Analgesic Use and Risk for Acute Coronary Events in Patients With Osteoarthritis: A Population-based, Nested Case–control Study

Caridad Pontes, MD, PhD[1,2]; Josep Ramon Marsal, MStat[3,4]; Josep Maria Elorza, MD[5,6]; Maria Aragón, CE[5]; Daniel Prieto-Alhambra, MD, PhD[7,8]; and Rosa Morros, MD, PhD[1,5]

[1]Departament de Farmacologia, de Terapèutica i de Toxicologia, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Hospital de Sabadell, Institut Universitari Parc Taulí. Sabadell, Spain; [3]Unitat de Suport a la Recerca de Lleida, IDIAP Jordi Gol, Lleida, Spain; [4]Unitat d'Epidemiologia del Servei de Cardiologia, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]Institut d'Investigació d'Atenció Primària Jordi Gol, Barcelona, Spain; [6]CAP Ripollet, Servei d'Atenció Primària Vallés Occidental, Direcció d'Atenció Primària Metropolitana Nord, Institut Català de la Salut; Barcelona, Spain; [7]URFOA-IMIM and RETICEF, Internal Medicine, Parc de Salut Mar-Instituto Carlos III, Barcelona, Spain; and [8]Musculoskeletal Epidemiology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

ABSTRACT

Purpose: Recent controversies on the safety profiles of opioids and paracetamol (acetaminophen) have led to changes in clinical guidance on osteoarthritis (OA) management. We studied the existing association between the use of different OA drug therapies and the risk for acute coronary events.

Methods: A cohort of patients with clinically diagnosed OA (according to ICD-10 codes) was identified in the SIDIAP database. Within the cohort, cases with incident acute coronary events (acute myocardial infarction or unstable angina) between 2008 and 2012 were identified using ICD-10 codes and data from hospital admission. Controls were matched 3:1 to acute coronary event–free patients matched by sex, age (±5 years), geographic area, and years since OA diagnosis (±2 years). Linked pharmacy dispensation data were used for assessing exposure to drug therapies. Multivariate conditional logistic regression models were fitted to estimate adjusted odds ratios of acute coronary events.

Findings: Totals of 5663 cases and 16,989 controls were studied. Previous morbidity and cardiovascular risk were higher in cases than in controls, with no significant differences in type or number of joints with OA. Multivariate adjusted analyses showed increased risks (odds ratio; 95% CI) related to the use of diclofenac (1.16; 1.06–1.27), naproxen (1.25; 1.04–1.48), and opioid analgesics (1.13; 1.03–1.24). No significant associations were observed with cyclooxygenase-2 selective NSAIDs, topical NSAIDs, glucosamine, chondroitin sulfate, paracetamol, or metamizole.

Implications: In patients with clinically diagnosed OA, the use of nonselective NSAIDs or opioid analgesics is associated with an increased risk for acute coronary events. These risks should be considered when selecting treatments of OA in patients at high cardiovascular risk. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: drug therapy, electronic health records, myocardial infarction, osteoarthritis, unstable angina.

Data from this study were presented as an oral communication at the Annual Congress of the European League Against Rheumatism (Rome, Italy; 2015), as a poster communication at the XXVII Congress of the Sociedad Española de Farmacología Clínica (Seville, Spain; 2014), and at the 12th Congress of the European Association for Clinical Pharmacology and Therapeutics (Madrid, Spain; 2015).

Accepted for publication December 14, 2017.
https://doi.org/10.1016/j.clinthera.2017.12.011
0149-2918/$ - see front matter

INTRODUCTION

Osteoarthritis (OA) is the most prevalent rheumatic disease in the elderly population and is associated with a greater risk for mortality than in the general population.[1–6] In a recent British study conducted in primary care, a 70% increased risk (standardized mortality ratio [95% CI], 1.71 [1.49–1.98]) was reported, with walking disability identified as major risk factor, together with a history of diabetes, cancer, and/or cardiovascular disease.[7]

After the description of an increased cardiovascular risk with the use of cyclooxygenase (COX)-2 selective NSAIDs in clinical trials,[8,9] an increased cardiovascular risk among users of nonselective NSAIDs was also reported.[10] A recent meta-analysis of data from 31 clinical trials concluded that the use of various NSAIDs, both COX-2 selective and not, was associated with a >30% increased cardiovascular risk.[11] The use of alternative therapies such as paracetamol (acetaminophen) and opioid analgesics have also been associated with cardiovascular, gastrointestinal, and/or skeletal adverse events, leading to modifications of existing guidelines.[12]

The prevalence of NSAID use in the general population in Spain, excluding over-the-counter use, is <40%,[13,14] and this figure increases to >60% in the population with OA.[15,16] According to the Spanish Society of Rheumatology, 10% of Spain's population has knee pain suggestive of OA, and 6% report hand OA.[17] The baseline cardiovascular risk in the Mediterranean population is known to be different from that in northern European countries but is similarly modified by the use of analgesic drugs.[14]

A number of risk-management recommendations and interventions aimed at reducing the risks associated with the use of prescription NSAIDs have been implemented in Spain, and also at the regional level in Catalonia in the past decade.[18] Also, the publication of several regulatory alerts on NSAID use may have affected clinical practice with regard to not only drug selection but also the dosing and duration of treatments.[13] These effects may have modified the risk at the population level, as the uptake of information and interventions might have affected risk.

To assess the risk for acute coronary events related to the use of various drugs commonly used for the treatment of OA in our setting, we conducted a nested case–control study within a cohort of patients with clinically diagnosed OA in Catalonia, Spain.

MATERIALS AND METHODS

Data Source

We obtained data from electronic medical records from the SIDIAP database (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria [Information System for the Development of Research in Primary Care]),[19] the data from which have been shown to be suitable for the study of cardiovascular diseases.[20] This database contains longitudinal data (2006–present) on demographics, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10)-coded health problems, clinical visits to primary care centers, and results of laboratory testing obtained from the computerized medical records of 274 primary care centers in Catalonia, covering a population of >5.8 million patients (>80% of the population of Catalonia). The billing records for pharmacy drug dispensation of Catalonia's Health System (Servei Català de la Salut; CATSALUT) were linked to the medical records, including information on product codes according to the Anatomical Therapeutic Chemical Classification System, number of defined daily doses (DDDs) dispensed, dosing regimens, and the strengths of pharmaceutical formulations dispensed. This pharmacy drug-dispensation database includes only data on reimbursed drugs dispensed from prescriptions, so over-the-counter drugs could not be captured. Information on hospital admissions was obtained from the oficial regional CATSALUT data base (Conjunt Minim Bàsic de Dades a l'Alta Hospitalaria; CMBD) using a trusted third-party deterministic linkage system to maintain data confidentiality and protection. This third party has no access to clinical information but only to codes and identification numbers.[21] Data from SIDIAP are anonymized, so it is not possible to re-identify individuals.

Ethical Considerations

The study protocol was approved by the independent ethics committee of the Institut d'Investigació Primària Jordi Gol (Barcelona, Spain) before any data extraction.