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Original article

Nabumetone use and risk of acute pancreatitis in a case-control study

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ABSTRACT

Background: It remains unknown whether nabumetone increases or decreases acute pancreatitis risk. To investigate this, we conducted a population-based case–control study using the database from the Taiwan National Health Insurance Program.

Methods: We analysed 5384 cases aged 20–84 years who had their first attack of acute pancreatitis during 1998–2011 and 21,536 controls without acute pancreatitis, and matched them according to sex, age and year in which acute pancreatitis was diagnosed. Never use of nabumetone was defined as subjects who had never received a nabumetone prescription; active use as subjects receiving a minimum of one prescription for nabumetone within 7 days before acute pancreatitis diagnosis and non-active use of nabumetone as subjects who did not receive a prescription for nabumetone within 7 days before but received at least one prescription for nabumetone ≥8 days before. The odds ratio and 95% confidence interval (CI) were estimated to investigate the risk of acute pancreatitis associated with nabumetone use, using the multivariable unconditional logistic regression model.

Results: The adjusted odds ratio of acute pancreatitis was 3.69 (95%CI 1.69, 8.05) for subjects with active use of nabumetone compared with those with never use. The odds ratios decreased to 1.0 (95%CI 0.88, 1.12) for subjects with non-active use.

Conclusions: Active use of nabumetone may increase the risk of acute pancreatitis.

Introduction

Acute pancreatitis has impacted individual health and the healthcare system for decades. However, preventing acute pancreatitis remains as challenge worldwide [1,2]. Peery AF reported acute pancreatitis was the most common gastrointestinal admission diagnosis and estimated 2.6 billion dollars in patients cost in the United States in 2012 [3]. Acute pancreatitis was not only the burden of health care, but might also result in loss of productivity [4].

In Asia, acute pancreatitis patients and related health burdens also showed an upward trend. A nationwide epidemiological survey showed that the estimated acute pancreatitis prevalence rate per 100,000 people rose from 45.1 in 2007 to 49.4 in 2011 in Japan [5,6]. In Taiwan, the annual incidence of the first attack of acute pancreatitis was estimated at 36.9 per 100,000 people and changed only slightly between 2000 and 2009. However, patients with acute pancreatitis used significant medical resources [7,8].

Though the mortality rate of acute pancreatitis has decreased in these years, the annual incidence of acute pancreatitis persistently increases [6,9]. Alcohol and cholelithiasis have been generally acknowledged as two of the most important causes of acute

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pancreatitis [10], there are other risk factors mentioned associated with acute pancreatitis such as certain medications [11].

Over 100 drugs have been implicated in case reports in causing acute pancreatitis [12]. Even though drugs are a relatively rare cause of acute pancreatitis, with an estimated incidence of less than 2% [13], the diagnosis of drug-induced acute pancreatitis could be underestimated [14]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are well-known for their analgesic and anti-inflammatory effects and notorious for their multiple adverse drug reactions. For most NSAIDs, gastrointestinal problems, such as upper gastrointestinal bleeding and nephrotoxicity, are usually the main concerns. For selective cyclooxygenase 2 (COX-2) inhibitors—marketed and claimed for less gastrointestinal adverse reactions—the cardiovascular risk is worrisome.

Recently, the correlation between NSAIDs and acute pancreatitis was also debated, focusing on both traditional non-selective NSAIDs and COX-2 inhibitors [15]. The correlation between nabumetone and acute pancreatitis was infrequently discussed. Nabumetone, also widely used to treat pain and arthritis, is the only one non-acidic NSAID. Via its active metabolite, nabumetone preferentially blocks COX-2 activity. The United States Food and Drug Administration (FDA) have reported that among 3925 people had side effects when taking nabumetone. Eleven people (0.28%) claimed it was related to acute pancreatitis but did not mention a causal relationship [16]. To date, there have been neither case reports nor systematic population-based studies that focused on the relationship between nabumetone and acute pancreatitis.

Using nationwide claims data, this study tended to explore the association of nabumetone and acute pancreatitis.

Methods

Design and study population

A population-based case–control study using the database from the Taiwan National Health Insurance (NHI) Program was conducted to investigate a possible correlation between nabumetone and acute pancreatitis. This insurance program is a government-run universal healthcare program that began in March 1995 and presently covers over 99% of the total 23 million people in Taiwan [17]. This study used a longitudinal dataset consisting of one million insured people who were randomly selected from all people covered by the NHI, based on population of the year 2000. The details of the program were also written in previous papers [18–20]. Using a unique scrambled personal identification from the National Health Research Institute, medical histories and demographic variables aided analysis without violating patient privacy. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Study subjects and comorbidities

Subjects aged 20–84 years with their first attack of acute pancreatitis according to International Classification of Diseases 9th Revision Clinical Modification (ICD-9 code 577.0), and made at least twice continuous claims during the period of 1998–2011 were included in the study group. The index date for each case was defined as the date of acute pancreatitis diagnosis. For each case of acute pancreatitis, four control subjects without acute pancreatitis were randomly selected from the same database as the control group. The case group and the control group were matched for sex, age (per 5 years) and the year the acute pancreatitis was diagnosed. Subjects, who had either chronic pancreatitis (ICD-9 code 577.1) or pancreatic cancer (ICD-9 code 157) before the date of acute pancreatitis diagnosis, were excluded from this study. To decrease bias, subjects who had prescriptions for other cyclooxygenase-2 inhibitors available in Taiwan (celecoxib, etoricoxib, etololac, meloxicam, and nimesulide) were also excluded from this study. Comorbidities potentially related to acute pancreatitis before the index date were selected as follows: alcohol-related disease, biliary stones, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B and C, hyperparathyroidism, hypertriglyceridemia, as well as cardiovascular diseases including coronary artery disease, heart failure, cerebrovascular disease and peripheral atherosclerosis. All comorbidities were diagnosed with ICD-9 codes.

Definition of nabumetone exposure

According to the exposure or not, we grouped subjects into three categories: never use, active use and non-active use of nabumetone, All Taiwan Food and Drug approved medicine contained nabumetone, including brand and generic forms, were listed. 6-methoxy-2-naphthylacetic acid (6-MNA) as the main active metabolite of nabumetone undergoes biotransformation in the liver; approximately 75% of a radiolabeled dose was recovered in urine in 48 h, and 80% in 168 h [21]. We then adapted 7 days as the cut-off for classifying active use of medication. The absence of a subject who never received and never used a nabumetone prescription was defined as never use of nabumetone. Active use of nabumetone was defined as subjects at least receiving one prescription for nabumetone within seven days before the date of diagnosis of acute pancreatitis. Non-active use of nabumetone was defined as subjects who did not receive a prescription for nabumetone within seven days, but who received at least receiving one prescription for nabumetone $\geq$8 days before the date of acute pancreatitis diagnosis. In further analysis, non-active users of nabumetone were grouped into non-active use (8–14 days) and non-active use ($\geq$15days) to show the risk distribution.

Statistical analysis

The distributions of sex, age, nabumetone use and comorbidities were compared between the study and control groups using the Chi-square test and Fisher-exact test for categorized variables and the t-test for continuous variables. Variables found significantly related to acute pancreatitis in the univariable unconditional logistic regression model were further included in the multivariable unconditional logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were estimated to investigate the risk of acute pancreatitis correlated with nabumetone use and comorbidities. All data processing and statistical analyses were performed with the SAS software version 9.2 (SAS Institute, Inc., Cary, North Carolina, USA). A two-tailed P value of <0.05 was considered statistically significant.

Results

Characteristics of the study population

Table 1 presents the distributions of sex, age, nabumetone use and comorbidities between the case and the control groups. There were 5384 cases with acute pancreatitis and 21,536 controls with a similar sex and age distribution. The cases had significantly higher proportions of ever use of nabumetone, alcohol-related diseases, biliary stones, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B and C, hyperparathyroidism and hypertriglyceridemia than the controls (Fisher exact test, $P = 0.02$ for hyperparathyroidism and Chi-square test, $P < 0.001$ for others).

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