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Use of proton pump inhibitors and risk of fragility hip fracture in a Mediterranean region

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ABSTRACT

Objective: To determine whether there is an increased risk of hip fracture associated with the use of proton pump inhibitors in a Mediterranean area after adjusting for other potential risk factors.
Methods: Retrospective multicenter case–control study carried out in 6 primary health care centers in Catalonia, Spain. Cases were patients aged 50 years and over with a fragility hip fracture registered between January 2007 and December 2010, matched with 2 controls by sex and age. Data collected: use of proton pump inhibitors (type, dosage) in the 5 years previous to the hip fracture, socio-demographic data, body mass index, alcohol and tobacco consumption as well as health conditions and drugs associated with an increase risk of fragility hip fracture.
Results: 358 cases were matched with 698 controls. The mean age was 82 years old in both groups. Women represented 77.1% in the case group and 76.9% in the control group. Crude association between proton pump inhibitors and hip fracture was 1.44 (95% CI, 1.09–1.89) and adjusted OR was 1.24 (95% CI, 0.93–1.65). No association was found with the continuous or discontinuous use of proton pump inhibitors, OR 1.17 (95% CI, 0.77–1.79), and OR of 1.16 (95% CI, 0.85–1.60) respectively. No association was found when restricting the analysis by sex, OR of 1.19 (95% CI, 0.27–5.14) or by age, younger or older than 80 years, OR of 0.72 (95% CI, 0.24–2.15).
Conclusion: The use of proton pump inhibitors was not associated with an increased risk of hip fracture after adjusting for other risk factors in a Mediterranean area. This result suggests the existence of protective environmental factors linked to this southern area of Europe that eventually could compensate for the potential harm produced by proton pump inhibitors.

Introduction

Hip fractures are considered not only a major medical health problem but also a social, and economic issue for health care systems of developed countries. Up to 30% of the patients with hip fracture will die during the first 6 months [1], and its costs are expected to increase more than 48% by the year 2025 [2]. Incidence of hip fracture varies depending on the country, ranging from 975.3 per 100.000 persons per year in the United States [3] to 511 per 100.000 persons per year in Spain [4], and it is expected to increase due to the aging population and an increase in chronic diseases. As a consequence of this, in recent years many research initiatives have been initiated to identify potential risk factors of fragility hip fracture [5], such as certain medical conditions, a tendency to fall [6], and the use of proton pump inhibitors (PPI) [7–10].

The PPI are used as first line treatment for intestinal tract disorders or for the prevention of the gastric injuries induced by non-steroidal anti-inflammatory drugs (NSAIDs). In the past few years there has been an increasing concern about the possible over-prescribing of these medications [11] and their possible side effects [12].

The relationship between hip fracture and the use of PPI has been studied in recent years with uneven results. The first publication on this topic found an increased risk of hip fracture with the consumption of PPI that was stronger with the length of the exposure [7–10]. On the other hand, more recent studies have not found a clear association between use of PPI and risk of hip fracture [13–16], reflecting a contrast with that which had been previously published.

Abbreviations: PPI, Proton pump inhibitor; NSAIDs, Non-steroidal anti-inflammatory drugs; H2 RA, H2 receptor antagonist; SSRI, Selective serotonin reuptake inhibitor antidepressants; BMI, Body mass index.

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Considering that most of the studies have been carried out in Nordic or Anglo-Saxon countries with a higher prevalence of hip fracture, the aim of this study is to determine whether there is an increase of risk of hip fracture with the intake of PPI in a Mediterranean area, adjusting for other risk factors.

Methods

Study design and data source

We conducted a retrospective multi-center case–control study in six primary health care centers in Catalonia, Spain. All of the clinical information and the prescriptions were obtained from the computerized medical records of each of the primary care centers participating in this study.

Identification of the cases and controls

Cases were defined as patients aged 50 years and over with a diagnosis of fragility hip fracture, registered and visited in any of the six centers participating in the study between January 2007 and December 2010.

Fragility hip fracture was defined as a fracture produced by a fall no higher than a person's height, considering this a low trauma fracture. All patients with a fracture caused by a neoplastic process were excluded. The following diagnoses were identified in the medical records using the International Disease Classification (ICD-9): hip fracture (ICD-9: 820.8), femur fracture (ICD-9: 821.0), femoral neck fracture (ICD-9: 820.8), fracture (ICD-9: 829.0) and hip prosthesis (ICD-9: 84.47). If it happened that two fragility fractures were detected in the period of study, the oldest one was selected, naming it: "Index hip fracture". Cases were matched by sex and age with two controls.

Controls were defined as patients aged 50 years and over without a diagnosis of hip fracture registered in their medical record at any previous time. Their age was within 2 years of their matched case at the moment of the "index hip fracture".

The selection of cases, matching them with controls and data registration was done separately in each of the primary care centers using the same questionnaire and the same protocol. All the data was collected through a questionnaire-designed ad-hoc. The creation of the database, the data entry into the database and the statistical analysis were centralized in one of the centers to avoid inter-observer variation.

Determination of exposure

All the prescriptions of PPI, in the 5 years previous to the index hip fracture of the case were registered in the questionnaire. The PPI registered were: esomeprazole (20 and 40 mg), lansoprazole (15 and 30 mg), omeprazole (10, 20 and 40 mg), pantoprazole (20 and 40 mg), and rabeprazole (10 and 20 mg).

A case was considered to be exposed when there was at least one prescription of PPI in the 5 years previous to the index hip fracture. It was assumed that each prescription equated to a monthly medical treatment. The number of prescriptions for every dose of PPI was counted and registered. The date of the first prescription of PPI during the study period was also registered separately in order to calculate the continuous or discontinuous exposure.

It was considered to be continuous exposure if the number of prescriptions registered, between the date of the first prescription of PPI and the date of the index hip fracture of the case, equaled or exceeded the number of months between these two dates. Discontinuous exposure was defined as having a number of prescriptions of PPI inferior to the number of months between the first PPI and the date of the index hip fracture of the case, without being able to determine the pattern of consumption more accurately.

Variables

All the relevant clinical and therapeutic information registered in the medical records in the 5 years previous to the index hip fracture was collected.

The main variable registered was the index hip fracture of the case. Any hip fracture registered in the medical record previously to the study period was also registered separately.

Other variables registered were: body mass index (BMI), tobacco and alcohol consumption, diagnosis of hypertension, diabetes, rheumatoid arthritis, ischemic heart disease, chronic obstructive pulmonary disease, epilepsy, depression, schizophrenia, dementia, solid organ transplant, osteoporosis, substance abuse, visual or hearing impairment, unsteadiness, gastrectomy, pernicious anemia or history of fragility fracture other than the hip.

The following medication was also registered: anti-anginal medication, anticoagulant, androgen deprivation therapy, calcium and vitamin D, non-steroidal anti-inflammatory drugs (NSAIDs), neuroleptics, lithium, benzodiazepines, thiazidic and non thiazidic diuretics, beta-blockers, corticoids, thyroid hormone, oral antidiabetic, insulin, statins, osteoporosis treatment, selective serotonin reuptake inhibitor antidepressants (SSRI) and non SSRI antidepressants. It was considered that a patient had been exposed to any of these drugs if there was at least one prescription registered in their medical record in the four months previous to the date of the index hip fracture. In the case of corticoids, they were registered only if the patient had consumed at least 5 mg per day for 3 months.

Exclusions

A total of 377 hip fractures met the inclusion criteria, although 19 of them were excluded due to missing information in the questionnaires. When a case was excluded, the matching controls were also excluded, if a control was excluded the case was kept, and the statistical analysis was adjusted.

Sample size and statistical analysis

Assuming an estimated proportion of controls exposed to PPI of 45%, matching each case with 2 controls and an alpha error of 0.05, the required sample size calculated to detect an odds ratio of at least 1.5 with a power of 80% was 303 cases and 606 controls (Granmo 7.11 [software]). Means, standard deviation, percentage and 95% confidence intervals were used to describe the continuous and categorical variables. Chi-square test for categorical variables and t-test for continuous variables were used to compare cases with controls. Conditional logistic regression for matched case–control groups was used to calculate associated odds ratio to PPI exposure. The multivariate model was fitted adjusting for some co-variables identified either by their clinical relevance or by their statistical relevance as a result of bivariate analysis. A p value of less than 0.05 was considered to be statistically significant. All statistical analyses were done with STATA statistical software (Version 9.2).

Results

Baseline results

The analysis was based on 358 cases that were matched with 698 controls. Baseline characteristics of cases and controls are shown in Table 1. The mean age of the population studied was 82 years, standard deviation of 8.8 years (ranging from 49.9 to 99.6 years), and the median (P50) of cases and controls was 83.58 and 83.52 respectively, without finding statistical differences between cases and controls. The majority of cases and controls were women, with no statistical difference between groups ($p = 0.95$) and 8% of the cases had had a hip fracture