Use of Oral Bisphosphonates and the Risk of Aseptic Osteonecrosis: A Nested Case-Control Study

MAHYAR ETMINAN, KEVIN AMINZADEH, IAN R. MATTHEW, and JAMES M. BROPHY

ABSTRACT. ***Objective.*** To determine whether use of oral bisphosphonates is associated with an increased risk of aseptic osteonecrosis (AON) among a cohort of elderly cardiovascular patients.

Methods. We conducted a nested case-control study within a previously defined cardiovascular cohort of elderly Quebec patients using linked administrative health databases. Cases were defined as those with the diagnosis of hospitalization secondary to AON at a nonspecified site. For each case, 10 controls were randomly selected and matched to the cases by age, calendar time, and length of followup. The main outcome measure was the risk ratio (RR) of AON among ever-users of oral bisphosphonates compared to that among nonusers. As a quality measure, RR for AON among users of statin and angiotensin-converting enzyme inhibitors (ACE-I) compared to nonusers were also calculated.

Results. The initial cohort consisted of 87,837 subjects. In the primary analysis, the adjusted RR for AON among bisphosphonate users was 2.87 (95% CI 1.71–5.05). The adjusted RR for alendronate, etidronate, and risedronate were 2.87 (95% CI 1.46–5.67), 2.43 (95% CI 1.05–5.62), and 3.34 (95% CI 1.04–10.67), respectively. There were no significant differences in RR for AON among current users (most recent drug exposure within 90 days of diagnosis) and past users (drug exposure between 91 and 365 days before diagnosis) of bisphosphonates. The adjusted RR for both statins and ACE-I were 0.79 (95% CI 0.49–1.07) and 1.16 (95% CI 0.79–1.70), respectively.

Conclusion. In this cohort of elderly cardiovascular patients, an association was observed between oral bisphosphonate use and aseptic osteonecrosis. Further research into this putative association is required. (First Release Jan 15 2008; J Rheumatol 2008;35:691–5)

Key Indexing Terms:
OSTEONECROSIS JAW NECROSIS BISPHOSPHONATES COHORT STUDY

Bisphosphonates are frequently prescribed for the prevention of osteoporotic fractures and management of both Paget's disease and bony metastasis in different types of cancer. Bisphosphonates function by inhibiting osteoclastic bone resorption[1]. In 2004, 55 million prescriptions for bisphosphonates were written in the United States[2]. Recent reports have linked bisphosphonate use to osteonecrosis, specifically osteonecrosis of the jaw (ONJ)[3-5], a serious condition that may lead to chronic pain, dysfunction, and disfigurement. The pathophysiology of this condition is unknown but is believed to be secondary to bisphosphonates' ability to inhibit bone turnover[6,7].

The evidence for the putative association between bisphosphonate use, generally by intravenous administration, and ONJ is limited to published case reports and case series of ONJ[3,4], with only a few isolated reports of oral bisphosphonate use[8,9]. In 2006, 170 worldwide cases of ONJ with alendronate were reported to the manufacturer[10]. Almost all reported cases of bisphosphonate-associated osteonecrosis have involved the jaw, with the exception of one publication of osteonecrosis occurring in the auditory canal[11]. The extent to which bisphosphonate use may be associated with osteonecrosis at any site has not been fully described. We investigated the risk of nonspecific aseptic osteonecrosis (AON) and bisphosphonate use by conducting a pharmacoepidemiologic study among elderly residents in the province of Quebec, Canada.

MATERIALS AND METHODS

Data source. The data for this study were obtained from the computerized administrative health insurance and vital statistics databases of the province of Quebec. These databases were developed as a result of the universal healthcare programs offered to Quebec residents. Data sources for this study included: (1) the beneficiary database, managed by the Régie de l'Assurance-Maladie du Québec (RAMQ), providing sociodemographic information and dates of coverage; (2) the prescription drugs database, which contained information on all outpatient prescriptions dispensed to residents 65 years of age

From the Center for Clinical Epidemiology and Evaluation, Vancouver General Hospital; Eagle Creek Dental Center; Department of Oral and Maxillofacial Surgery, University of British Columbia, Vancouver, BC; and the Department of Medicine, McGill University and University of Montreal, Montreal, Quebec, Canada.

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M. Etminan, PharmD, MSc, Center for Clinical Epidemiology and Evaluation, Vancouver General Hospital; K. Aminzadeh, DDS, Eagle Creek Dental Center; I.R. Matthew, PhD, MDentSc, BDS, FDSRCS (Eng & Ed), Department of Oral and Maxillofacial Surgery, University of British Columbia; J.M. Brophy, MD, PhD, FRCPC, Department of Medicine, McGill University and University of Montreal.

Address reprint requests to Dr. M. Etminan, Center for Clinical Epidemiology and Evaluation, Vancouver General Hospital, 800 West 12th Avenue, Vancouver, British Columbia V7L 1M1, Canada.
E-mail: metminan@shaw.ca

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and older (prescription drug use for those younger than 65 is not complete), including drug name, strength, quantity, days supplied, and dispensing date; (3) the hospitalizations database, which provided information on all hospitalizations, including date of admission and discharge, a primary diagnosis, and up to 15 secondary diagnoses coded according to International Classification of Diseases, 9th Revision (ICD-9) standards, and an indicator of hospital mortality when applicable; and (4) the vital statistics database, which provided information on all deaths, including date and cause. Each resident is represented in these databases by an encrypted unique identifier, thus enabling record linkage at the level of the individual. These databases have been previously validated[12,13] and extensively used in epidemiologic research[14,15]. Approval for access to the study data was provided by the ethics board of Québec (Commission d'accès à l'information du Québec) and the Royal Victoria Hospital, McGill University.

Cohort definition. This is a retrospective cohort study with a time-matched case-control analysis[16]. We used a previously constructed database of Quebec seniors (65 years or older) who had undergone either a diagnostic (coronary angiogram) or therapeutic (percutaneous coronary angioplasty, coronary artery bypass grafting, or pacemaker implant) cardiac intervention from April 1995 to December 2002[14]. Cohort entry was defined as the date of the first diagnostic or therapeutic cardiac intervention. Cohort members were followed to: (1) the termination of study period; (2) death; or (3) termination of the health insurance coverage. This cohort has been used for various pharmacoepidemiologic studies[14,15,17].

Cases and controls. Within the cohort we conducted a nested case-control analysis. Cases were defined as hospitalization secondary to AON at any nonspecified site (ICD-9 code 733.4). The date of the first diagnosis was designated as the index date. For each case, 10 controls were randomly selected from the cohort. Controls were matched to the cases by age, calendar time, and length of followup.

Exposure assessment. In light of the possible use of bisphosphonates in the treatment of avascular necrosis of the hip[18], we identified only bisphosphonate prescriptions occurring in the 1-year prior to the index date. Since only outpatient medications are covered under the Quebec universal drug plan, only oral bisphosphonates were considered, and included alendronate, etidronate, and risedronate. Current users were defined as those who received at least one prescription for a bisphosphonate within 90 days of the index date. Past users were defined as those who used a bisphosphonate prescription earlier than 90 days. Ever-users in the last year included both current and past users. Time to diagnosis was calculated as the number of days from the first bisphosphonate prescription to the index date. To reduce the possibility of a systematic error, we also examined the relationship of AON to 2 classes of cardiovascular drugs: (1) 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (also known as statins); and (2) angiotensin-converting enzyme inhibitors (ACE-I) not suspected to be associated to this condition. In order to examine the effect of persistence to bisphosphonate therapy on the risk of AON, we stratified the risk of AON among those receiving greater than or less than the median number of prescriptions during the year prior to the index date.

Statistical analysis. The risk in the exposed groups (bisphosphonates as well as statins and ACE-I) was compared to the risk of those not taking the drugs (reference group). We used conditional logistic regression to compute adjusted risk ratios (RR). In the logistic model, we controlled for potential confounders including sex, comorbidity (measured as the total number of prescription drugs used prior to the index date[19]), history of fractures, coronary artery bypass graft surgery (CABG), malignancies including breast cancer, lung cancer, prostate cancer, multiple myeloma, lymphoma and leukemia, use of medications such as oral corticosteroids and diabetic medications, and dental procedures (including dental extractions, dental implant placement, periodontal surgery, and inflammatory dental disease). All analyses were done using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Our initial cohort consisted of 87,837 subjects. There were 196 cases of AON, whose clinical characteristics are shown in Table 1 along with the 1960 matched controls. The overall incidence of AON in this cohort was 267 per million person-years. There were more women than men among the cases; also, the patients had higher comorbidity as well as a higher percentage of corticosteroid use and a lower percentage of diabetic medication use (Table 1). The crude unadjusted RR are presented in Table 2. After controlling for covariates, the adjusted RR for ever-users (all 3 drugs combined) was 2.87 [95% confidence interval (CI) 1.71–5.05] (Table 2). The adjusted RR for alendronate, etidronate, and risedronate were 2.87 (95% CI 1.46–5.67), 2.43 (95% CI 1.05–5.62), and 3.34 (95% CI 1.04–10.67), respectively. For current users, the adjusted RR for bisphosphonate use was 3.14 (95% CI 1.68–5.88). The adjusted RR for current users of alendronate, etidronate, and risedronate were 3.27 (95% CI 1.52–7.05), 1.68 (95% CI 0.46–6.2), and 3.50 (95% CI 0.90–13.60), respectively. The adjusted RR for AON among statin and ACE-I users were 0.79 (95% CI 0.49–1.07) and 1.17 (95% CI 0.75–1.82), respectively, when compared to nonusers.

Combined past users of all 3 drugs also had an elevated risk of 2.52 (95% CI 1.01–6.26) (Table 2). Among past users of either statins or ACE-I, no association was again identified [RR 0.49 (95% CI 0.24–1.00), RR 1.15 (95% CI 0.66–1.99), respectively]. The RR for current and past bisphosphonate users were not statistically different. The average time from the first bisphosphonate medication to the first diagnosis of AON for ever-bisphosphonate use was 740 days (± 650).

Among the cases, the median number of bisphosphonate prescriptions during the year prior to the index date was 10. The adjusted RR for those using greater and less than 10 prescriptions in the year prior to the index were 4.94 (95% CI 2.08–11.72) and 2.11 (95% CI 0.90–4.99), respectively (p = 0.15 for the comparison).

DISCUSSION

The results of our study demonstrate that bisphosphonate use

Table 1. Characteristics of cases and controls.

Characteristic	Cases	Controls
Number	196	1960
Age, yrs (mean ± SD)	75.1 ± 5.8	75.8 ± 5.3
Followup, yrs (mean ± SD)	5.2 ± 3.4	5.3 ± 3.5
Sex (% female)	55.6	41.1
Comorbidities		
No. of prescription drugs*	65.3	60.0
Use of oral corticosteroids, %	18.4	5.6
Use of diabetic drugs, %	11.7	13.3
Cancer, %	3.1	1.9
Inflammatory dental conditions, %	0.0	0.1
CABG, %	30.1	37.0
Fractures, %	1.5	1.0

* computed as the total number of prescriptions in the year prior to index, CABG: coronary artery bypass graft surgery.

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Table 2. Crude and adjusted rate ratios of bisphosphonate use and aseptic osteonecrosis (all sites).

	Cases	Controls	Crude RR	Adjusted RR†, Rate Ratio (95% CI)
No. of subjects	196	1960		
All bisphosphonates, %				
Ever use	14.8	3.8	4.61 (2.87–7.81)	2.87 (1.71–5.05)
Current use	11.2	2.5	5.35 (3.09–9.26)	3.14 (1.68–5.88)
Past use	3.5	1.2	3.24 (1.36–7.72)	2.52 (1.01–6.26)
Alendronate, %				
Ever use	9.1	1.9	5.26 (2.89–9.60)	2.87 (1.46–5.67)
Current use	7.6	1.3	6.51 (3.33–12.73)	3.27 (1.52–7.05)
Past use	1.5	0.6	2.67 (0.74–9.58)	1.98 (0.58–7.29)
Etidronate, %				
Ever use	4.5	1.3	3.65 (1.67–7.97)	2.43 (1.05–5.62)
Current use	1.5	0.7	2.26 (0.64–7.98)	1.68 (0.46–6.2)
Past use	3.0	0.6	5.26 (1.93–14.29)	3.21 (1.10–9.41)
Risedronate, %				
Ever use	3.0	0.6	4.93 (1.81–13.45)	3.34 (1.04–10.67)
Current use	2.0	0.4	4.65 (1.39–15.56)	3.50 (0.90–13.60)
Past use	1.0	0.2	5.65 (0.92–34.59)	2.95 (0.34–25.58)
Statins, %				
Ever use	27.5	29.6	0.88 (0.62–1.26)	0.79 (0.49–1.07)
Current use	21.9	20.6	1.02 (0.69–1.51)	0.83 (0.54–1.27)
Past use	5.6	9.0	0.58 (0.30–1.12)	0.49 (0.24–1.00)
ACE-I, %				
Ever use	29.0	23.7	1.35 (0.96–1.90)	1.16 (0.79–1.70)
Current use	18.9	15.3	1.37 (0.92–2.04)	1.17 (0.75–1.82)
Past use	10.2	8.4	1.33 (0.80–2.20)	1.15 (0.66–1.99)

† Rate ratios were adjusted for sex, comorbidity (measured as the total number of prescription drugs used prior to the index date), coronary artery bypass graft surgery, history of fractures, malignancies including breast cancer, lung cancer, prostate cancer, multiple myeloma, lymphoma and leukemia, oral corticosteroids, diabetic medications and dental procedures. ACE-I: angiotensin-converting enzyme inhibitors.

is associated with an increased risk of AON, a relatively rare but potentially serious adverse event, that was not previously reported in randomized trials[20,21]. Our study demonstrates that this association is present in older adults who are generally healthy and have been exposed to oral bisphosphonates, although the overall risk appears small. The relatively low incidence of this adverse event and the potentially long incubation period may explain why this condition was not observed in the large randomized trials of bisphosphonates[20,21]. Therefore our study is the first large-scale observational study suggesting a potential link between bisphosphonate use and an increase in the risk of osteonecrosis.

Published cases of ONJ with bisphosphonates have largely been limited in patients who have had history of cancer, suggesting that osteonecrosis may be more prevalent in patients with malignancies[4,5]. Our study demonstrates that an association between bisphosphonate use and nonspecific AON may exist in a wider population. In light of the estimated 190 million prescriptions written for bisphosphonates worldwide[22], any harmful association between bisphosphonate use and AON may have important public health implications. Exposure to bisphosphonates may substantially increase in the future as the possible link between estrogen use and breast cancer[23] prompts more women to switch from estrogen therapy to bisphosphonate therapy for osteoporotic fracture prevention.

In our study, the average time from the use of the first bisphosphonate medication to the first diagnosis of AON was roughly 2 years, consistent with one case report on oral bisphosphonates and ONJ[9]. This may suggest that the association between bisphosphonates and ONJ may take several months to develop. Bisphosphonates are potent inhibitors of bone resorption, with half-lives of up to 10 years[24], allowing them to persist in the bone for long periods of time. By inhibiting bone turnover, bisphosphonates gradually interfere with bone metabolism, thereby disrupting the biomechanical integrity of the bone[25,26]. This in turn makes the bone more susceptible to micro-damage, especially in the presence of triggers such as infection or trauma.

Our study has several strengths including its large and representative sample size, with complete and detailed longterm followup, which enhances our ability to detect rare adverse drug events. Moreover our study design insures that exposure antedates the outcome, thereby avoiding protopathic bias.

Our study also has several limitations. Due to the administrative structure of our data sources, we could not identify the site where the osteonecrosis occurred. The ICD-9 code for ONJ was only recently introduced[27] and therefore not record-

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ed in our database. We therefore suspect that the majority of the cases identified in this study are osteonecrosis, possibly of the hip, and not ONJ, especially since most of the patients had been prescribed corticosteroids (Table 1). Also, while the diagnostic utility of these administrative codes has been validated for several other diagnoses[12,13,28], they have not been validated for our measured outcomes of AON. Residual confounding through unbalancing of either these measured or other unmeasured confounders is, of course, a concern for any observational study. In this regard, the neutral results with statins and ACE-I exposure is reassuring for our internal study validity. Further, the generalizability of our study findings to other noncardiovascular cohorts is unknown, although there is no prior reason to believe that our population would be at unique risk for this putative association. Due to the nature of the data, we could not identify cases that did not require hospitalization. Also we had limited statistical power to investigate the importance of duration of therapy on this association, although the risk of AON appeared to be present even with fewer than 10 prescriptions in the preceding year prior to diagnosis. Finally, as with other pharmacoepidemiologic studies that use administrative databases, we could not ascertain information on medication compliance or information on some of the potential clinical confounders including use of alcohol and smoking[9]. These limitations, as well as the low prevalence of the disease and the long followup necessary to adequately study this association, highlight the challenges for future studies. As our study is an observational study it could not establish causality between bisphosphonate use and AON.

The link between AON and ONJ is still unclear and needs to be further investigated. The American Association of Oral and Maxillofacial Surgeons[29] and The American Dental Association (ADA)[30] have made recommendations on this issue. Both associations recommend that all patients receiving oral bisphosphonates be adequately informed of the risk of compromised bone healing. The ADA recommends that all patients who are otherwise healthy taking oral bisphosphonates should be given a comprehensive oral evaluation by a dentist and be familiar with the signs and symptoms of the disease. Whether other professional societies need to follow this lead in discussing the risks of oral bisphosphonate use will depend on the results of future research.

Specifically, additional studies are needed not only to confirm these preliminary observations but also to investigate further the role of specific bisphosphonates, their dose-response relationship, duration of therapy, and the exact sites of bone necrosis.

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