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Modest increase in risk of acute coronary syndrome associated with morphine use in cancer patients: A population-based nested case-control study

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A B S T R A C T

Background: Morphine is widely used for pain management in cancer patients. Use of heroin, a morphine derivative, is a risk factor for acute coronary syndrome (ACS).
Objective: This study investigates the risk of ACS associated with morphine use by comparing the incidence of ACS in cancer patients treated with and without morphine.
Methods: This is a population-based nested case-control study using the Longitudinal Health Insurance Database 2000 in Taiwan. In total, 31,384 patients on the database were diagnosed with cancer without prior history of ACS during 1998–2010. In this cohort, 499 patients subsequently developed ACS and 30,885 patients did not. The 499 patients were designated as the ACS group; controls were selected from the remaining 30,885 patients and matched 3:1 to each case for age, sex, 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, sex, and Charlson comorbidity score.
Results: Cancer patients who received morphine had a 32% higher risk of developing ACS than non-morphine users. This increase in risk was significant when evaluating the overall cancer patients, but non-significant when evaluating any specific cancer type. The risk of ACS increased significantly with increasing morphine dosage (to ≥65 mg/y).
Conclusion: Morphine treatment is associated with a modest increase in risk of ACS in patients with malignancy, but this association displays low significance in specific cancer types.

Introduction

The management of chronic pain is essential in the palliative care of cancer patients (Portenoy, 2011). The overall prevalence of cancer-related pain ranges from 14% to 100%, depending on the study population and the specific pain type (Goudas et al., 2005). In 1986, the World Health Organization (WHO) proposed the 3-step treatment plan for pain relief, proceeding from non-opioids to weak and then strong opioids as needed. This treatment plan is considered the most suitable form of palliative treatment for advanced cancer patients (Ventafridda et al., 1987). Since 1986, opioids have continued to represent a central component in all treatment guidelines for the management of cancer pain (Gordon et al., 2005), with morphine viewed as the gold standard (Quigley, 2008; Koyyalagunta et al., 2012; Wiffen and McQuay, 2007; Flemming, 2010). With 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 United States (Siegel et al., 2012) and Taiwan (unpublished estimation), respectively. Therefore, with improved survival rates, the management of pain remains a key challenge in cancer care.

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The long-term use of opioids is controversial for several reasons. The primary reasons are psychological addiction, abuse, and medication diversion. With increasing opioid availability, these problems have increased in severity (Benyamin et al., 2008). Heroin is the most commonly abused morphine derivative, and its abuse is associated with several pathological effects on the central nervous system (CNS). These effects include neurovascular complications such as ischemic stroke or microvascular ischemic changes (Borne et al., 2005; Caplan et al., 1982; Sloan et al., 1991; Jensen et al., 1990). Heroin can also induce bradycardia and increases in automaticity to precipitate increases in ectopic activity, atrial fibrillation, idioventricular rhythm, or potentially lethal ventricular tachyarrhythmias (Lipski et al., 1973; Ghuran and Nolan, 2000). In addition, heroin and other opiates can cause arrhythmias and noncardiac pulmonary edema, and reduce cardiac output (Frishman et al., 2003). Therefore, opioid use might be associated with cardiovascular manifestations.

Given 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 ACS. No previous epidemiological study has investigated the effects of long-term morphine treatment on the incidence of ACS in human populations. To evaluate potential morphine exposure-induced ACS, this study compared the incidence of ACS in cancer patients treated with and without morphine using data from the National Health Insurance Research Database (NHIRD) of Taiwan.

Materials and methods

This nested case-control study used data from the Longitudinal Health Insurance Database 2000 (LHID2000) and registry database of catastrophic illness, which are components of Taiwan's NHIRD. The LHID2000 contains data on 1 million insurants randomly selected from the beneficiaries of Taiwan's National Health Insurance program in 2000. Age and sex distribution showed non-significant differences between the insurants of the LHID2000 and the original beneficiaries of the NHIRD. Taiwan's National Health Insurance program is compulsory and covered more than 99% of the population in 2010. According to the Personal Information Protection Act, the identification of all beneficiaries is encrypted before release for research purposes. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101-012). The LHID2000 includes data on all medical visits, including inpatient and outpatient treatment records from 1996 to 2010. Disease diagnosis was based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The registry collect all reimbursed medication usage of patients, and this relies on both clinician entry and a double-check process by the dispensary. Morphine is a controlled substance in Taiwan, and can only be obtained legally under the doctor's prescription. Moreover, the quantity of morphine used in the hospital has to be reported to the Food and Drug Administration, Ministry of Health and Welfare in Taiwan. Therefore, the validity and reliability of the data of morphine usage is very high.

First, a cancer cohort was established. All 41 604 patients with newly diagnosed cancer from 1998 to 2010 were selected from the registry database of catastrophic illness. Patients with ACS (ICD-9-CM code 410 and 411.1, $n = 2632$) and treated with morphine prior to the date of cancer diagnosis ($n = 7588$) were excluded. The cancer cohort contained 31 384 cancer patients, from which 499 cancer patients with ACS were selected to represent the ACS group. The control group was selected from the cancer cohort patients without developed ACS. Three controls were frequency matched to each case according to age, sex, year of cancer diagnosis, and year of ACS diagnosis. The figure displays a flow chart for the selection of study patients. (Fig. 1).

The chi-square test was used to evaluate the differences in age (<65, 65–74 and ≥75 y), sex, and Charlson comorbidity score level (0–2 and ≥3) between the ACS and control groups. The patients' Charlson comorbidity scores were used to indicate their individual comorbid conditions (Charlson et al., 1987; Deyo et al., 1992). Logistic regression was used to estimate the odds risk and 95% confidence interval (95% CI) for the association between ACS and morphine use. The multivariable model was applied to control for age, sex, and Charlson comorbidity score. The association between ACS and morphine use was evaluated in the 5 most common cancer types, including colorectal cancer (ICD-9-CM code 153–154), liver cancer (ICD-9-CM code 155), female breast cancer (ICD-9-CM code 174), prostate cancer (ICD-9-CM code 185), and kidney cancer (ICD-9-CM code 188). The association between ACS and morphine dosage (mg/y, y = year) was also evaluated. Morphine dosages were categorized into 2 groups according to their median values.

Results

In this nested case-control study, we collected data on 499 ACS patients and 1476 controls from a cancer cohort. The mean age was 71.4 years (SD = 12.4) and men formed the majority (59.5%) of the ACS group. Compared to controls, ACS patients displayed higher Charlson comorbidity scores (mean score 3.41 vs. 2.65) and were more likely to have received morphine treatment (27.7% vs. 21.3%; Table 1).

Table 2 displays the odds ratios and 95% CIs for the association between ACS and morphine use. According to crude and adjusted logistic regression models, the overall risk of ACS was 1.42-fold (95% CI = 1.12–1.79) and 1.32-fold (95% CI = 1.04–1.68) higher, respectively, in patients who received morphine than in patients who did not receive morphine treatment. We further evaluated the association between ACS and morphine use in the 5 most common cancer types. Using the crude model for evaluation, we observed a significant association only in patients with liver cancer (OR = 2.39, 95% CI = 1.05–5.46).

We also evaluated the relationship between ACS and morphine dosage (Table 3). We identified that a higher percentage of ACS patients received a high morphine dosage than controls (14.4% vs 9.76%). Patients treated with a high morphine dosage (≥65 mg/y) displayed a 51% higher risk of developing ACS compared to patients who did not receive morphine treatment.

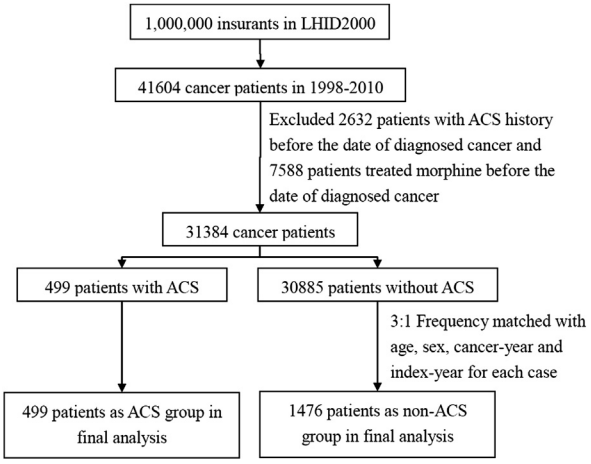

Fig. 1. Flow chart for the selection of study patients.