Use of methimazole and risk of acute pancreatitis: A case–control study in Taiwan

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ABSTRACT

Objective: Some cases of acute pancreatitis have been reported to be associated with use of methimazole. The aim of this study was to investigate the relationship between use of methimazole and risk of acute pancreatitis on the basis of a systematic analysis.

Methods: This was a population-based case–control study analyzing the database of the Taiwan National Health Insurance Program. There were 5764 individuals aged 20–84 years with a first attack of acute pancreatitis from 1998 to 2011 as the cases and 23,056 randomly selected sex- and age-matched individuals without acute pancreatitis as the controls. Use of methimazole was categorized as “never use” and “ever use.” We estimated the relative risk of acute pancreatitis associated with the use of methimazole by calculating the odds ratio (OR) with 95% confidence interval (CI) using a multivariable logistic regression model.

Results: After adjustment for confounding factors, the OR of acute pancreatitis was 0.91 in individuals with ever use of methimazole, when compared with individuals with never use of methimazole (95% CI, 0.60–1.38). Unlike methimazole use, alcohol-related disease, biliary stone, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, and hypertriglyceridemia were factors significantly associated with acute pancreatitis.

Conclusions: Our study does not detect a substantial association between the use of methimazole and risk of acute pancreatitis on the basis of systematic analysis. There appears to be a discrepancy between case reports and our systematic analysis about the association between the use of methimazole and risk of acute pancreatitis.

KEY WORDS: Acute pancreatitis, alcoholism, biliary stone, diabetes mellitus, methimazole

Introduction

Acute pancreatitis is an acute inflammatory disorder of the pancreas. Clinically, it can potentially lead to severe morbidity and mortality. In Appelros and Borgström study in Sweden, the annual incidence of the first attack of acute pancreatitis was 23.4 cases per 100,000 population, and the annual mortality rate for acute pancreatitis was 1.3 cases per 100,000 population.[1]

Although many causes of acute pancreatitis have been well-established,[1-3] drug-induced pancreatitis has also been discovered.[4] To date, five cases of acute pancreatitis were reported to be associated with the use of methimazole.[5-9] Methimazole is a drug frequently used to treat hyperthyroidism and Graves' disease. Its adverse effects mainly include rash, pruritus, arthralgia, and leucopenia,[10] but acute pancreatitis is rarely mentioned.
Case reports are frequently used to detect adverse drug effects. There is still a lack of formal epidemiological studies to support the relationship between the use of methimazole and risk of acute pancreatitis. Due to severe morbidity and mortality associated with acute pancreatitis, it is necessary to estimate the risk of acute pancreatitis in users of methimazole. We therefore conducted a population-based case–control study to investigate whether there is an association between the use of methimazole and risk of acute pancreatitis.

Methods

Design and Data Source

A population-based case–control study was conducted to analyze the database of the Taiwan National Health Insurance Program. This insurance program launched in March 1995 and has covered 99% of the entire population of 23 million people living in Taiwan. The details of the insurance program were well-addressed in previous studies. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Cases and Controls

Individuals aged 20–84 years with a first attack of acute pancreatitis in 1998–2011 were identified as the cases, according to the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9 code 577.0). The index date for each case was defined as the date of diagnosing acute pancreatitis. The controls were aged 20–84 years randomly selected from those without acute pancreatitis in a ratio of 1:4 (cases vs. controls). Both cases and controls were matched for sex, age (per 5 years), and the year of diagnosing acute pancreatitis. Individuals who had ever used carbimazole or propylthiouracil were excluded from this study. Individuals with complete thyroidectomy, thyroid cancer, chronic pancreatitis, or pancreatic cancer before the index date were also excluded from this study.

Definition of Methimazole Exposure

To investigate the association between the use of methimazole and risk of acute pancreatitis, history of methimazole prescription before the index date was examined. Individuals who never had a methimazole prescription were defined as never use of methimazole. Individuals who ever had a methimazole prescription were defined as ever use of methimazole.

Potential Confounding Factors

Other medical conditions potentially associated with acute pancreatitis were included as covariables such as alcohol-related disease, biliary stone, and cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease and peripheral atherosclerosis, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, and hypertriglyceridemia were more prevalent among the cases with acute pancreatitis (Chi-square test, \( P < 0.001 \) for all) [Table 1]. There was no significant difference in ever use of methimazole between the cases and controls (\( P = 0.32 \)). The mean ages (standard deviation) were 51.89 (16.58) years in the cases and 52.35 (16.41) years in the controls (\( P = 0.06 \) for \( t \)-test).

Odds Ratio of Acute Pancreatitis Associated with Use of Methimazole and Other Medical Conditions

After adjustment for confounding factors, the OR of acute pancreatitis was 0.91 in individuals with ever use of methimazole, when compared with individuals with never use of methimazole (95% CI, 0.60–1.38). Unlike methimazole use, alcohol-related disease, biliary stone, cardiovascular disease,

### Table 1:

| Variable | Cases, \( n=5764 \) | Controls, \( n=23,056 \) | \( P \) |
|----------|---------------------|------------------------|------|
| Sex      |                     |                        |      |
| Male     | 3738 (64.85)        | 14,952 (64.85)         | 0.99 |
| Female   | 2026 (35.15)        | 8104 (35.15)           |      |
| Age group (year) |           |                        |      |
| 20-39    | 1570 (27.23)        | 6278 (27.23)           | 0.99 |
| 40-64    | 2680 (46.50)        | 10,722 (46.50)         |      |
| 65-84    | 1514 (26.27)        | 6056 (26.27)           |      |
| Use of methimazole |               |                        |      |
| Never use | 5725 (99.32)        | 22,926 (99.44)         | 0.32 |
| Ever use | 39 (0.68)           | 130 (0.56)             |      |
| Comorbidities before index date |           |                        |      |
| Alcohol-related disease | 675 (11.71) | 232 (1.01)             | <0.001 |
| Biliary stone | 1237 (21.46) | 524 (2.27)             | <0.001 |
| Cardiovascular disease | 1774 (30.78) | 4707 (20.42)           | <0.001 |
| Chronic obstructive pulmonary disease | 1164 (20.19) | 3301 (14.3)           | <0.001 |
| Diabetes mellitus | 1511 (26.21) | 2980 (12.93)           | <0.001 |
| Hepatitis B | 439 (7.62)       | 831 (3.60)             | <0.001 |
| Hepatitis C | 271 (4.70)       | 365 (1.58)             | <0.001 |
| Hypertriglyceridemia | 138 (2.39) | 214 (0.93)             | <0.001 |

Data are presented as the number of subjects in each group, with percentages given in parentheses. *Chi-square test comparing subjects with and without acute pancreatitis.
chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, and hypertriglyceridemia were factors significantly associated with acute pancreatitis [Table 2].

Discussion

In this population-based case–control study, we did not notice any increased odds of acute pancreatitis in users of methimazole. In further analysis, methimazole users were divided into two subgroups: Current use and past use of methimazole. No significant association was found between current use or past use of methimazole and acute pancreatitis (data not shown). To date, only five cases of acute pancreatitis were reported to be associated with use of methimazole, including four cases having a definite causal relationship after rechallenge test[5,6,8,9] and one case only with probable association without rechallenge test.[7] There appears to be a discrepancy between case reports and this present population-based data on the association between use of methimazole and risk of acute pancreatitis. Therefore, we cannot confirm the hypothesis of methimazole-associated acute pancreatitis previously raised in case reports.

Some important issues need to be considered in the interpretation of our data. First, although methimazole is no longer used in some countries and so its relevance is low, methimazole is a drug frequently used to treat hyperthyroidism and Graves’ disease worldwide. Before analysis, nobody knows whether individuals with acute pancreatitis have a higher proportion of ever use of methimazole. Among the cases with acute pancreatitis in this study, only 39 individuals (0.68%) had ever used methimazole. Among the controls, only 130 individuals (0.56%) had ever used methimazole. There was no significant difference in ever use of methimazole between the cases and controls. Moreover, it is relatively difficult to detect any association in this case–control study involving only a small number of individuals using methimazole. Further studies with more individuals using methimazole are needed to clarify this association. Second, due to the intrinsic limitation of this database, the exact causes of acute pancreatitis in this study were not registered. Therefore, we did not make sure whether or not a few cases could be potentially associated with use of methimazole. Third, we hope to show the original differences of medical conditions between the cases and controls. Both cases and controls were only matched for sex and age, but not for medical conditions. That is why the prevalent rates of acute pancreatitis-related factors were higher in the cases than the controls [Table 1]. Fourth, causal-effect assessment is a relatively critical and complex field in pharmacovigilance. Because an association between methimazole use and acute pancreatitis cannot be detected through our conventional statistical methodology, spontaneous adverse drug reaction reports remain to be important to dedicate pharmacovigilance databases.

Conclusions

We cannot detect an association between methimazole use and acute pancreatitis on the basis of systematic analysis. Therefore, we cannot confirm the hypothesis of methimazole-associated acute pancreatitis previously raised in case reports.

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Conflicts of Interest

There are no conflicts of interest.

References

1. Appelros S, Borgström A. Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. Br J Surg 1999;86:465-70.
2. Lai SW, Miao CH, Liao KF, Sung FC, Chen PC. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: A population-based cohort study in Taiwan. Am J Gastroenterol 2011;106:1697-704.
3. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA Intern Med 2013;173:162-4.
4. Mallory A, Kern F Jr. Drug-induced pancreatitis: A critical review. Gastroenterology 1980;78:813-20.
5. Taguchi M, Yokota M, Koyano H, Endo Y, Ozawa Y. Acute pancreatitis and parotitis induced by methimazole in a patient with Graves’ disease. Clin Endocrinol (Oxf) 1999;51:667-70.
6. Yang M, Qu H, Deng H. Acute pancreatitis induced by methimazole in a patient

Table 2:

| Variable                  | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------|-------------------|----------------------|
| Sex (male versus female) | 1.00 (0.94-1.06)  | -                    |
| Age (per 1 year)         | 1.00 (1.00-1.003) | -                    |
| Use of methimazole       | -                 | -                    |
| Ever use                 | 1.20 (0.84-1.72)  | 0.91 (0.60-1.38)     |
| Comorbidities before index date (yes versus no) | -                 | -                    |
| Alcohol-related disease  | 13.05 (11.20-15.19) | 15.62 (13.36-18.26) |
| Biliary stone            | 11.75 (10.56-13.01) | 11.52 (10.32-12.87) |
| Cardiovascular disease   | 1.73 (1.63-1.85)  | 1.17 (1.08-1.27)     |
| Chronic obstructive pulmonary disease | 1.52 (1.41-1.63) | 1.12 (1.02-1.22)     |
| Diabetes mellitus        | 2.39 (2.23-2.57)  | 2.05 (1.88-2.22)     |
| Hepatitis B              | 2.21 (1.96-2.49)  | 1.69 (1.47-1.94)     |
| Hepatitis C              | 3.07 (2.61-3.60)  | 1.90 (1.58-2.29)     |
| Hypertriglyceridemia     | 2.62 (2.11-3.25)  | 1.89 (1.49-2.41)     |

*Variables which were significantly associated with acute pancreatitis in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model. Additionally, adjusted for alcohol-related disease, biliary stone, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, and hypertriglyceridemia. CI=Confidence interval, OR=Odds ratio
with Graves' disease. Thyroid 2012;22:94-6.
7. Abraham A, Raghavan P, Patel R, Rajan D, Singh J, Mustacchia P. Acute pancreatitis induced by methimazole therapy. Case Rep Gastroenterol 2012;6:223-31.
8. Jung JH, Hahn JR, Jung J, Kim SK, Kim S, Kim KY, et al. Acute pancreatitis induced by methimazole treatment in a 51-year-old korean man: A case report. J Korean Med Sci 2014;29:1170-3.
9. Agito K, Manni A. Acute pancreatitis induced by methimazole in a patient with subclinical hyperthyroidism. J Investig Med High Impact Case Rep 2015;3:1-4.
10. Sundaresh V, Brito JP, Wang Z, Prokop LJ, Stan MN, Murad MH, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: A systematic review and network meta-analysis. J Clin Endocrinol Metab 2013;98:3671-7.
11. National Health Insurance Research Database. Taiwan. http://nhird.nhri.org.tw/en/index.html. [Last cited on 2015 Dec 01].
12. Lai SW, Liao KF, Liao CC, Muo CH, Liu CS, Sung FC. Polypharmacy correlates with increased risk for hip fracture in the elderly: A population-based study. Medicine (Baltimore) 2010;89:295-9.
13. Liao KF, Lai SW, Li CI, Chen WC. Diabetes mellitus correlates with increased risk of pancreatic cancer: A population-based cohort study in Taiwan. J Gastroenterol Hepatol 2012;27:709-13.
14. Lai SW, Liao KF, Muo CH, Hsieh DP. No association between statin use and pancreatic cancer risk in Taiwan. Kuwait Med J 2013;45:251-2.
15. Lai SW, Sung FC, Lin CL, Liao KF. Use of proton pump inhibitors correlates with increased risk of pancreatic cancer: A case-control study in Taiwan. Kuwait Med J 2014;46:44-8.
16. Liao KF, Lin CL, Lai SW, Chen WC. Parkinson's disease and risk of pancreatic cancer: A population-based case-control study in Taiwan. Neurol Asia 2015;20:251-5.
17. Lai SW, Lai HC, Lin CL, Liao KF. Zopiclone use associated with increased risk of acute pancreatitis: A case-control study in Taiwan. Int J Clin Pract 2015;69:1275-80.