Use of Acid-Suppressing Drugs and the Risk of Bacterial Gastroenteritis

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Background & Aims: **Gastric acid is a defense mechanism against gastrointestinal infections caused by ingested bacteria. Studies have suggested that the use of acid-suppressing drugs may increase the risk of gastroenteritis (GE).** ***Methods:*** **Patients aged 20–74 years with an episode of acute bacterial GE (n = 6414) were identified. A control group from the same study population without a diagnosis of GE (n = 50,000) was frequency-matched by age, sex, and calendar year to the case group. Unconditional logistic regression was used to calculate the adjusted relative risk (RR) of GE in patients using proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H_2RAs).** ***Results:*** **Current use of PPIs was associated with an increased risk of bacterial GE compared with nonuse, regardless of the treatment duration (RR, 2.9; 95% confidence interval [CI], 2.5–3.5), whereas no association was observed with H_2RA use (RR, 1.1; 95% CI, 0.9–1.4). Doubling the PPI dose further increased the risk of developing bacterial GE (RR, 5.0; 95% CI, 2.7–9.3). The effect of PPI use did not vary significantly with regard to treatment indication. The increased risk associated with PPI use was similar for both omeprazole (RR, 3.0; 95% CI, 2.5–3.7) and lansoprazole (RR, 2.1; 95% CI, 1.4–3.0), whereas neither cimetidine nor ranitidine showed any increased risk. *Campylobacter* (n = 4124) and *Salmonella* (n = 1885) were the 2 species most frequently responsible for GE episodes in the case group. When analyzed separately, both species reproduced the increased risk associated with PPI use and not H_2RA use. *Clostridium* GE cases were rare (n = 31).** ***Conclusions:*** **This study suggests that gastric acid suppression induced by PPIs but not H_2RAs is associated with an increased risk of *Campylobacter* and *Salmonella* GE.**

Proton pump inhibitors (PPIs) and H_2 receptor antagonists (H_2RAs) are potent drugs suppressing gastric acid secretion. Consequently, they are highly effective for treating acid-related disorders, but have raised concerns that suppression of gastric acid by these drugs will alter the bacterial flora of the upper-gastrointestinal tract and lead to complications such as malabsorption, enteric infections, and infections outside the gastrointestinal tract.

A number of recent epidemiologic studies have reported an increased risk of *Clostridium difficile* infections in hospitalized patients[1] and in the general population[2] associated with the use of gastric acid–suppressing agents. However, conflicting data have been produced on the risk of bacterial enteral infections associated with the use of acid-suppressing drugs.[3,4] A recent review concluded that further research is required to more fully quantify the risk of enteric infections associated with the use of acid-suppressing drugs.[5] The widespread use of PPIs and other gastric-suppressing agents in the general population underscores the importance of evaluating their effect on the risk of bacterial gastroenteritis in the general population. We thus assessed whether the use of gastric acid–suppressant drugs is associated with an increased risk of bacterial enteral infections, whether the risk is dose dependent, and whether there are factors that could act as modifiers of this risk.

Methods

Study Design

We conducted a nested case-control study using the General Practice Research Database. The General Practice Research Database is a population-based database in the United Kingdom where general practitioners store their practice database with clinical information on their patients including demographics, diagnoses, and free text comments, referral information, and records of all prescriptions issued by them.[6] Data on about 3 million patients are recorded systematically and sent anonymously to the Medicines Control Agency. The Medicines Control Agency collects and organizes this information to be used for research projects. An additional requirement for participating practices is recording of the indication for new courses of therapy. A modification of the Oxford Medical Information System classification system is used to code specific diagnoses, and a drug dictionary based on data from the Prescription Pricing Authority is used to code drugs. Its completeness, validity, and quality of data have been widely reported by several studies in gastrointestinal diseases.[7,8]

Study Population

We recently evaluated the risk of developing inflammatory bowel disease in patients after an episode of infectious gastroenteritis.[9] We used the same study population that comprised persons age 20–74 years of age between January 1992 and December 2001, who had been enrolled at least 2 years with the general practitioner (GP), had at least 1 year elapsed since their first computerized prescription, and were free of cancer, alcohol-related disease, inflammatory bowel disease (including specific inflammatory bowel disease therapy), previous episode of gastroenteritis, gastrointestinal infectious disease, or enteritis/colitis before start date. All study members were followed up

Abbreviations used in this paper: GE, gastroenteritis; GP, general practitioner; PPI, proton pump inhibitors; H_2RA, H_2 receptor antagonists; RR, relative risk.

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from start date until they had a recorded entry of gastroenteritis, one of the earlier-mentioned exclusion criteria, 75th birthday, death, or until December 2001, whichever came first.

Case Ascertainment

For all patients identified with a code suggesting infectious gastroenteritis (GE), computerized patient profiles free of all personal identifiers were produced and reviewed. Finally, 6414 patients were considered to have documented bacterial gastroenteritis: this required the patient to present with symptoms compatible with an episode of gastroenteritis and to have a positive stool culture for a specific bacteria (*Salmonella*, *Campylobacter*, *Shigella*, *Clostridium*, or other bacteria). We used the day of first recording of GE as the index date. A more detailed description on case ascertainment can be found in our recent study.[9]

Controls

Controls were sampled randomly from the study population so that the likelihood of being selected as a control was proportional to the person-time at risk. Specifically, a date during the study period was generated at random for each of the members of the source population. If the random date of a study member was included in his or her eligible person-time, we used his or her random date as the index date and marked that person as an eligible control. The same exclusion criteria were applied to controls as to cases. Fifty thousand controls, frequency-matched to cases by age (within 1 year), sex, and calendar year were selected randomly from the pool of eligible controls.

Definition of Variables

Exposure to PPI and H_2RA were first considered independently and categorized as follows: *current*, when the supply of the most recent prescription lasted until the index date or ended in the week before the index date based on the length of drug therapy as prescribed by the GP; *recent*, when it ended 7–90 days before the index date; *past*, when it ended 91–365 days before the index date; and *nonuse*, when there was no recorded use in the year before the index date. Then, we created a single variable encompassing the use of any acid-suppressing drug (PPI and H_2RA) with the following categories: nonuse was defined as no use of acid-suppressing drugs in the year before the index date; current single use of PPI was defined as use in the week before the index date conditional on no use of H_2RA in the month before the index date; and current single use of H_2RA was defined as use in the week before the index date conditional on no use of PPI in the month before the index date. Among current single users we studied the effect of duration, dose, and treatment indication. We evaluated the duration of use, adding the periods of consecutive prescriptions, defined as an interval of less than 2 months between 2 prescriptions. The effect of daily dose was studied in 3 categories: low, medium, and high, using the defined daily dose as a cut-off value. We also evaluated the risk among current single users of the most frequently used individual acid-suppressing drugs (omeprazole, lansoprazole, cimetidine, and ranitidine).

Exposure to other drugs such as antidiarrheics, antibiotics, antacids, and nonsteroidal anti-inflammatory drugs also was evaluated using similar time windows as those for acid-suppressing drugs. We ascertained information from the database on gastrointestinal disorders any time before the index date. Body mass index, expressed in kilograms per square meter, was calculated from recorded height and weight (weight [kg]/(height $-$)^2). Alcohol intake and smoking status were used as directly recorded by the GP on computer files.

Analysis

We computed estimates of odds ratios and 95% confidence intervals (CIs) of bacterial GE associated with current use of PPI and H_2RA compared with nonuse with unconditional logistic regression. Under our study design, the odds ratio was an unbiased estimator of the relative risk (RR). All estimates of RR were adjusted for age, sex, calendar year, and number of visits to the GP in the year before the index date. Adjustment for additional variables changed the estimates of acid-suppressing drugs by less than 10% and were not included in the final multivariate regression model. Specific subgroup analyses were performed by sex, age, and use of antidiarrheics. Finally, estimates of risk were computed according to the specific bacteria isolated in the stool culture.

Results

Selected characteristics of cases and controls are presented in Table 1. Because of the matching, cases and controls had a similar distribution of age and sex. Excessive alcohol consumers presented a greater risk than abstainers, as shown in Table 1. The risk of developing gastroenteritis was more than twice as great in summer than in the colder seasons. Leanness (body mass index $<$ 20) conferred a close to 25% reduced risk of bacterial GE compared with normal-weight individuals. Current use of antidiarrheics was associated with a greatly increased risk of GE, but the risk completely disappeared with past use. When we analyzed the effect according to treatment duration among current users, the risk was restricted mainly to antidiarrheic treatment initiated within 1 week before the recording of GE: the estimate of RR among users with a treatment duration greater than 3 months was 1.4 (95% CI, 0.8–2.6). The same pattern was observed with antibiotic use although with a much smaller increased risk. Patients treated with antibiotics for longer than 1 week presented no increased risk of GE (1.0; 95% CI, 0.8–1.3).

Table 2 shows the estimates of risk among users of PPI and H_2RA. The RR of bacterial GE comparing current use of PPI with nonuse was 2.9 (95% CI, 2.5–3.5). Individuals who had stopped taking PPIs for longer than 3 months (past users) had a similar risk to that in nonusers (RR = 1.1; 95%, 0.9–1.4). The increased risk of GE observed among PPI users was fairly constant over treatment duration. Higher doses of PPI were associated with a greater risk. We analyzed the effect of dosage regimen among users of high-dose PPIs. Users of a high dose with a once-daily regimen presented a RR of 3.2 (95% CI, 0.5–19.4), and users of a high dose with a twice-daily regimen presented a RR of 5.3 (95% CI, 2.8–10.3). Yet, it should be noted that numbers were small in the high-dose category (2 cases on a once-daily regimen and 18 on a twice-daily regimen) and consequently CIs for the dose-specific RRs were overlapping with each other. The RR when comparing high daily dose of a PPI vs low-medium was 1.9 (95% CI, 1.0–3.6). Current use of H_2RA was associated with a RR of 1.1 (95% CI, 0.9–1.4). The use of H_2RA did not present an increased risk of GE irrespective of treatment duration or daily dose.