Annals of Epidemiology 24 (2014) 286–290

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Proton-pump inhibitor use and hip fractures in men: a population-based case-control study

Annette L. Adams PhD, MPH *, Mary Helen Black PhD, Jian L. Zhang MS, Jiaxiao M. Shi PhD, Steven J. Jacobsen MD, PhD

Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena

ARTICLE INFO

Article history:
Received 31 July 2013
Accepted 2 January 2014
Available online 16 January 2014

Keywords:
Epidemiology
Pharmacoepidemiology
Proton pump inhibitor
PPI
Hip fractures

ABSTRACT

Purpose: To estimate the association between proton-pump inhibitor (PPI) use and hip fracture.
Methods: We conducted a case-control study of 6774 pairs of men aged 45 years or older, matched on age, race, and medical center. Cases sustained incident hip fractures in 1997–2006. Fracture date was index date for each case-control pair. PPI exposure was identified from electronic pharmacy records, 1991–2006. PPI use was measured as (1) ever versus never; (2) adherence; (3) duration; and (4) recentness. Omeprazole and pantoprazole were analyzed separately using conditional logistic regression, adjusted for comorbidities. Nonusers were the referent group.
Results: Eight hundred ninety-six (13.2%) cases and 713 (10.5%) controls used omeprazole before index date (matched odds ratio [OR], 1.13; 95% confidence interval [CI], 1.01–1.27). Greatest adherence (medication possession ratio > 80%) (OR, 1.33; 95% CI, 1.09–1.62), highest tertile of duration (OR, 1.23; 95% CI, 1.02–1.48), and recent use (OR, 1.22; 95% CI, 1.02–1.47) were associated with hip fracture. Six hundred ninety-four (10.2%) cases and 576 (8.5%) controls had used pantoprazole (OR, 1.10; 95% CI, 0.97–1.24). Longest duration (OR, 1.25; 95% CI, 1.02–1.53) and most recent use (OR, 1.38; 95% CI, 1.12–1.71) were associated with hip fracture. Our study suggests that PPI use and hip fractures are associated, with risk increasing with longer duration and more recent use.

Introduction

Proton-pump inhibitor (PPI) medications, introduced in 1989 and used for the treatment of gastroesophageal reflux disease, ulcers, *Helicobacter pylori*, and other gastrointestinal conditions, are among the most commonly prescribed drugs worldwide [1]. As these agents are often used to treat chronic conditions, many patients could be on these medications for extended periods. In addition, in some clinical instances, use of doses higher than the defined daily dose may be recommended for periods. Use of antisecretory medications may negatively affect bone metabolism and reduce bone mineral density via impaired calcium absorption [2] or induction of secondary hyperparathyroidism [3]. Either of these possible mechanisms of reduced bone mineral density could theoretically be amplified by the use of acid inhibitors for long durations and/or at high dosages.

Hip fractures are among the most important possible negative outcomes of reduced bone density and osteoporosis, resulting in considerable morbidity and mortality [4]. Over the past several years, a number of studies have examined the possible association between long-term use of PPIs and hip fractures in older adults. Although a small number of studies have not observed any apparent increases in hip fracture risk with the use of PPIs [5–7], several studies have demonstrated such associations [8–15], and recently published meta-analyses have also reported pooled results suggesting the presence of an association [11,16–21]. The apparent heterogeneity of results may be at least partially attributable to variations in study methodologies and handling of multiple possible confounding factors, with exposure definitions and ascertainment being particularly variable. Regardless, the question of whether PPI use and subsequent increases in hip fracture risk are associated remains open.

With an aim of providing additional information that might help resolve this question, we conducted a population-based case-control study of men enrolled in a large integrated care system to assess the possible associations of hip fracture and use of the two most commonly prescribed PPIs, omeprazole and pantoprazole, using pharmacy dispense records to measure exposure in three

* Corresponding author. Department of Research and Evaluation, Kaiser Permanente Southern California, 100 Los Robles, 2nd Floor, Pasadena, CA 91101. Tel.: +1 626 564 3916; fax: +1 626 564 3409.
E-mail address: Annette.L.Adams@kp.org (A.L. Adams).

1047-2797/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.annepidem.2014.01.004

different ways: prescription adherence, duration of use, and recentness of use.

Methods

Study design, setting, subjects

This population-based case-control study was conducted within the Southern California region of Kaiser Permanente (KPSC), using methods that have been previously described [22]. KPSC is a large integrated health care system serving a racially, ethnically, and socioeconomically diverse population of approximately 3.5 million people. Based on geographic proximity, all KPSC members are assigned to one of the 14 medical centers and also receive outpatient services from among approximately 200 facilities throughout the region. All health care encounters across all care settings (inpatient, outpatient, emergency department) are documented in the electronic health record (EHR). The EHR includes information on diagnoses associated with each encounter, laboratory results, and all dispensed pharmacy prescriptions. All KPSC members are assigned a unique medical record number for life, which allows for linkage of patient records over time, even bridging periods of nonenrollment.

Case subjects were men, aged 45 years or older, who sustained an incident hip fracture during the study period, 1997–2006. Hip fractures were identified from electronic medical records and claims using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes 820–820.9. For each subject identified as having a possible qualifying fracture, the EHR for all available preceding years, including years before the study period, was examined for any indication of a previous hip fracture. Case subjects with any evidence of prior fracture preceding the study period were excluded to minimize confounding by factors related to recurrent hip fracture. For each case subject, the date of hip fracture was defined as the index date. Control subjects were also men from the same underlying population, aged 45 years or older, who had no evidence of hip fracture in the EHR. Case and control subjects were optimally matched [23] 1:1 on age, race/ethnicity, medical center, and membership in the health plan on the fracture/index date. Each control subject was assigned the same index date as their matched case subject.

Measurements

The exposure of interest, PPI use, was ascertained from pharmacy dispensing records from 1991, when the electronic pharmacy files were instituted, through 2006, the end of the study period. We collected information on date of the earliest identified prescription, and for each prescription dispensed, we collected date, amount of individual dose, amount dispensed, number of total doses, and the total dose dispensed. PPI use was then operationalized in four different ways: (1) ever used versus never used; (2) adherence; (3) duration of use; and (4) recentness of use. Adherence was summarized with the medication possession ratio (MPR) [24,25], which is calculated as the total number of days supplied divided by the total number of days between first and last prescription. Duration of use was defined as the total day supply of medication dispensed before the index date. Recentness of use was defined as the time in days between the last use and the index date. Last use was considered to be the time at which the last dispensed medication supply would have been expected to be exhausted. For example, if a 30-day supply was the last dispensed, then the last use date would be the dispense date plus 30 days.

We also collected information on other comorbid conditions for each subject, looking back in the medical record for 2 years before index. Overall comorbid burden was summarized using the Deyo adaptation [26] of the Charlson Index [27]. Overall comorbid burden and the specific presence of diabetes mellitus and/or hypertension were considered as potential confounders.

Statistical analysis

Case and control subjects were described with regard to age, race/ethnicity, comorbidity burden, and PPI use characteristics. For descriptive purposes, age and Charlson scores were categorized. Categorical variables were summarized with counts and proportions. Continuous variables were summarized with medians and interquartile ranges (IQR). Associations between each measure of PPI use and hip fracture were estimated from conditional logistic regression models to account for the 1:1 matching of case and control subjects and were expressed using odds ratios (ORs) and 95% confidence intervals (CIs). Omeprazole and pantoprazole were analyzed separately. Subjects who used both omeprazole and pantoprazole at any time during the study period contributed to both analyses, with adherence, duration, and recentness of use calculated separately for each of the medications. Duration and recentness of use were each categorized into tertiles of exposure, with no exposure as the referent group. Adherence was categorized as 80% or more or less than 80%, again with no exposure as the referent group. All final models were adjusted for continuous Charlson score. Finally, using the point estimates for ever versus never use of each medication, we calculated estimates of etiologic fractions [28], the proportions of hip fractures among the exposed subjects attributable to exposure to omeprazole or pantoprazole.

Results

Over the 10-year study period, 6774 men were identified as having an incident hip fracture and were matched to 6774 men without evidence of fracture in the EHR, for a total study sample of 13,548 men. Approximately 69% of men were aged older than 70 years (Table 1). The majority of the study group was non-Hispanic white (70%). Hip fracture cases tended to have greater overall burden of comorbidity than control subjects, with 51% of case subjects having a Charlson Index score 3 or higher compared with 36% of control subjects ($P < .001$).

Omeprazole was used by 1609 (11.9%) of the men overall—896 case (13.2%) and 713 control (10.5%) subjects. Median duration of use was 150 days (IQR 50–485 days), and 468 men (29.1%) had an MPR 80% or higher. The unadjusted odds ratio between any omeprazole use and subsequent hip fracture was 1.31 (95% CI, 1.18–1.46). After adjustment for comorbidities, the matched OR was 1.13 (95% CI, 1.01–1.27) (Table 2). Among medication users, greater medication adherence, defined as an MPR of 80% or higher, was associated with an increased risk of hip fracture (OR, 1.33; 95% CI, 1.09–1.62), after adjustment for comorbidities. Exposure to omeprazole with adherence of less than 80% was not significantly associated with any increased risk of hip fracture after controlling for comorbid conditions. Both the intermediate and longest duration of use tertiles were associated with very similar increased risk of hip fracture. The matched OR for intermediate duration of use (75–329 days) was 1.21 (95% CI, 1.01–1.46) and for the longest duration of use (≥330 days) was 1.23 (95% CI, 1.02–1.48) (value of *P* for trend, .006). Recentness of use, less than 7 days before index date, was associated with at 22% increase in risk of hip fracture (OR, 1.22; 95% CI, 1.02–1.47). Furthermore, risk of hip fracture increased monotonically with more recent use (value of *P* for trend, .01), although only OR estimates for the tertile characterizing the most recent use achieved statistical significance. Among subjects ever