend towards an increased risk associated with PPI use, whereas another small trial has reported a protective effect compared to H_2 blockers [13,14]. However, these findings were not corroborated by the largest trial comparing PPIs to H_2 blockers [15]. Hence, the objective of the present study was to determine whether the use of PPIs increases the risk of nosocomial pneumonia in a medical intensive care unit (MICU) population after adjusting for other confounding factors.

2. Methods

2.1. Study design

This retrospective cohort study included all patients admitted to the MICU of the Hôpital du Sacré-Coeur de Montréal between March 14, 2002, and May 31, 2004. The date of admission to the unit was considered the index date. For patients who had multiple stays in the MICU during the study period, only the first admission was considered. Patients were considered as having an NP if there was a clinical diagnostic for NP between their second day of admission to the MICU and until MICU discharge.

2.2. Study sample

The study population was composed of patients admitted during the study period who stayed in the unit for more than 24 hours. Patients were excluded from the cohort if they had a diagnostic of NP during the first 48 hours after MICU admission. The presence of a new or progressive radiographic infiltrate plus at least 2 of 3 clinical features (fever >38°C, leukocytosis or leucopenia, and purulent secretions) for patients who have been in ICU for 48 hours or longer defined a clinical diagnosis of nosocomial pneumonia [2]. This does follow Centers for Disease Control and Prevention's National Nosocomial Infections Surveillance System definition of an ICU-associated infection defined by an infection that is not present or incubating at patient's admission to ICU but becomes apparent during ICU stay or within 48 hours after transfer from ICU [16].

The following data were extracted for all subjects from the database: date of admission and discharge from hospital and MICU and patient's sex, age, and origin (in or outpatient). Patients who had no prior hospitalization or patients who had been in the emergency care unit for less than 24 hours were considered as outpatients. Variables associated with procedures and therapies were collected, including exposure to pharmacologic agents (PPIs, H_2 blockers, antibiotics, cytotoxic or immunologic agents, and continuous administration of sedative agents or neuromuscular blockers for $\geq$48 hours), presence of nasogastric tube or central venous catheter (CVC), invasive diagnostic or curative procedures to the GI tract, neurosurgery, and hemodialysis. Data collection also included invasive procedures to the respiratory tract (presence for $\geq$48 hours of an oral or nasal tracheal tube, tracheotomy, chest tubes, bronchoscopy, and surgeries). Neoplams, diabetes mellitus, ischemic heart diseases, diseases of pulmonary circulation, cerebrovascular or vascular diseases, chronic or acute renal failure, presence of GI bleeding, chronic obstructive pulmonary disease (COPD) and other pulmonary conditions, coma and alteration of consciousness, uremia, and severe sepsis at the time of admission were considered as possible independent risk factors and were noted as dichotomous variables. The presence of 2 or more comorbidities listed above or any other comorbidity was also noted as a possible risk factor. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of the severity of disease were calculated whenever it was possible. All treatments had to be received during MICU stay except H_2 blockers, PPIs, antibiotics, and chemotherapy (for up to 14 days preceding MICU admission). Patients who received last dosage or treatment for more than 14 days preceding NP diagnostic are considered as nonexposed. Age was defined as the age at time of admission. Antibiotic exposure was calculated as total cumulative days exposed to an antibiotic within a class. Given that the risk of acquiring NP increases cumulatively to the length of hospital stay, length of hospitalization preceding MICU admission was also considered.

2.3. Data source

The local Project IMPACT (Project IMPACT CCM Inc., Bel Air, Maryland) dataset was used to obtain patients data [17]. Project IMPACT is the data system originally developed by the Society of Critical Care Medicine to measure and describes the care of ICU patients. To ensure uniform data collection, all data originating from patient medical and nursing files were collected by the same trained research nurse who was unaware of the study hypothesis.