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

Shih-Chang Hung a, b, 1, Kuan-Fu Liaoc, d, e, 1, Hung-Chang Hung f, Cheng-Li Lin g, h, Shih-Wei Lai g, i, 1, Chih-Hsueh Ling i

a Department of Emergency Medicine, Nantou Hospital, Nantou, Taiwan
b Department of Healthcare Administration, Central Taiwan University of Science and Technology, Taichung, Taiwan
c College of Medicine, Tzu Chi University, Hualien, Taiwan
d Department of Internal Medicine, Taichung Tzu Chi General Hospital, Taichung, Taiwan
e Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
f Department of Internal Medicine, Nantou Hospital, Nantou, Taiwan
g College of Medicine, China Medical University, Taichung, Taiwan
h Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
i Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan

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.

Copyright © 2016, IAP and EPC. Published by Elsevier India, a division of Reed Elsevier India Pvt. Ltd. All rights reserved.

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...
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 the 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 who had side effects when taking nabumetone, 11 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 ≥ 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 (≥ 15 days) 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).
alcohol-related diseases and biliary stones. This result indicates that even in those with never use of nabumetone and without alcohol-related diseases and biliary stones (95% CI 1.86, 9.22), when compared with those with active use of nabumetone and without alcohol-related diseases or biliary stones.

Risk of acute pancreatitis associated with nabumetone use

After adjustment for potential confounding factors, the multi-variable unconditional logistic regression model demonstrated that the adjusted odds ratio of acute pancreatitis was 3.69 for subjects with active use of nabumetone (95% CI 1.69, 8.05) compared with subjects with never use of nabumetone. The adjusted OR decreased to 2.23 for subjects with non-active use (8–14 days) of nabumetone (95% CI 0.39, 2.23); and 0.99 for subjects with non-active use (>15 days) (95% CI 0.88, 1.12) (Table 2). Overall, the adjusted OR was 1.0 for whole with non-active use (95% CI 0.88, 1.12).

Risk of acute pancreatitis between active use of nabumetone and alcohol-related diseases or biliary stones.

In an additional analysis, after adjustment for cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridemia, the adjusted OR was 4.14 in those with active use of nabumetone and without alcohol-related disease and biliary stone (95% CI 1.86, 9.22), when compared with those with never use of nabumetone and without alcohol-related disease and biliary stones. This result indicates that even in absence of alcohol-related disease and biliary stones, the active use of nabumetone correlated with increased odds of acute pancreatitis (Table 3).

Discussion

Our study demonstrated that the active use of nabumetone correlated with an increased risk of acute pancreatitis within seven days of using the drug. To the best of our knowledge, this is the first population-based case–control study using national insurance claims data that aims to address the correlation between active use of nabumetone and acute pancreatitis.

Because alcohol-related diseases and biliary stones are commonly found to be associated with acute pancreatitis, to examine whether the risk of acute pancreatitis correlated with active use of nabumetone is confounded by alcohol-related diseases or biliary stones, we did an additional analysis to examine the risk of acute pancreatitis stratified by active use of nabumetone, alcohol-related diseases and biliary stones. We found that even in the absence of acute pancreatitis and disease, patients with active use of nabumetone correlated with increased risk of acute pancreatitis (adjusted OR 4.14, Table 3).

Badalov N et al. searched the MEDLINE data base from 1955 to 2006 to conduct an evidence-based review of drug-induced acute pancreatitis. In that study, drugs, which might be associated with acute pancreatitis, were categorized into four classes, and finally 120 drugs were listed as causing pancreatitis [22]. Drugs classified as Class I have at least one case report with positive rechallenge, Class II with at least four cases in the literature, Class III with at least two cases in the literature and Class IV for others published in the medical literature. Several NSAIDs were also involved and categorized: sulindac was categorized as Class I drug, acetaminophen as Class II, indomethacin, ketorolac and naproxen as Class III, diclofenac, ketoprofen, mefenamic acid and oxyphenbutazone as Class IV drugs. However, because FDA data were not used in that analysis,
the risk of nabumetone was not evaluated. The latest literature search date was 1 July 2006 and some recent studies, in which COX-2 inhibitors involved, might also have been missed.

The detailed mechanism of acute pancreatitis is still being discussed, and multiple risk factors might co-exist to trigger the development of acute pancreatitis. The most descriptive hypothesis of acute pancreatitis was described as gallstone induced [11]. Increased duct pressure following obstruction led to serious enzyme reactions ended into acute pancreatitis. On the other hand, mechanisms of alcohol-induced acute pancreatitis, and other cases of drug-induced pancreatitis are not well understood. Genetic and environmental factors might also be involved in the development of alcohol-related acute pancreatitis [23]. Some drug reactions were also related to genetics [24]. Whether drug-induced acute pancreatitis is also related to congenital factors, environmental factors or other existing co-factors needs further examination [11].

Even though NSAIDs are a diverse group of chemically unrelated compounds with same the anti-inflammatory therapeutic properties, differences in chemical structures should also be considered when examining the risk of acute pancreatitis. For example, sulindac, the only one NSAID which was categorized as a Class I drug, was an acetic acid derivative; three other NSAIDs, including indomethacin, diclofenac and ketorolac were also acetic acid derivatives. Nabumetone was non-acidic, but its principal metabolite, 6-MNA, has a similar chemical structure as sulindac.

Whether the correlation between NSAIDs and acute pancreatitis was related to COX-2 selectivity was also a concern [25]. By using the same claims data, we illustrated the association meloxicam, celebrex and acute pancreatitis [26,27]. The principal metabolite of nabumetone, 6-MNA, is COX-2 selective [28]. However, Sørensen HJT et al. conducted a study and showed no correlation between COX-2 selectivity of other NSAIDs and the risk of acute pancreatitis [29]. Confounding factors might be an important concern in NSAID-related acute pancreatitis. Patients searching for medical help with upper abdominal pain and gastrointestinal upset might receive some medication, including NSAIDs, before a final diagnosis is confirmed. However, the pharmacokinetics of nabumetone, (non-injection form) and relatively slower onset prevent nabumetone from being used as the first choice for patients with acute abdominal pain [30]. Acid-suppressing drugs were prescribed for symptoms of acute pancreatitis [31]. NSAIDs, with or without other drugs, were also used to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, which occurred 24 h after the procedure. However, diclofenac sodium and indomethacin via rectal administration rather than nabumetone were usually recommended [32].

There were some strengths of our study. As with other COX-2 inhibitors, nabumetone was only legally available via physicians’ prescriptions. All of those were recorded in the national single pay health insurance claims data. The high coverage rate and high accessibility of medical records made our study result more reliable.

By using claims data, our study does not account for the inherent limitations. Information on life style and physical examination status was not available, such as the amount of alcohol consumed by different subjects [33]. Serum amylase and lipase levels and imaging studies to confirm the diagnosis of acute pancreatitis, such as abdominal sonography and/or computer tomography, were also not available for each subject. The concern about incorrect coding and over-diagnosis remained in the claims data [11]. As with other drugs related to acute pancreatitis, the mechanism of nabumetone active use induced-acute pancreatitis could not be answered by this epidemiology study. Patients not using the National Health Insurance Program for diseases might not be included as cases and those with or without comorbidities might be missed. However, as mentioned above, the high National Health Insurance coverage rate and high accessibility to medical care service in Taiwan probably make the omissions negligible. Finally, despite the large size of the population, only 16 active nabumetone use patients developed acute pancreatitis within the defined exposure period. Other studies will be required to confirm this putative association.

Conclusion

Although nabumetone was not thought of as having a positive correlation with acute pancreatitis, reports were sporadic. This case–control study demonstrates that active use of nabumetone might significantly increase the risk of acute pancreatitis. This risk returned to non-specific seven days later when compared with subjects who never used nabumetone.

Specific author contributions

Shih-Chang Hung and Hung-Chang Hung substantially contributed to the conception of this article. They initiated the draft of the article and critically revised the article. Cheng-Li Lin and Chih- Huei Lin conducted the data analysis and critically revised the article. Kuan-Fu Liao and Shih-Wei Lai substantially contributed to the conception of this article. They planned and conducted the article. They critically revised the article.

Acknowledgements

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-113-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), National Research Program for Bio-pharmaceuticals (NRBP) Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. This funding agency did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Table 3

Interaction effect on acute pancreatitis between active use of nabumetone and alcohol-related disease or biliary stone during the period of 1998–2011.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Never use</th>
<th>Active use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casenumber/control number</td>
<td>OR (95% CI)</td>
<td>Casenumber/control number</td>
</tr>
<tr>
<td>No alcohol-related disease and no biliary stone</td>
<td>3751/19,907</td>
<td>As a reference</td>
</tr>
<tr>
<td>Presence of alcohol-related disease or biliary stone</td>
<td>1127/331</td>
<td>16.8 (14.7, 19.1)</td>
</tr>
</tbody>
</table>

The interaction between active use of nabumetone and presence of alcohol-related disease or biliary stone was significant (P value for interaction — 0.047).

* Adjustment for cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus; hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridemia.

Please cite this article in press as: Hung S-C, et al., Nabumetone use and risk of acute pancreatitis in a case-control study, Pancreatology (2016), http://dx.doi.org/10.1016/j.pan.2016.03.003
References


