Osteoporos Int (2013) 24:2519–2524
DOI 10.1007/s00198-013-2331-8

ORIGINAL ARTICLE

Bisphosphonate treatment may reduce osteoporosis risk in female cancer patients with morphine use: a population-based nested case–control study

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Received: 31 January 2013 / Accepted: 21 February 2013 / Published online: 8 March 2013

Abstract
Summary Chronic use of morphine is a risk factor for endocrinopathy and osteoporosis. Bisphosphonates accentuated the protective effect to develop osteoporosis in female patients with malignancy with morphine treatment.
Introduction This study investigates the risk of osteoporosis associated with morphine use by comparing the incidence of osteoporosis in female cancer patients treated with and without morphine.
Methods A population-based nested case–control retrospective analysis was performed using the Longitudinal Health Insurance Database 2000 and Registry for Catastrophic Illness Patients of Taiwan. A malignancy cohort of 12,467 female patients without a history of osteoporosis during 1998–2010, and then 639 patients who subsequently developed osteoporosis as the osteoporosis group, were evaluated. Control-group patients were selected from the malignancy cohort without osteoporosis and frequency matched to each osteoporosis case 2:1 for age, year of cancer diagnosis, and index year. Logistic regression was used to estimate the odds ratios and 95 % confidence intervals, and the multivariable model was applied to control for age.
Results Female cancer patients who received morphine had a 10 % lower risk of developing osteoporosis than non-morphine users, but this risk reduction was not significant. For patients treated with bisphosphonates, the morphine group had significantly lower odds in developing osteoporosis than the non-morphine group.
Conclusion Morphine treatment is not associated with the incidence of osteoporosis, and bisphosphonates accentuated the protective effect of morphine in the development of osteoporosis in female patients with malignancy in Taiwan.

Keywords Bisphosphonates · Cancer · Morphine · Osteoporosis

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Introduction

Long-term opioid therapy often induces hypogonadism because of the central suppression of the hypothalamic secretion of the gonadotropin-releasing hormone. Symptoms of opioid-

induced hypogonadism include loss of libido, infertility, fatigue, depression, anxiety, loss of muscle strength and mass, and osteoporosis [1, 2]. An increased fracture risk is observed in users of morphine and opiates [3]. Low bone mineral density in patients receiving methadone or diacetylmorphine maintenance treatment has been reported [4–6]. A recent case report of a patient who suffered from a clinically significant testosterone deficiency also suggested that osteoporosis is related to the use of long-term oral opioids for chronic nonmalignant pain [7]. Routine screening for bone mass density has been suggested in the management of males who have been prescribed opioids for chronic pain because it may prevent additional health problems associated with osteoporosis [8]. Opioids may contribute to osteoporosis and increased fracture risk by directly interfering in bone formation [9]. This possibility was supported by studies documenting lowered serum osteocalcin levels in heroin addicts [10], the presence of an endogenous opiate in bone and joint tissues [11], the profound expression of opioid receptors in osteoblasts [12], inhibition of the growth of human osteoblast cultures by opioids and prevention of this inhibition by an opioid antagonist [11], and inhibition of the osteocalcin production by a μ-opioid receptor agonist in osteoblast cell cultures [12].

The management of chronic pain is essential in the palliative care of cancer patients [13]. The overall prevalence of cancer-related pain ranges from 14 to 100 %, depending on the study population and specific pain type [14]. In 1986, the World Health Organization (WHO) proposed the three-step treatment plan for pain relief, proceeding from non-opioids to weak and then strong opioids as necessary. This treatment plan is considered the most suitable form of palliative treatment for advanced cancer patients [15]. Since 1986, opioids have continued to represent a central component in all treatment guidelines for the management of cancer pain [16], with morphine viewed as the gold standard [17–20]. Because of major advances in oncological therapies, cancer is no longer considered a terminal disease. More than 50 % of all cancer patients survive longer than 2 years post-diagnosis, and approximately 13.7 and 0.35 million cancer survivors currently reside in the USA [21] and Taiwan (unpublished estimation), respectively. Because of improved survival rates, the management of chronic pain remains a key challenge in cancer care.

Owing to the increased periods of morphine exposure in cancer patients because of prolonged pain management, it is important to understand the possible effects of morphine on the incidence of osteoporosis. No epidemiological study has investigated the effects of long-term morphine treatment on the incidence of osteoporosis in Taiwan. To evaluate the potential for morphine exposure-induced osteoporosis, we compared the incidence of osteoporosis in female cancer patients treated with and without morphine by using data from the National Health Insurance Research Database (NHIRD) of Taiwan.

Methods

Data source

Taiwan's NHIRD provided the data source. The National Health Insurance (NHI) is a compulsory universal health insurance program that has been in place since 1995, and provides coverage to over 99 % of the Taiwanese population. The National Health Research Institutes compiled all inpatient and outpatient medical benefit claims in the NHI program and released the data for research purposes. The details of the NHIRD have been described in previous studies.

This study analyzed one million beneficiaries randomly selected from all insurants for the period 1996–2000; sex and age distributions were nearly identical to the entire population. We also used the catastrophic illness certificate database (CICD) to identify cancer patients. For a patient to be issued a catastrophic illness certificate for cancer, histological or cytological evidence of such a disease is required.

Study patients

We established a nested case–control study. Figure 1 shows the flow chart for selecting the study patients. First, we enrolled female patients with cancer (International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), ICD-9-CM code 140–208) in the claims database between January 1, 1998 and December 31, 2010 (n=15,049). Patients were excluded if they had a history of osteoporosis (ICD-9-CM 733.0) or had received morphine treatment before the cancer diagnosis date. In total, 639 patients with osteoporosis comprised the case group. The control patients were frequency matched 1:2 for age, cancer-year, and index year to the case group (n=1,254; Fig. 1).

The diagnosis of osteoporosis was made in individuals who sustained a low-trauma fracture, or established by the measurement of spine and hip bone mineral density (BMD) as less than or equal to 2.5 standard deviations below the young normal mean (T-score less than −2.5). The most widely validated technique to measure BMD is central dual energy X-ray absorptiometry (DXA), and BMD measured by DXA at the one third (33 %) radius site can be used to assist in making the diagnosis of osteoporosis when the spine and hip cannot be measured (2010 the ISCD of the Asia-Pacific consensus). The bone lesion due to cancer metastasis was examined by at least one of the following imaging techniques: Tc-99 m bone scan, X-ray, CT/MRI, and PET. The bone lesion by cancer metastasis was not included in the area of the BMD measurement.

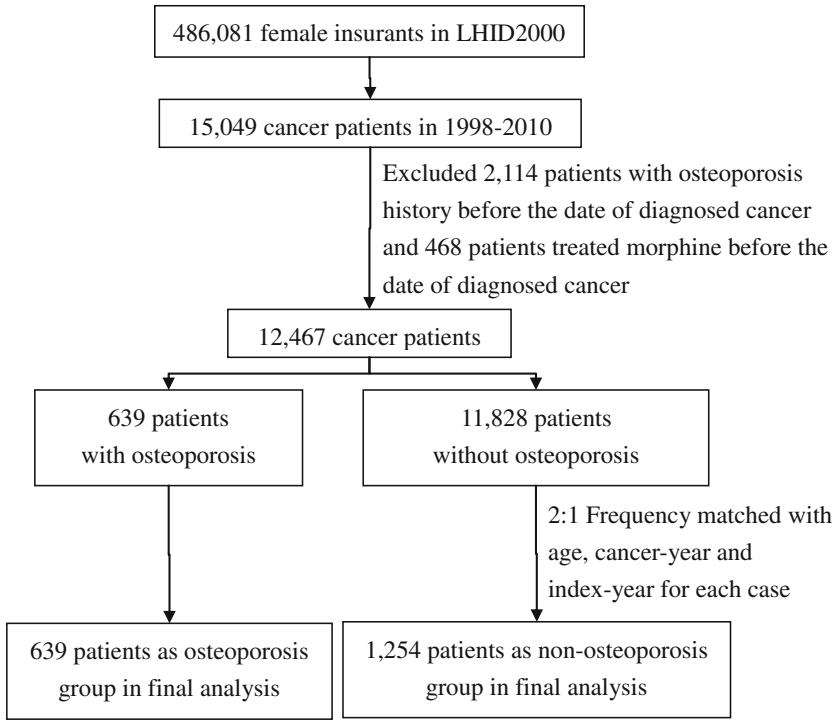

Fig. 1 Flow chart for selecting study subjects

Exposure ascertainment

The main exposure of interest was the use of morphine (ATC N02AA01), which was introduced into the Taiwanese market in March 1995. We collected information on prescriptions, dosage, date of prescription, supply days, and total number of pills dispensed from the database. We calculated the cumulative dosage for each patient by using the follow-up duration. Other medications, such as bisphosphonates (ATC M05BA), were also recorded and reported.

Statistical analysis

We compared the baseline characteristics between osteoporosis cases and non-osteoporosis controls by using the chi-square test. Logistic regression was used to estimate the odds ratio (OR) and 95 % confidence interval (CI) for the association between osteoporosis and morphine use.

A two-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.2 for Windows; SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 lists the characteristics of the patients with and without osteoporosis. Of the 1,893 study patients, 108 (16.9 %) and 230 (18.3 %) patients received morphine treatment before entering the osteoporosis and non-osteoporosis group, respectively. Patients in the osteoporosis group were the same age as their matched controls (mean age±SD, 63.3±13.4 vs 62.9±13.1 years, $P=0.46$). Distributions of the Charlson comorbidity score were essentially the same between the two groups ($P=0.19$).

After controlling for age in the multivariate analyses, no significant relationships were found between osteoporosis and morphine in cancer patients overall (OR=0.90, 95 % CI=0.70–1.16), in cervical cancer patients (OR=0.53, 95 % CI=0.28–1.03), in breast cancer patients (OR=1.08, 95 % CI=0.61–1.93), in ovarian cancer patients (OR=2.97, 95 % CI=0.92–9.61), in lung cancer patients (OR=1.56, 95 % CI=0.44–5.45), or in other cancer patients (OR=0.86, 95 % CI=0.60–1.22), respectively (Table 2).

Compared with non-morphine patients, we found a trend of protective effects for osteoporosis in morphine patients receiving a higher cumulative morphine dosage, but it was not statistically significant (OR=0.96, 95 % CI=0.69–1.34 for 1–64 mg/treatment year; OR=0.85, 95 % CI=0.60–1.20 for≥65 mg/treatment year; P for trend=0.36; Table 3).

Furthermore, we estimated the effect of bisphosphonates on the association between osteoporosis and morphine use (Table 4). Compared with patients without morphine use in the bisphosphonates group, those with morphine use were associated with a significantly reduced risk of osteoporosis (OR=0.25, 95 % CI=0.08–0.80).

Table 1 Demographics between osteoporosis and non-osteoporosis group in women

Variable	Osteoporosis		Non-osteoporosis		*p* value
	N=639		*N*=1,254		
	n	%	*n*	%	
Morphine	108	16.9	230	18.3	0.44
Age, year					0.64
<55	195	30.5	389	31.0	
55–64	192	30.1	397	31.7	
≥65	252	39.4	468	37.3	
Mean (SD)	63.3	(13.4)	62.9	(13.1)	0.46
Charlson comorbidity score					0.19
0	581	90.9	1,116	89.0	
≥1	58	9.08	138	11.0	
Mean (SD)	1.09	(0.29)	1.11	(0.31)	0.18

Chi-square test

Discussion

Our results indicated that morphine use is not associated with the incidence of osteoporosis in female patients with malignancy. This risk was reduced with increased morphine dosage, and the "protective" effect was most significant in patients who also received bisphosphonates. Our findings support the notion that morphine is safe to use for pain management in female cancer patients for the risk of developing osteoporosis [22].

Bisphosphonates are pyrophosphate compounds that inhibit the osteoclast-mediated reabsorption of the bone [23]. Bisphosphonates effectively reduce skeletal-related events caused by a malignancy metastatic to the bone, and are incorporated in breast cancer treatment regimens to combat osteoporosis caused by chemotherapy [24]. Our results indicate that in patients receiving bisphosphonates, morphine use is associated with a significant reduced risk of osteoporosis (OR=0.25). In the contrast, in patients without bisphosphonate treatment, this "protection" effect of morphine does not exist (OR=0.91,

Table 2 Odds ratios for osteoporosis between morphine did and did not use among cancer type

Cancer type (ICD-9-CM)	Osteoporosis		Non-osteoporosis		Age-adjusted OR (95 % CI)
	N	%	*N*	%	
Overall					
Without morphine	531	83.1	1,024	81.7	1.00
With morphine	108	16.9	230	18.3	0.90 (0.70–1.16)
Cervical cancer (180)					
Without morphine	109	87.2	131	79.9	1.00
With morphine	16	12.8	33	20.1	0.53 (0.28–1.03)
Breast cancer (174)					
Without morphine	151	88.3	312	88.6	1.00
With morphine	20	11.7	40	11.4	1.08 (0.61–1.93)
Ovarian cancer (183)					
Without morphine	20	60.6	26	78.8	1.00
With morphine	13	39.4	7	21.2	2.97 (0.92–9.61)
Lung cancer (162)					
Without morphine	10	66.7	47	72.3	1.00
With morphine	5	33.3	18	27.7	1.56 (0.44–5.45)
Other cancer					
Without morphine	241	81.7	508	79.4	1.00
With morphine	54	18.3	132	20.6	0.86 (0.60–1.22)

Table 3 Odds ratios for osteoporosis and dosage of morphine

Dosage, mg/treatment year	Osteoporosis		Non-osteoporosis		OR	95 % CI
	n	%	n	%		
None	531	83.1	1,024	81.7	1.00	Reference
Morphine used						
1–64	57	8.92	114	9.09	0.96	0.69–1.34
≥ 65	51	7.98	116	9.25	0.85	0.60–1.20
P for trend		0.36				

Adjusted for age

95 % CI=0.70–1.19). No previous report has examined the interactions between morphine and bisphosphonates, and our results suggest that these two drugs might share the same functional pathways in the bone formation/absorption either directly or indirectly. Further investigation using animal and cell models to identify the underlying cellular mechanisms for this novel finding is warranted.

The study of Vestergaard et. al. [3] showed that morphine could be associated with fracture risk, and they concluded that the reason for this might be related to the risk of falls due to central nervous system effects such as dizziness. In this study, the trend of a protective effect of morphine was shown in patients receiving bisphosphonates but not in those who were not treated with bisphosphonates. Previous reports, especially those investigated heroin/methadone users, mainly studied male subjects since 70 % of the drug addicts are men. In our study, only data of the female patients are reported due to the low incidence of osteoporosis in male cancer patients (n=190 and 41 in the non-morphine and morphine group, respectively). Combining data from both men and women might be inappropriate because of the different cancer types and potential hormonal effects on bone mass density. The gender difference is likely the cause of the deviation between our results and the previous reports since the bone density is partly regulated by the sex hormones. We hypothesize that morphine can enhance the inhibition effect of bisphosphonates in the osteoclast-mediated reabsorption of the bone via some unknown androgen/estrogen-dependent molecular mechanism. Whether the μ-opioid receptor is involved in this direct or indirect regulation could be demonstrated using gene-specific knockout animals in the future.

The strengths of our study include its use of population-based data and evaluation of NHIRD records rather than self-reported drug use. However, this study also suffers from a few limitations that should be mentioned. First, the NHIRD lacked some important data, including detailed demographic information on smoking habits, alcohol consumption, body mass index, socioeconomic status, and family history of systemic diseases. These are potential risk factors for cancer or osteoporosis and are indirectly associated with morphine use. Therefore, we were unable to correlate the increased morphine dosage with the inactivity status and/or malnutrition because the NHIRD does not contain the lifestyle data. However, because the NHIRD covers a highly representative sample of Taiwan's general population, and because the reimbursement policy is universal, these factors are unlikely to have affected the prescription of morphine in the sample group. Second, because the cancer disease itself might influence mobility and muscle strength, we used the nested case–control method to eliminate/equalize the confounding factors due to cancer itself. Yet, evidence derived from a nested case–control study is generally of lower quality than that from randomized trials. This is because a nested case–control study design is subject to several biases related to adjustments for confounding variables. Despite a meticulous study design with adequate control of confounding factors, a key limitation of this study is that bias could remain if unmeasured or unknown confounders are present. Third, the diagnoses recorded in the NHI claims are primarily used for administrative billing, and are not verified for

Table 4 Odds ratios for osteoporosis stratified by bisphosphonates

	Osteoporosis		Non-osteoporosis		OR	95 % CI
	n	%	*n*	%		
Without bisphosphonates use						
Without morphine	488	83.4	1,015	82.1	1.00	
With morphine	97	16.6	221	17.9	0.91	0.70–1.19
Bisphosphonates use						
Without morphine	43	79.6	9	50.0	1.00	
With morphine	11	20.4	9	50.0	0.25	0.08–0.80*

Adjusted for age
Interaction P=0.03
*P<0.05

scientific purposes. We were unable to contact patients directly to inquire about their morphine use because all beneficiaries listed on the NHIRD are protected by anonymity. We were also unable to consider morphine prescriptions issued before 1996. This omission could have led to the underestimation of cumulative dosages and might have weakened the observed association. However, the data we obtained on morphine prescription and diagnoses of cancer and osteoporosis were reliable. Fourth, although our study has included the largest number of cancer patients suffering osteoporosis and under bisphosphonate treatment (n=54) to date, our study size is indeed a limitation to give the power for elucidating the relationship clearly, and further well-designed randomized controlled trials are needed to confirm our findings.

Our results indicate that morphine treatment is not associated with the incidence of osteoporosis in female cancer patients, and that bisphosphonates accentuated the protective effect of morphine in the development of osteoporosis. However, further large population-based studies or large-scale randomized clinical trials are required to confirm these findings before any definitive conclusions can be drawn.

Acknowledgments The study was supported by grants from the study hospital (DMR-102-014 and DMR-102-023); Taiwan Department of Health Clinical Trial and Research Center and for Excellence (DOH102-TD-B-111-004), Taiwan Department of Health Cancer Research Center for Excellence (DOH102-TD-C-111-005); and International Research-Intensive Centers of Excellence in Taiwan (I-RiCE) (NSC101-2911-I-002-303).

Conflicts of interest None.

References

1. Katz N, Mazer NA (2009) The impact of opioids on the endocrine system. Clin J Pain 25:170–175
2. Elliott JA, Opper SE, Agarwal S, Fibuch EE (2012) Non-analgesic effects of opioids: opioids and the endocrine system. Curr Pharm Des 18:6070–6078
3. Vestergaard P, Rejnmark L, Mosekilde L (2006) Fracture risk associated with the use of morphine and opiates. J Intern Med 260:76–87
4. Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH (2006) Low bone density in patients receiving methadone maintenance treatment. Drug Alcohol Depend 85:258–262
5. Dursteler-MacFarland KM, Kowalewski R, Bloch N, Wiesbeck GA, Kraenzlin ME, Stohler R (2011) Patients on injectable diacetyl morphine maintenance have low bone mass. Drug Alcohol Rev 30:577–582
6. Sharma A, Cohen HW, Freeman R, Santoro N, Schoenbaum EE (2011) Prospective evaluation of bone mineral density among middle-aged HIV-infected and uninfected women: association between methadone use and bone loss. Maturitas 70:295–301
7. Elliott JA, Horton E, Fibuch EE (2011) The endocrine effects of long-term oral opioid therapy: a case report and review of the literature. J Opioid Manag 7:145–154
8. Fortin JD, Bailey GM, Vilensky JA (2008) Does opioid use for pain management warrant routine bone mass density screening in men? Pain Phys 11:539–541
9. Daniell HW (2004) Opioid osteoporosis. Arch Intern Med 164:338
10. Rico H, Costales C, Cabranes JA, Escudero M (1990) Lower serum osteocalcin levels in pregnant drug users and their newborns at the time of delivery. Obstet Gynecol 75:998–1000
11. Elhassan AM, Lindgren JU, Hultenby K, Bergstrom J, Adem A (1998) Methionine-enkephalin in bone and joint tissues. J Bone Miner Res 13:88–95
12. Pérez-Castrillón JL, Olmos JM, Gómez JJ, Barrallo A, Riancho JA, Perera L, Valero C, Amado JA, González-Macías J (2000) Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. Neuroendocrinology 72:187–194
13. Portenoy RK (2011) Treatment of cancer pain. Lancet 377:2236–2247
14. Goudas LC, Bloch R, Gialeli-Goudas M, Lau J, Carr DB (2005) The epidemiology of cancer pain. Cancer Invest 23:182–190
15. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F (1987) A validation study of the WHO method for cancer pain relief. Cancer 59:850–856
16. Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, Lipman AG, Bookbinder M, Sanders SH, Turk DC, Carr DB (2005) American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 165:1574–1580
17. Quigley C (2008) Opioids in people with cancer-related pain. Clin Evid (Online) pii: 2408.
18. Koyyalagunta D, Bruera E, Solanki DR, Nouri KH, Burton AW, Toro MP, Bruel BM, Manchikanti L (2012) A systematic review of randomized trials on the effectiveness of opioids for cancer pain. Pain Phys 15:ES39–ES58
19. Wiffen PJ, McQuay HJ (2007) Oral morphine for cancer pain. Cochrane Database Syst Rev (4): CD003868.
20. Flemming K (2010) The use of morphine to treat cancer-related pain: a synthesis of quantitative and qualitative research. J Pain Symptom Manage 39:139–154
21. Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E (2012) Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62:220–241
22. Wickham R (2011) Osteoporosis related to disease or therapy in patients with cancer. Clin J Oncol Nurs 15:E90–E104
23. Fleisch H (2002) Development of bisphosphonates. Breast Cancer Res 4:30–34
24. Morris GJ, Mitchell EP (2007) Bisphosphonate therapy for women with breast cancer and at high risk for osteoporosis. J Natl Med Assoc 99:35–45