Association Between Recent Use of Proton Pump Inhibitors and Nontyphoid Salmonellosis: A Nested Case-Control Study

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Background. The association between proton pump inhibitors (PPIs) and nontyphoid salmonellosis (NTS) continues to be debated. The current study was designed to determine the association between use of oral PPIs and the diagnosis of NTS.

Methods. The Taiwan National Health Insurance Research Database from 2000 to 2010 was searched for cases of NTS, defined by the International Classification of Disease, Ninth revision, Clinical Modification. A nested case-control study in hospitalized population was conducted using 4 controls for each case patient (14,736 case patients and 58,944 controls), matched for age, month and year of entry, Charlson comorbidity index score, and well-known predisposing factors for NTS, including autoimmune diseases, acquired immunodeficiency syndrome, diabetes, cirrhosis, transplantation, gastrointestinal operations or diseases, and malignancies.

Results. Persons with NTS had a higher rate of using oral PPIs within the prior year (adjusted odds ratio [OR], 2.09; 95% confidence interval [CI], 1.95–2.24; P < .001). The association was greatest for current PPI use (adjusted OR, 5.39; 95% CI, 4.79–6.06; P < .001). Although use of H2-receptor antagonists (adjusted OR, 1.84; 95% CI, 1.71–1.98), antibiotics (5.21; 4.81–5.64), steroids (3.18; 2.99–3.39), and nonsteroidal anti-inflammatory drugs (2.37; 2.26–2.48) within the 30 days were also associated with NTS, the linkage between PPI use and NTS remained significant in the subgroup without these medications.

Conclusions. The use of oral PPIs was associated with the occurrence of NTS. The risk waned with time after discontinuation.

Keywords. proton pump inhibitors; nontyphoid salmonellosis; risks.

Nontyphoid salmonellosis (NTS) is one of the most common foodborne diseases worldwide, affecting millions of persons each year [1, 2]. Usually acquired by consumption of contaminated food, especially eggs and poultry products, NTS may cause gastroenteritis, bacteremia, and focal infections [3]. Predisposing host factors include gastric hypoacidity [1], diabetes [3, 4], autoimmune diseases [1, 4], cancer [5], hepatic cirrhosis [3, gallstones [1], previous gastrointestinal surgery [6], AIDS [7, 8], and prior use of antimicrobial agents [3, 7, 8]. Proton pump inhibitors (PPIs) have also been associated with NTS [9–11]. This association is thought to be due to disruption of the natural gut microbial ecology [12] caused by inhibition of gastric acid secretion, mucosal permeability [13], and neutrophil bactericidal activity [14]. Most studies have shown an association between PPI use and susceptibility to NTS but failed to consider the confounding effects of host factors.

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that enhance susceptibility to NTS [9–11]. A recent study, which controlled for individual confounding factors by using the patients as their own control over a 12-month period, found no association between PPIs use and NTS, suggesting that predisposing factors other than PPIs may contribute to the increased rate of NTS [15].

Because of the conflicting results in the literature, problems of selection bias [16], and differences in the intervals of time between the use of a PPI and onset of NTS we believed that a large, community-based study was needed to adjust for the effect of predisposing host factors and to determine the critical interval between use of a PPI and the onset of NTS. To accomplish this we conducted a nested case-control study, matching for demographic and predisposing host factors for NTS. The Taiwan National Health Insurance Research Database (NHIRD) 2000–2010 was used to identify a large number of case patients and controls during an 11-year period.

METHODS

Data Sources
Taiwan National Health Insurance was established in 1995. It includes 98% of the population because of mandatory, universal enrollment. All of diagnoses are in accord with the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). All procedures and medications of the patients enrolled in the insurance system are recorded and stored in the NHIRD maintained by the National Health Research Institute. Two databases derived from the original NHIRD were used in this study. The first contains all beneficiaries with all infection-related ICD-9-CM codes during 1996–2010 from the original NHIRD (ID database). The other is the Longitudinal Health Insurance Database data set containing complete data for 1 000 000 randomly sampled beneficiaries during 1996–2010 from the original NHIRD. The data set used in this study consists of deidentified secondary data released to the public for research purposes. This study was approved by the institutional review board of the National Health Research Institute.

Settings and Participants
This hospitalized population-based nested case-control study consisted of patients with a diagnosis of NTS and matched controls during 2000–2010 in Taiwan. We used the database from January 1996 to December 1999 to ensure that all individuals were available for at least a 4-year follow-up before enrollment to confirm comorbid conditions [17] and matching. Case patients were selected from the ID Database if they had a diagnosis of NTS (ICD-9-CM 003.XX) and the coding date was deemed the index date. A pool of potential eligible controls with the same follow-up period as the case patient but without a previous ICD-9 code for NTS was extracted from the Longitudinal Health Insurance Database. From these eligible controls, 4 were selected as their own control over a 12-month period.

Table 1. Characteristics of Patients With Nontyphoid Salmonellosis (Case Patients) and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case Patients (n = 14 736)</th>
<th>Controls (n = 58 944)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), year</td>
<td>55.0 (19.8)</td>
<td>54.8 (19.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Male sex</td>
<td>8083 (64.9)</td>
<td>32 323 (54.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3098 (21.0)</td>
<td>12 360 (21.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>1</td>
<td>2478 (16.8)</td>
<td>9938 (16.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>2</td>
<td>2054 (13.9)</td>
<td>8335 (14.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>3</td>
<td>1680 (11.4)</td>
<td>6755 (11.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>≥4</td>
<td>5426 (36.8)</td>
<td>21 556 (36.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Risk factors for NTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>535 (3.6)</td>
<td>2140 (3.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Gallstones</td>
<td>1500 (10.2)</td>
<td>6000 (10.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4181 (28.4)</td>
<td>16 724 (28.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>954 (6.5)</td>
<td>3816 (6.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>15 (0.1)</td>
<td>60 (0.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>187 (1.3)</td>
<td>748 (1.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>2582 (17.5)</td>
<td>10 328 (17.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Hematologic or metastatic cancer</td>
<td>624 (4.2)</td>
<td>2496 (4.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>4433 (30.1)</td>
<td>16 633 (28.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0–19 100 NT$</td>
<td>3068 (20.8)</td>
<td>12 966 (22.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>19 100–42 000 NT$</td>
<td>6338 (43.0)</td>
<td>25 101 (42.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>&gt;42 000 NT$</td>
<td>897 (6.1)</td>
<td>4244 (7.2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Urbanization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>7657 (52.0)</td>
<td>32 472 (55.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Level 2</td>
<td>5650 (38.3)</td>
<td>21 052 (35.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Level 3</td>
<td>1222 (8.3)</td>
<td>4621 (7.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Level 4</td>
<td>207 (1.4)</td>
<td>799 (1.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Comorbid disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6673 (45.3)</td>
<td>25 291 (42.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4312 (29.3)</td>
<td>16 415 (27.8)</td>
<td>&gt;.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4111 (27.9)</td>
<td>17 419 (29.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Concurrent medicationb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>1966 (13.3)</td>
<td>1390 (2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NSAID</td>
<td>4770 (32.4)</td>
<td>8094 (13.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steroid</td>
<td>2572 (17.5)</td>
<td>3167 (5.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>H2-receptor antagonist</td>
<td>1680 (11.4)</td>
<td>2631 (4.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; NT$, Taiwanese new dollar; NTS, nontyphoid salmonellosis; SD, standard deviation.

*Data represent No. (%) unless otherwise indicated.

b A prescription termination date (date of dispensation plus number of days of supply) 1–30 days before or overlapping with the index date.
diseases [1, 4], AIDS [7, 8], diabetes [3, 4], gallstones [1], kidney transplantation [19], hepatic cirrhosis [3], previous gastrointestinal surgery [6], and solid tumors and hematologic or metastatic cancer [5, 8]. Medications that have been shown to be associated with NTS [7–9, 15] were included in the analysis; these included antibiotics, corticosteroids, H2-receptor antagonists, and nonsteroidal anti-inflammatory drugs (NSAIDs).

**Exposure Assessment**

We identified all oral PPIs prescribed in the year before the index date; PPIs included omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. We classified PPI use as current, recent, or past use, based on the timing of the prescription termination date (date of dispensation plus number of days of supply) and the NTS index date [20]. Current users were defined as those in whom NTS was diagnosed during the PPI prescription period. Recent and past users were defined as those in whom NTS was diagnosed 1–30 or 31–365 days after the prescription termination date, respectively.

**Statistical Analysis**

The demographic characteristics of the patients and controls were compared by means of $\chi^2$ tests for categorical variables and independent $t$ tests or Mann–Whitney $U$ tests for continuous variables. Odds ratios (ORs) were used to compare the exposure to PPIs among patients with NTS and controls. Conditional logistic regression was used to adjust for confounding. Variables with $P$ values <.05 in the univariate analysis were eligible for inclusion in the model. McFadden’s adjusted $R^2$ was used to test for the fit of our model. The Microsoft SQL Server 2008 R2 (Microsoft) was used for data linkage, processing, and sampling. All analyses were performed using SAS software, version 9.2 (SAS Institute), with 2-sided tests of significance at $P < .05$.

**RESULTS**

We identified 14,736 patients with NTS and 58,944 corresponding controls during the 11-year study period. The characteristics of the case patients and controls are shown in Table 1. Patients with NTS were more likely than controls to have had hypertension or coronary artery disease and to have received concurrent medications, including antibiotics, H2-receptor antagonists, steroids, and NSAIDs.

Table 2 shows crude and adjusted ORs for PPI use in case patients with a diagnosis of NTS, compared to controls, after
adjustment for all variables with P values < .05 in Table 1. The
P value of McFadden’s adjusted $R^2$ for the fit of our model was
.243. Both crude and adjusted ORs for PPI usage within 30 days
before the index date were significantly greater ($P < .001$) in case
patients than in controls. There was a relationship between the
time of PPI use and the onset of NTS. The adjusted OR for cur-
cent PPI use was 5.39 ($P < .001$). This dropped to 4.20 ($P < .001$)
for PPIs discontinued within 7 days before the index date and to
1.90 ($P < .001$) for PPIs discontinued 8–30 days before the index
date. The median time from termination of the PPI prescription
to diagnosis of NTS was 9 days for recent users (interquartile
range, 3–18 days) and 155 days (84–244 days) for past PPI
users. There was no significant difference in past PPI use (>30
days) between case patients and controls ($P = .86$).

Although the recent or current use of H2-receptor antagonists,
antibiotics, steroids, and NSAIDs was also associated with NTS
(all $P < .001$; Table 2), the linkage between PPI use and NTS re-
mained significant in the subgroup without use of these medica-
tions (adjusted OR, 2.34; 95% confidence interval, 2.11–2.59;
$P < .001$). Similarly, we found that the odds of having current or
recent, but not past use of PPI in patients with a diagnosis of cam-
pylolobacteriosis were significantly higher than in those without
campylobacteriosis (Supplementary Table 1). We did not find a
similar association for shigellosis (Supplementary Table 2).

**DISCUSSION**

This nested case-control study provides further evidence that PPI
use is associated with an increased risk of NTS after matching for
well-known predisposing factors. The risk of acquisition of NTS
was highest among current users and waned with time after use
of PPIs. Proton pump inhibitors reduce acid secretion by selective
inhibition of gastric hydrogen-potassium adenosine triphospha-
tase. They are currently the major drugs for treatment of gastro-
esophageal reflux and peptic ulcer diseases [21]. Thus, the
potential side effects of PPIs are of imperative concern because
of their widespread use. Many studies have shown an association
between PPIs use and enteric infections [9–11, 22]. The adjusted
relative risk of the associations ranged from 4.2 to 8.3 in case-
control studies [23]. The association between NTS and H2-receptor
antagonists found in our study and others [9, 11] also supports
the notion that acid suppression is associated with increased
risk of gastrointestinal infections.

The association between PPI use and NTS was reevaluated in a
population-based cohort study comparing the incidence rates of
NTS in PPI users and nonusers [15]. After adjusting for un-
measured confounding and eliminating the effect of time inter-
vals, the authors concluded that the risk is probably attributable
to predisposing factors among PPI users, rather than to the PPIs
themselves; the problem with the study, however, was that it
compared the incidence of NTS 12 months before and after
the use of PPIs, and this design probably diluted the immediate
effect of PPIs. It has been shown elsewhere that the effect of
PPIs on increasing susceptibility to NTS appeared within 3
months after PPI treatment ended [10]. Our study, like previous
ones [9–11, 22], still demonstrated the significant association
between the risk of NTS and PPI use. In addition, if predispos-
ing factors were the main culprits, the risk for NTS should not
have decreased with time after discontinuation of PPIs.

The strengths of the current study include the large numbers
of case patients and controls representative of the entire country
of Taiwan, the ability to carefully match for well-known predis-
posing factors, and the ability to define the interval between
receipt of a PPI and occurrence of NTS and the long-term fol-
low-up period provided by our databases. The study also had
several limitations. It was confined to inpatients, in whom mi-
crobiologic examination could be conducted more thoroughly
than outpatients. Some risk factors for NTS, such as traveling
abroad and ingestion of products containing raw eggs, were
not adjusted for. There may have been surveillance bias, because
the diagnosis of NTS might have been influenced by a history of
prior PPI use. The low incidence rate of NTS did not allow a
prospective design, and the study design may not allow to dem-
onstrate causality. PPIs could be prescribed for symptoms that
turned out to be due to NTS. There might be bias with the use of
PPIs for prophylaxis of gastrointestinal bleeding, because gas-
trointestinal bleeding and NTS share several risk factors (eg, ste-
roid use); this was not an issue in our study, however, because
the strict reimbursement policy in Taiwan requires that the use
of H2 blockers rather than oral PPIs for prophylaxis of gastro-
intestinal bleeding.

In conclusion, we found a temporal association between the
use of PPIs and increased susceptibility to NTS after matching for
predisposing factors. Healthcare providers should consider
the increased risk of NTS even within 30 days after the PPI
being discontinued.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors
should be addressed to the author.

**Notes**

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Potential conflicts of interests. T. L. C. is a medical advisor for TTY Biopharm. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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