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ORIGINAL ARTICLE

Proton pump inhibitor usage and the associated risk of pneumonia in patients with chronic kidney disease

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Background: Chronic kidney disease (CKD) is a serious medical problem and public health issue in Taiwan. Gastrointestinal symptoms frequently occur in patients with CKD, and proton pump inhibitors (PPIs) have therapeutic indications for gastrointestinal disorders involving excessive acid production. However, PPIs may also increase the risk of developing pneumonia through acute and irreversible gastric acid suppression. This study aimed to characterize differences in the risk of pneumonia in patients with CKD who use PPIs.
Methods: This population-based case—control cohort study in Taiwan collected data from the Taiwan Health Insurance Research Database. Cases studied consisted of all patients in the database with an initial diagnosis of CKD during the 5-year period from 1997 to 2002. Each

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patient with CKD who used PPIs during this 5-year period was tracked to identify the occurrence of any type of pneumonia. We estimated the adjusted hazard ratios (HRs) and 95% confidence interval (95% CI) by using multiple logistic regression analysis.
Results: The adjusted HR of the risk of pneumonia for patients with CKD using PPIs was 2.21 (95% CI = 1.59–3.07, $p < 0.001$). The risk of pneumonia was found to be positively associated with administration of PPIs. We observed a greater risk of pneumonia in patients with CKD using PPIs than in patients not using PPIs.
Conclusion: Results of this study suggest that use of PPIs in CKD patients may be associated with increasing the risk of pneumonia. Physicians should exercise caution while prescribing PPIs for patients with CKD.

Introduction

Proton pump inhibitors (PPIs) are drugs that have been widely used for treating gastroesophageal reflux disease (GERD), acute peptic ulcer, and other acid-peptic-related diseases, for more than 20 years.[1] A lack of gastric acid in the stomach will reduce indigestion, pain, and heartburn and aid in the healing of peptic ulcers. However, a related concern is the risk of respiratory tract infection resulting from profound acid inhibition due to the use of PPIs. Some earlier studies have shown that treatment with PPIs may be associated with increased risk of community-acquired pneumonia.[2–4] However, several other studies did not support this finding.[5–7] Consequently, this result has been under debate for many years, without a consensus.

Chronic kidney disease (CKD) is a major public health problem worldwide and especially so in Taiwan, where the national prevalence of CKD was 11.9% with an increasing incidence and prevalence of end-stage renal disease (ESRD) requiring dialysis.[8,9] Patients with CKD have a high incidence of gastrointestinal disorders such as GERD and peptic ulcers.[10,11] PPIs are prescribed for most of these patients to treat gastrointestinal symptoms. An overuse of PPIs in patients with CKD could produce adverse effects. Currently, no study exists that investigates the risk of pneumonia in patients with CKD who have received PPI therapy. We studied the outpatient and inpatient claims data in the cohort database of the Longitudinal Health Insurance Database (LHID) 2005, a nationwide population-based dataset that provided an excellent resource for evaluating the risk of pneumonia among patients with CKD.

This study aimed to investigate the risk that patients with CKD receiving PPI therapy could develop pneumonia. It also aimed to characterize differences in the rate of occurrence of pneumonia associated with different types of PPIs.

Patients and methods

Data sources

In this study, data were collected from LHID 2005 released by the Taiwan National Health Research Institutes (NHRI) in 2007. This sample population accounted for 5% of all enrollees in the National Health Insurance (NHI) program. There were no statistically significant differences in age or sex distribution between the patients in the sample group and the original population approved by NHRI.

We used the data from all individuals with claims between January 1997 and December 2007. This study was approved by the Institutional Review Board of the Far Eastern Memorial Hospital (IRB No. 101013-E), New Taipei, Taiwan.

Study design

A retrospective cohort study was designed in our study. Our study sample consisted of all patients with ambulatory care visits for CKD between January 1997 and December 2002 ($n = 23{,}734$) who matched any of the principal diagnoses of the *International Classification of Diseases*, Ninth Revision (ICD-9-CM) code of CKD. We defined patients with CKD as those in whom an event was diagnosed that was described under chronic glomerulonephritis (ICD-9-CM codes 582.9, 582.1, 582.4, 582.21), chronic pyelonephritis (590.00), chronic renal failure (585), diabetes mellitus with nephropathy (583.81), immunoglobulin (Ig)A or IgM nephritis (583.589), nephritis and nephropathy (583.9), nephrotic syndrome (581.x), and renal failure (586).

Study sample

We limited the study sample to the CKD population, excluding patients with fewer than three visits with the diagnosis of CKD and in whom CKD had been diagnosed prior to 1997. We selected only the first ambulatory care visits for newly diagnosed CKD in this cohort database since 1997 and the patients that had more than three visits during the study period. Classification study groups including determination of PPI and non-PPI groups. We excluded patients who had received a prescription for any PPIs prior to the study.

ICD-9 code of diagnosis (variables of interest)

The primary objective of this study was to observe whether patients with CKD receiving PPIs developed pneumonia or not. Patients included those who had any inpatient diagnosis of a type of pneumonia with an ICD-9-CM code 481,