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Incidence of *Clostridium difficile*-associated diarrhea in patients using proton pump inhibitors: A Japanese study

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ABSTRACT

Objective: The incidence of *Clostridium difficile*-associated diarrhea (CDAD) has increased in many developed countries. In addition to previous use of antimicrobials, use of proton pump inhibitors (PPIs) is thought to increase the incidence of CDAD. However, most previous studies that showed a positive relationship between PPI use and CDAD were conducted retrospectively in Western countries. We investigated whether the use of PPIs increases the incidence of CDAD in Japan. Methods: The study was carried out with all the patients admitted to the department of internal medicine of Teikyo University Hospital from April 2009 to June 2009. Clinical data were obtained from medical records. CDAD was defined as detection of CD toxin from stool samples in diarrheal patients. PPI users were defined as patients that were prescribed with PPI for more than 30 days at the detection of CD toxin. The results of *Clostridium difficile* (CD) toxin were collected until April 2011. Results: A total of 793 patients were included, and PPIs were prescribed to 489 patients (59.8%). The average age of PPI users was higher than that of PPI nonusers (68.9 vs. 63.1 years). Among the 489 PPI users, 19 patients developed CDAD, while 4 developed CDAD among the 304 PPI nonusers. The relative risk of PPI use on the incidence of CDAD was 3.20 in univariate analysis (95% confidence interval, 1.10 to 9.32, p = 0.04), although the hazard ratio in multivariate analysis was 1.23 (95% confidence interval, 0.35 to 3.83, p = 0.82). Conclusions: There was no association between CDAD occurrence and PPI use in patients in Japan.

Keywords: *Clostridium difficile*-Associated Diarrhea; Proton Pump Inhibitors; Risk Factor

1. INTRODUCTION

Clostridium difficile is a gram-positive anaerobe that causes a spectrum of diseases from asymptomatic carriage to mild diarrhea to severe pseudomembranous colitis. There has been a dramatic increase in the incidence of *C. difficile*-associated diarrhea (CDAD) in many developed countries. Development of CDAD in hospitalized patients is associated with length of hospital stay, resulting in higher health care costs [1]. The dominant risk factor is antibiotic use [2,3], but other postulated risk factors include advanced age, severe underlying illnesses [4], hospitalization [2], non-surgical gastrointestinal procedures [5], antineoplastic chemotherapy and immunosuppressant agents. In addition to these risk factors, long-term use of proton pump inhibitors (PPIs) has been suggested to be a risk factor for CDAD [6-10]. However, most previous epidemiological studies that showed a positive relationship between PPI use and CDAD were conducted retrospectively in Western countries. In this study, we investigated whether use of PPIs increases the incidence of CDAD at a single institution in Japan.

2. METHODS

2.1. Study Population

We enrolled all of the patients admitted to the Department of Internal Medicine of Teikyo University Hospital (teaching hospital, 1154 beds) in Japan from April 2009 to June 2009, and observed these patients from April 2009 to April 2011. This study design had hospital ethics committee approval; informed consent was waived.

2.2. Case Definition

PPI users were defined as patients prescribed PPIs for

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more than 30 days. CDAD was defined as detection of CD toxin from stool samples in diarrheal patients. Usage of immunosuppressants was defined as use of more than 20 mg of prednisolone for more than 30 days. Long hospital stay was defined as a case of total hospitalization for more than 30 days. Comorbid diseases were defined as: renal failure, estimated glomerular filtration rate (eGFR) <30 ml/min; diabetes mellitus, fasting blood sugar levels of 126 mg/dl, or HbA1c ≥6.1%, or past treatment history; solid tumors, radiologically or pathologically verified masses; hematological malignancy, pathologically verified leukemia or lymphoma.

2.3. Evaluation of Clinical Background Data

Clinical data were obtained from medical records, and the results of C. difficile toxin analysis were collected until April 2011. Clinical courses of the patients were retrospectively reviewed to determine the following demographic characteristics: age; gender; comorbid diseases; usage of drugs; hospital stay and occurrence of CDAD.

2.4. Statistical Analysis

The student's t-test for continuous variables and chi-squared test were used when appropriate to compare proportions. For multivariate analysis, the logistic regression analysis was used. All p values were two-sided and were considered to be statistically significant when $p < 0.05$.

3. RESULTS

3.1. Clinical Factors in PPI Users and Nonusers

A total of 793 patients were included in this study. PPIs were prescribed to 489 patients (61.6%) (**Table 1**). The average age of PPI users was higher than that of PPI nonusers (68.9 ± 13.8 vs. 63.1 ± 17.8 years, $p < 0.01$), and the proportion of male patients among PPI users was also higher than that among PPI nonusers (male/female ratio, 2.26 vs. 1.36, $p = 0.04$). Among the 487 PPI users, 19 patients developed CDAD, while 4 developed CDAD among the 304 PPI nonusers. The relative risk of PPI use on the incidence of CDAD was 3.20 (95% confidence interval, 1.10 to 9.32, $p = 0.04$). The proportion of patients with ICU stay was higher in PPI users than that of PPI nonusers (8% vs. 4%, $p = 0.03$). Multiple logistic regression analysis showed that age, sex, use of H_2 receptor antagonists, long hospital stay, and ICU stay were associated with use of PPI (**Table 2**). We could not demonstrate association between use of antibiotics, CDAD and use of PPI (**Table 2**).

Table 1. Clinical characteristics of proton pump inhibitor users and nonusers.

Categories	PPI user (n = 489)	PPI nonuser (n = 304)	p
Age (years, mean ± S.D.)	68.9 ± 13.8	63.1 ± 17.8	<0.01
Sex (male)	338	189	0.04
Cormobid diseases			
Renal failure	14	8	0.85
Diabetes	41	32	0.31
Solid tumor	32	21	0.84
Hematological malignancy	25	10	0.22
Inflammatory bowel disease	2	2	0.53
Peptic ulcer	16	7	0.43
Collagen disease	15	12	0.51
Cirrhosis	7	3	0.59
Usage of drugs			
Antibiotics (duration; days)			<0.01
<4	229	183	
4 - 14	72	50	
>14	186	71	
H_2 receptor antagonist	21	66	<0.01
Laxative	78	54	0.51
Immunosuppresant	62	34	0.53
Anticancer drug	53	34	0.88
Hospital stay			
Long stay (>30 days)	246	71	<0.01
ICU stay	40	13	0.03
CDAD	19	4	0.04

Abbreviations: PPI, proton pump inhibitor; S.D., standard deviation; ICU, intensive care unit; CDAD, *Clostoridium difficile*-associated diarrhea.

Table 2. Clinical characteristics of proton pump inhibitor users and nonusers.

Categories	HR	95% CI	p
Age (≥65 years)	1.21	1.29 - 2.51	<0.001
Sex (male)	1.71	1.22 - 2.40	0.002
Usage of drugs			
Antibiotics (duration; days)			
<4	1.00		
4 - 14	1.26	0.72 - 1.77	0.61
>14	1.00	0.58 - 1.73	0.99
H_2 receptor antagonist	0.10	0.06 - 0.18	<0.001
Hospital stay			
Long stay (>30 days)	0.19	0.12 - 0.32	<0.001
ICU stay	2.86	1.42 - 5.78	0.006
CDAD	1.23	0.35 - 3.83	0.82

Abbreviations: HR, hazard ratio; ICU,CI, confidence interval; ICU, intensive care unit; CDAD, *Clostoridium difficile*-associated diarrhea.

3.2. Incidence of CDAD during the Study Period

The cumulative incidence of CDAD during the study period is shown in **Figure 1**. The onset of CDAD in more than half patients was within 200 days after admission in both PPI users and nonusers, although there were no significant differences between the two groups (12 cases in 19 PPI users, 2 cases in 4 PPI nonusers, p = 0.62).

4. DISCUSSION

PPIs are the major treatment for gastroesophageal diseases. From American College of Gastroenterology guidelines and a review article, indications for PPI use are as follows: gastroesophageal reflux disease, with complications such as Barrett's esophagus; presence of peptic ulcer disease (PUD) in the stomach or duodenum; use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin, and at least one other risk factor (among age over 70 years, medical history or complications of PUD, untreated *Helicobacter pylori* infection with a history of PUD, and/or medical history of gastric hemorrhage or perforation); and simultaneous use of antiplatelet agents, corticosteroids, anticoagulant drugs or selective serotonin reuptake inhibitors. In Japan, approximately half of physicians did not use international guidelines [11], and the most frequently chosen drug for comedication with NSAIDs was a mucoprotective drug with an approximately equal frequency of either PPI or H_2-receptor antagonist use [12]. In this study, the proportion of PPI use was 61.6%, which was higher than that in other reports in Japan. We believe that the reason for the higher proportion of PPI use is that patients with coronary disease are aggressively treated. Craig *et al.* noted that the majority of intravenous PPI prescriptions in hospital were inappropriate, particularly when initiated for non-upper gastroesophageal bleeding indications.

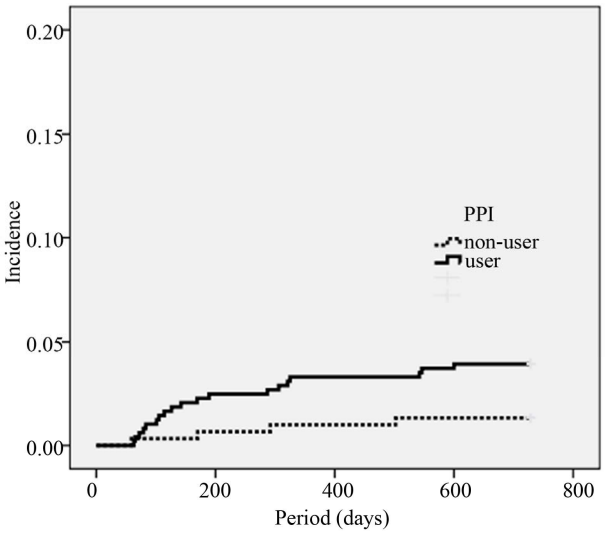

Figure 1. Cumulative incidence of *Clostridium difficile*-associated diarrhea (CDAD) during the study period. CDAD occurred continuously both in proton pump inhibitor (PPI) users and nonusers.

We did not investigate the appropriateness of PPI use in PPI users. If patients with inappropriate use of PPI were excluded from this study, the incidence of CDAD in PPI users may have been higher, as CDAD patients used PPI more frequently than non-CDAD patients, and the patients met the indications for PPI use. Among other risk factors for CDAD incidence, short duration (<4 days) of antibiotic administration was pre-dominant in PPI users and PPI nonusers in this study (47% and 62%, respectively). Stevens *et al*. reported that cumulative antibiotic exposure appears to be associated with the risk of CDAD, although the ratio of short duration of antibiotic use was 9% and 22%, respectively [13]. The high proportion of patients with short duration of antibiotic use might be due to prophylaxis for coronary intervention.

Our study showed that PPI users tended to have multiple risk factors for CDAD occurrence when compared with PPI nonusers. A previous cohort study reported that in addition to a higher incidence of CDAD, PPI users tended to stay in surgical or medical wards longer and were exposed to more than one antibiotic, which was consistent with our study [14]. However, among our data, average hospital stay in PPI users was shorter than that of PPI nonusers. We speculated this tendency because patients with coronary diseases were included among PPI users for the purpose of coronary angiography. From this finding, we believe that it is difficult to evaluate the influence of PPI usage on all hospitalized patients prospectively because more PPI users tend to receive intensive care, which can be biased towards the relationship between PPI usage and CDAD. To lessen the influence of other risk factors on CDAD occurrence by PPI usage, subanalysis of more patients may be required.

On univariate analysis, usage of PPIs was a significant risk factor for the onset of CDAD, but no such relationship was seen on multivariate analysis in this study. Several reports have noted that usage of PPI was significantly related to CDAD [6-9]. In contrast, several other reports have found no relationship between PPI usage and CDAD occurrence [15,16]; however, these studies used cohorts of elderly subjects. Age is also a risk factor for CDAD [17,18]. In our study, the average age of the patients was 66.5 years, which is consistent with other studies. Yearsley *et al.* reported that CDAD was independently associated with acid suppression therapy with PPI in the case-control study. The average age of the cases in the study was higher than that of our study, and ratio of the cases who had received antibiotics was high

(92%) [19]. Patients using PPIs tended to develop CDAD, but the statistical significance was weak. A meta-analysis conducted by Janarthan *et al*. suggested that PPIs increased the incidence of CDAD [20]. This analysis was included in the retrospective hospital-based studies and population-based case-control studies. Clinical backgrounds of the subjects influence the results in the study about association between PPIs and the incidence of CDAD.

In our study, CDAD occurred both soon after admission and later during hospitalization. Acquisition of *C. difficile* and occurrence of CDAD are considered to occur by two routes. The first route is that *C. difficile* intrinsically colonizes the host intestine and proliferates under selective pressure such as antibiotic exposure. The second route is that *C. difficile* is transmitted exogenously by the medical environment and proliferates after reductions in host microflora. We believe that CDAD mainly occurs by exogenous transmission rather than intrinsic proliferation.

In conclusion, there were trends observed between CDAD incidence and PPI use in patients with advanced age, antibiotic usage and shorter hospital stays, although statistical association between CDAD incidence and PPI use was not demonstrated.

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