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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,

482, 483, 485, and 486 between January 1998 and December 2008. These codes have been used by other studies.[12,13] In addition, we use the appearance of pneumonia as an outcome measure.

The ICD-9-CM of the diagnoses of comorbidities were cerebrovascular disease (CVA, 430-438), acute renal failure (584), ischemic heart disease (414.9), chronic obstructive pulmonary diseases (COPD, 496), asthma (493), and diabetes mellitus (250). The covariate information was collected at the time the patient entered the cohort. Incidence rates of pneumonia were calculated for exposed and unexposed individuals.

PPI classification and database codes

Five PPIs are currently available, including omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. We included both intravenous and oral drugs in this study. To avoid underestimation of some patients using more than one kind of PPIs, we selected total drug use number (except lansoprazole because no data were available in the study period) and patient number from the database. Drugs were classified according to the anatomic therapeutic chemical system developed for the NHI Research Database (NHIRD) drug utilization program. We used a defined daily dose (DDD) recommended by the World Health Organization (WHO) for measuring drug utilization.[14]

Each patient was individually tracked for 5 years, starting from his or her initial outpatient visit, to identify those who had developed pneumonia during the follow-up period. To calculate the number of patients with CKD who developed pneumonia during the 5-year period after their first outpatient visits, the data were also linked to the PPI drug use data in the NHIRD in Taiwan.

Cohort setting

Patients were eligible for inclusion if they received any PPI treatment between January 1998 and December 2002 and if pneumonia had been diagnosed. The date of the first diagnosis of CKD since January 1997 was used to determine the case group. A patient was recruited into our study group when three CKD diagnoses were collected. PPI prescriptions after the last date of three CKD diagnoses were collected to decide if the patient was in the PPI or non-PPI group. The patient was followed up until the development of pneumonia or up to 5 years in our study. If the patient has no pneumonia after 5 years of follow-up, he or she was considered censored. The cumulative incidence rate of pneumonia was estimated during the follow-up period, a maximum of 5 years. The exclusion criteria were used: previous diagnosis of CKD, any PPI use, or a diagnosis of pneumonia in the year preceding the cohort entry date.

Statistical analysis

The SAS version 9.1 statistical package (SAS Institute Inc., Cary, NC, USA) was used to perform all analyses in this study. The *t*-test and Pearson χ^2 test were used to examine the differences in demographic characteristics (age, sex) and potential confounders, including CVA, acute renal failure, ischemic heart diseases, COPD, asthma, and diabetes mellitus between patients either receiving or not receiving PPI therapy during the follow-up period.

We calculated the incidence of pneumonia during the 5-year follow-up period and examined the differences in the risk of pneumonia between the two groups. Multivariate logistic regressions were performed to estimate the hazard ratio (HR) of pneumonia occurring in the study and comparison groups. We also adjusted the potential confounder including age, sex, CVA, acute renal failure, ischemic heart diseases, COPD, asthma, and diabetes mellitus for the risk of development of pneumonia. The differences were established as statistically significant if a two-sided $p \leq 0.05$. Occurence of pneumonia was assessed using Kaplan–Meier analysis, with significance based on the log-rank test.

Results

We identified a total of 8,076 patients with CKD in this study cohort (Fig. 1). Among the 277 patients receiving PPIs, 53 (19.1%) had received a diagnosis of pneumonia. Of the 7,799 patients who did not receive PPIs, 566 (7.3%) had received a diagnosis of pneumonia (Table 1). The mean age of patients in the PPI exposure group was higher than that of the non-PPI exposure group (63.34 $\pm$ 13.03 vs. 54.2 $\pm$ 18.31, $p < 0.001$). In the PPI group, patients appeared more likely to have several pre-existing illnesses such as ischemic heart diseases, asthma, and diabetes mellitus ($p < 0.001$) than in the non-PPI group (Table 1). Using multivariate analysis, we adjusted all of the potential confounders between the two groups, including older age, sex, and the comorbidities. Table 2 shows the crude and adjusted HR to develop pneumonia. We stratified the patients' age into four groups and found that patients <20 years and >40 years had the risk of pneumonia. However, after adjusting the HR, older age groups (>60 years) had a high risk for pneumonia [adjusted HR: 1.06 (95% CI = 1.05–1.08)]. In this study, older patients with comorbid illness such as CVA, COPD, asthma, and diabetes mellitus had a high risk for pneumonia.

Although there are five PPIs currently available in Taiwan (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole), no data on lansoprazole exposure could be found in this study. Table 3 shows the risk of pneumonia with exposure to different PPIs. Among patients with CKD, those receiving esomeprazole, omeprazole, and rabeprazole had a higher incidence of pneumonia than those receiving pantoprazole. Based on the DDD, there was no significant difference in dose effect analysis in 30–60 DDD compared with the duration of PPI exposure. We observed that the risk of pneumonia in <30 DDD was 21.2% (HR: 3.44, 95% CI = 2.25–5.26) and the risk of pneumonia in >90 DDD was 25% (HR: 4.26, 95% CI = 1.64–9.85; Table 4).

Fig. 2 demonstrates Kaplan–Meier curves of the occurrence of pneumonia in patients with CKD receiving PPI treatment. The cumulative incidence of pneumonia was higher in the PPI exposure group than in the non-PPI exposure group throughout the 5-year follow-up period. The difference is significant by log-rank test.

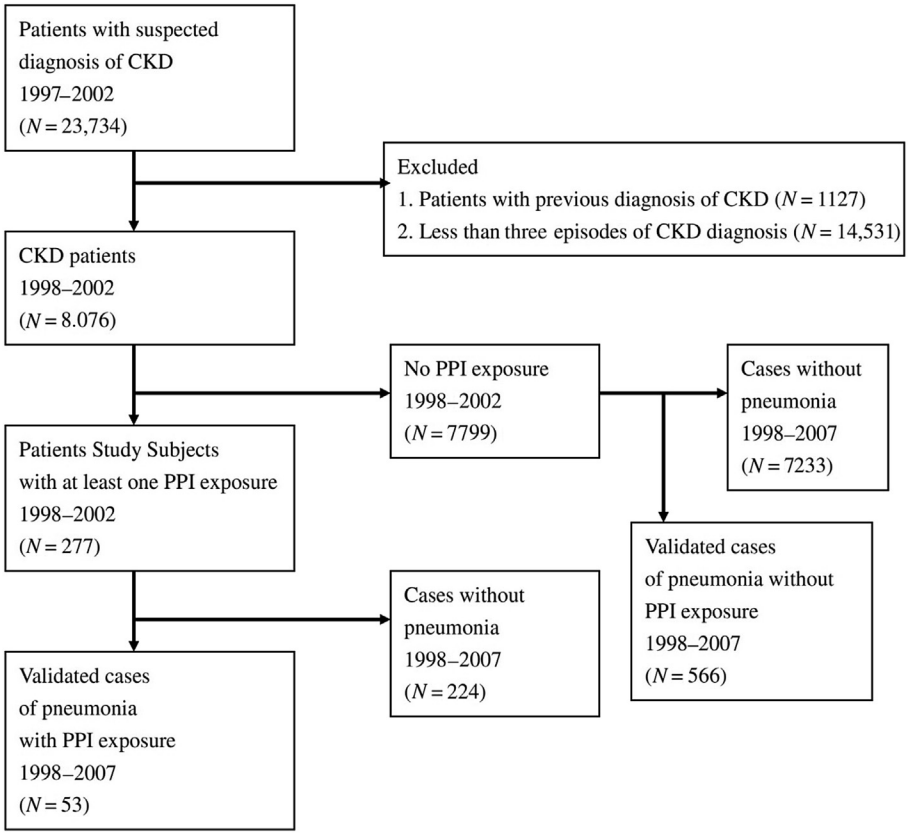

Figure 1. Flow chart of enrolled subjects from National Health Insurance Research Database of Taiwan. CKD = chronic kidney disease; PPI = proton pump inhibitor.

Discussion

In this large population-based study, we observed that PPI administration was strongly associated with the risk of pneumonia in CKD patients. Among the 277 patients receiving PPIs, pneumonia had been diagnosed in 53 (19.1%). Although some previous studies presented similar results, this is the first study to focus on patients with CKD.[2–4]

CKD not only reflects target organ injury and systemic vascular disease in the general population but is also recognized as resulting in a high risk of GERD, peptic ulcer,

Table 1 Comparisons of demographic characteristics of patients with chronic kidney disease with receiving and not receiving proton pump inhibitor in Taiwan, 1998—2002 (n = 8,076)

Category	Patients receiving PPI (n = 277)	Patients not receiving PPI (n = 7,799)	p
	No. (%)	No. (%)	
Occurrence of pneumonia	53 (19.1)	566 (7.3)	<0.001
Age (mean ± SD)	63.34 ± 13.03	54.20 ± 18.31	<0.001
Sex (male)	174 (62.82)	4090 (52.44)	<0.001
CVA	59 (21.29)	1107 (14.19)	<0.001
Acute renal failure	2 (0.72)	43 (0.55)	0.71
IHD	73 (26.35)	1075 (0.14)	<0.001
COPD	83 (29.96)	1289 (16.53)	<0.001
Asthma	71 (25.63)	1229 (15.73)	<0.001
Diabetes mellitus	86 (31.04)	1414 (18.13)	<0.001
Mean time of pneumonia (days)	954 ± 576	1544 ± 397	<0.001

COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular disease; IHD = ischemic heart disease; PPI = proton pump inhibitor; SD = standard deviation.

Table 2 Crude hazard ratio and multivariate logistic regression-adjusted hazard ratio of patients with chronic kidney disease receiving proton pump inhibitor and developing pneumonia, with respect to different confounders (n = 277)

Variables	Risk of pneumonia			
	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
PPI	3.02 (2.21–4.12)	<0.001	2.28 (1.64–3.15)	<0.001
Age (mean ± SD)	1.03 (1.03–1.04)	<0.001	1.01 (1.01–1.02)	<0.001
≤20	0.88 (0.83–0.94)	<0.001	0.92 (0.86–0.99)	0.03
21–40	1.01 (0.96–1.07)	0.64	1.01 (0.95–1.06)	0.95
41–60	1.05 (1.02–1.09)	<0.001	1.02 (0.98–1.05)	0.39
≥61	1.07 (1.05–1.09)	<0.001	1.06 (1.05–1.08)	<0.001
Sex (male)	1.19 (1.02–1.41)	0.03	1.05 (0.89–1.26)	0.55
CVA	3.06 (2.56–3.68)	<0.001	1.86 (1.52–2.27)	<0.001
COPD	2.89 (1.75–2.58)	<0.001	1.72 (1.39–2.11)	<0.001
Diabetes mellitus	2.29 (1.92–2.74)	<0.001	1.56 (1.29–1.89)	0.01
IHD	2.13 (1.75–2.58)	<0.001	1.13 (0.91–1.39)	0.27
Asthma	1.91 (1.58–2.31)	<0.001	1.34 (1.09–1.65)	0.01
Acute renal failure	1.86 (0.78–4.41)	0.16	1.50 (0.62–3.66)	0.37

Adjusted for age, sex, CVA, acute renal failure, IHD, COPD, asthma, and diabetes mellitus.
CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular disease; HR = hazard ratio; IHD = ischemic heart disease; SD = standard deviation.

and upper gastrointestinal (GI) bleeding, especially in patients with ESRD.[10,11] Therefore, caution should be exercised in the use of PPIs for such patients.

Since omeprazole was first launched in 1988, PPIs have become one of the most widely prescribed class of drugs currently on the market.[15] PPIs are able to increase gastric pH and decrease gastric volume by inhibiting H^+/K^+ adenosine triphosphatase, thus allowing bacterial colonization and overgrowth in the upper GI tract.[16,17] Thorens et al[16] found that most bacteria species that overgrew in the upper GI tract were similar to the bacteria colonizing the oral cavity and the pharynx. These microorganisms of oropharyngeal flora are strongly associated with the pathogens for patients with pneumonia receiving PPI therapy. We did not analyze the pathogens of pneumonia in this study due to the lack of availability of bacteria culture data in the LHID database. However, a recent report from The Netherlands showed that the pneumonia pathogens regarded as oropharyngeal flora (e.g., *Streptococcus pneumoniae*) were more commonly found in PPI users than in non-PPI users, whereas pathogens regarded as airborne or respiratory droplets (e.g., *Coxiella burnetii*) were less frequently found in PPI users than in non-PPI users.[18]

Table 3 Comparison of patients with chronic kidney disease and pneumonia receiving different proton pump inhibitors in Taiwan, 1998–2002 (n = 277)

Proton pump inhibitor[a]	No.	Patients with pneumonia	
		No.	%
Rabeprazole	53	12	36.36
Omeprazole	112	29	25.89
Esomeprazole	123	15	22.64
Pantoprazole	11	4	12.19
Total patients	277	53	19.13

[a] A few patients had more than one type of proton pump inhibitor use.

In this study, we found that patients receiving esomeprazole, omeprazole, and rabeprazole had a higher incidence of pneumonia than those receiving pantoprazole. This study is consistent with findings by Kirchheiner et al[19] showing that pantoprazole is less effective in lowering pH. For rabeprazole, the prevalence is 0.65% for patients with pneumonia and 0.09% for patients without pneumonia. The risk ratio of rabeprazole is even higher than other PPIs. The reason might be that rabeprazole as well as esomeprazole could achieve more rapid acid inhibition than other PPIs.[20] Therefore, repeated administration of PPIs would considerably delay gastric emptying and increase the risk of pneumonia caused by profound irreversible gastric acid suppression.[21]

Previous studies shows PPI use increases the risk of pneumonia in children and adults.[22] In our study, we found that patients older than 60 years with comorbid illness such as CVA, COPD, asthma, and diabetes mellitus had a high risk for pneumonia. This finding is compatible with another study.[2] It is difficult to explain because these comorbidities have repeatedly been associated with pneumonia with or without PPI administration. However, patients with COPD always had a high prevalence rate of GERD or peptic ulcer, especially in those who smoke.[18] PPIs cause few adverse effects with short-term use. However, it has been associated with an increased risk of pneumonia and other infections with long-term administration of PPIs.[23]

As for the dose and duration use, there was no significant difference in dose effect analysis in 30–60 DDD compared with the duration of PPI exposure. However, we observed

Table 4 Dose effect analysis of patients with chronic kidney disease who received proton pump inhibitor therapy[a]

	Patients with CKD and PPI exposure(n = 277)			
	<30 DDD	30–60 DDD	61–90 DDD	>90 DDD
	(n = 132)	(n = 82)	(n = 31)	(n = 32)
Pneumonia, n (%)	28 (21.21)	11 (13.41)	6 (19.35)	8 (25)
Crude HR	3.44**	1.98	3.07*	4.26**
(95% CI)	2.25–5.26	0.94–3.79	1.03–7.51	1.64–9.85
Adjusted HR	3.32**	1.97	2.94*	4.34**
(95% CI)	2.16–5.05	0.99–3.73	1.19–7.23	1.94–9.72

[a] The hazard ratios were adjusted for age, sex, cerebrovascular disease, acute renal failure, ischemia heart disease, chronic obstructive pulmonary disease, asthma, diabetes mellitus.
* $p < 0.05$.
** $p < 0.001$.
CI = confidence interval; CKD = chronic kidney disease; DDD = defined daily dose; HR = hazard ratio; PPI = proton pump inhibitor.

that patients receiving PPIs for <30 DDD or >90 DDD had a high risk of developing pneumonia. These interesting results were partly inconsistent with those of Sarkar et al,[24] who found that PPI therapy within 30 days was associated with an increased risk of pneumonia and were not associated with longer-term use of PPIs. Gulmez et al[3] also found that the highest odds ratio (OR) for PPI therapy started 0–7 days prior to the index date (OR, 5.0; 95% CI 2.1–11.7). After a longer term (> 84 days) of PPI therapy, OR decreased to 1.3 (95% CI, 1.2–1.4).

Nevertheless, there were some limitations in this study. First, we could not measure the drugs not claimed to the NHI because the NIHD was a secondary database. In Taiwan, PPIs could be claimed to the NIH only for the patients receiving endoscopic examination with a positive result of GERD or peptic ulcer. A large proportion of patients who refused endoscopic examination and bought PPIs by themselves from the local pharmacy could not be estimated. Second, we could not obtain the laboratory results or reports of radiographic findings of pneumonia from the claimed data from the NIHD.

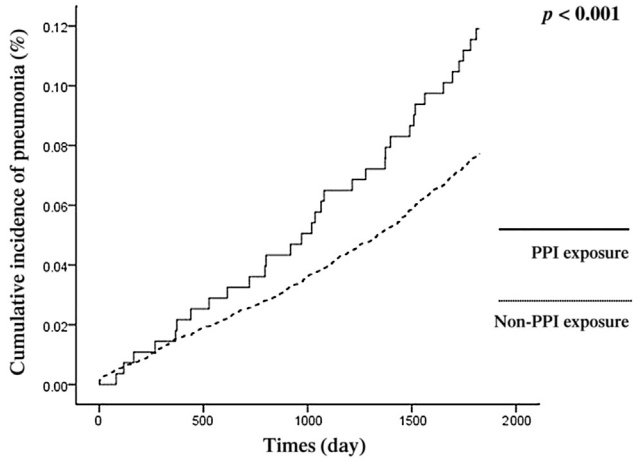

Figure 2. Kaplan–Meier curves of the occurrence of pneumonia in patients with chronic kidney disease. PPI = proton pump inhibitor.

In conclusion, the patients with CKD and PPI usage had a higher rate of pneumonia in comparison with those not using PPIs throughout the follow-up period. Therefore, PPI usage is a potential risk factor of pneumonia in patients with CKD. Although PPIs are indicated for use in patients with CKD, physicians should pay careful attention when prescribing PPIs for these patients.

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