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Actively using clopidogrel correlates with an increased risk of acute pancreatitis in Taiwan

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ABSTRACT

The aim of this study is to assess whether there is an association between clopidogrel use and risk of acute pancreatitis in Taiwan.

We conducted a case–control study using the database of the Taiwan National Health Insurance Program from 2000 to 2011. There were 5644 subjects aged 20–84 years with a first-time attack of acute pancreatitis as the case group and 22,576 randomly selected sex-matched and age-matched subjects without acute pancreatitis as the control group. We defined clopidogrel use as "actively using" if the final clopidogrel prescription was filled between 0 and 7 days before the date of diagnosing acute pancreatitis, or "not actively using" if the final clopidogrel prescription was filled ≧8 days before the date of diagnosing acute pancreatitis. Subjects who never used clopidogrel were defined as never used. The multivariable logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) of acute pancreatitis associated with clopidogrel use. Comparing the subjects actively using clopidogrel to those who never used clopidogrel, the adjusted OR of acute pancreatitis was 8.46 (95%CI 5.25, 13.7). The adjusted OR decreased to 1.16 among subjects not actively using clopidogrel (95%CI 0.95, 1.43).

Persons actively using clopidogrel are at an increased risk of acute pancreatitis. Further studies are necessary to prove the causal relationship.

1. Introduction

Acute pancreatitis is a life-threatening condition characterized by acute inflammation of the pancreas. The epidemiological studies have revealed that gallstones and alcoholism account for 75–80% of all cases of acute pancreatitis[1, 2]. In addition, a growing body of evidence shows that many drugs have been reported to be associated with acute pancreatitis, with estimation of 2% of all cases[2, 3].

Clopidogrel is an antiplatelet agent commonly used in cardiovascular disease with significant benefits. However, bleeding is the major adverse event of clopidogrel therapy, which may frequently result in discontinuation or noncompliance with this agent[4].

So far, no case of acute pancreatitis associated with clopidogrel use has been published, whereas US Food and Drug Administration (FDA) has reported that from 1999 to 2012, 240 persons (0.36%) had acute pancreatitis among 67298 persons reporting to have adverse events when using clopidogrel[5]. Since the causal relationship between clopidogrel use and risk of acute pancreatitis remains uncertain in the US FDA report, we conducted a population-based case–control study using the database of the Taiwan National Health Insurance Program to assess whether there is an association between clopidogrel use and risk of acute pancreatitis.

2. Materials and methods

A case–control study was conducted usingthe database of the Taiwan National Health Insurance Program. Briefly speaking, the insurance program started in March 1995 and it provided outpatient, hospitalization and emergency services. Nearly, 99% of 23 million citizens living in Taiwan were covered[6]. In this program, diseases were diagnosed based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 codes). The program details can be found in previous studies[6–8]. This study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital in Taiwan (CMU-REC-101-012).

2.1. Participants

From 2000 to 2011, subjects aged 20–84 with a first-time attack of acute pancreatitis were defined as the case group (ICD-9 code 577.0).We defined the index date for each case

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as the date of diagnosing acute pancreatitis. For each case with acute pancreatitis, we randomly selected four subjects without acute pancreatitis from the same database as the control group. Both groups were matched by sex, age (within five years), and index year of diagnosing acute pancreatitis. Subjects with chronic pancreatitis or pancreatic cancer before the date of diagnosing acute pancreatitis were excluded from this study.

2.2. Comorbidities potentially associated with acute pancreatitis risk

Comorbidities before the date of diagnosing acute pancreatitis potentially associated with acute pancreatitis risk were included as following: alcoholism, biliary stone, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B infection, hepatitis C infection, hypertriglyceridemia, as well as cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease and peripheral atherosclerosis[8–10]. All comorbidities were diagnosed based on ICD-9 codes.

2.3. Definition of clopidogrel exposure

Clopidogrel's active metabolite inhibits platelet adenosine diphosphate (ADP) receptor binding irreversibly[11, 12].Since the platelet lifespan is about 7–10 days, we used the period of 7 days as a cut-point. We defined clopidogrel use as "actively using" if the final clopidogrel prescription was filled between 0 and 7 days before the date of diagnosing acute pancreatitis, or "not actively using" if the final clopidogrel prescription was filled ≧8 days before the date of diagnosing acute pancreatitis. Subjects who never used clopidogrel were defined as never used.

2.4. Statistical analysis

In the beginning, we used the Chi-square test to compare the differences between the case group and the control group for the distributions of demographic profile, clopidogrel use and comorbidities. Then, all covariables were included in a univariable unconditional logistic regression model. Lastly, only those found significantly were further included in a multivariable unconditional logistic regression model to calculate the odds ratio (OR) and 95% confidence interval (CI) for risk of acute pancreatitis associated with clopidogrel use and comorbidities. The probability value<0.05 was considered statistically significant (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Characteristics of the study population

Totally, 5644 subjects with acute pancreatitis as cases and 22,576 subjects without acute pancreatitis as controls were included with equal distributions in sex and age (Table 1). The mean ages (standard deviation) were 53.59 (16.53) years in the case group and 53.13 (16.68) years in the control group. The cases tended to have higher proportions of clopidogrel use, alcoholism, biliary stone, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C and hypertriglyceridemia ($P < 0.001$ for all).

3.2. Odds ratio of acute pancreatitis associated with clopidogrel use and comorbidities

After adjusting for sex, age, alcoholism, biliary stone, cardiovascular disease, cardiovascular disease, diabetes mellitus, hepatitis B, hepatitis C and hypertriglyceridemia andcomparing the persons actively using clopidogrel to those who never used clopidogrel, the adjusted OR of acute pancreatitis was 8.46 (95%CI 5.25, 13.7). The adjusted OR decreased to 1.16 among persons not actively using clopidogrel (95%CI 0.95, 1.43) (Table 2). In addition, alcoholism (OR 12.90, 95%CI 11.00,15.30), biliary stone (OR 12.29, 95%CI 10.99,13.73), cardiovascular disease (OR 1.32, 95%CI 1.21,1.45), chronic obstructive pulmonary disease (OR 1.30,95%CI 1.19, 1.42), diabetes mellitus (OR 1.98, 95%CI 1.81, 2.16), hepatitis B (OR 1.56, 95%CI 1.36, 1.79), hepatitis C (OR 2.03, 95%CI 1.70, 2.44) and hypertriglyceridemia (OR 1.40, 95%CI 1.29,1.51) were also significantly associated with risk of acute pancreatitis.

3.3. Interaction effect between actively using clopidogrel and cardiovascular disease on risk of acute pancreatitis

In further analysis, as a reference of persons without cardiovascular disease and those who never used clopidogrel, the adjusted OR of acute pancreatitis was 1.82 among persons with cardiovascular disease and those who never used clopidogrel (95%CI 1.68, 1.97) and the adjusted OR significantly increased to 13.42 among persons with cardiovascular disease and those actively using clopidogrel (95%CI 8.54, 21.1) (Table 3).

4. Discussion

To the best of our knowledge, this is the first pharmacoepidemiological study using the population-basedclaim data to assess the association between clopidogrel use and risk of acute pancreatitis.

Table 1
Characteristics between persons with and without acute pancreatitis.

	Controls Number = 22,576		Cases Number = 5644		*P* value[a]
	n	(%)	n	(%)	
Sex					0.99
Male	8404	37.23	2101	37.23	
Female	14,172	62.77	3543	62.77	
Age group (years)					0.99
20–39	5558	24.62	1390	24.63	
40–64	10,466	46.36	2616	46.35	
65–84	6552	29.02	1638	29.02	
Clopidogrel use[b]					<0.001
Never used	22,124	98.00	5384	95.39	
Actively using	27	0.12	68	1.20	
Not actively using	425	1.88	192	3.40	
Comorbidities before index date[c]					
Alcoholism	217	0.96	583	10.33	<0.001
Biliary stone	554	2.45	1255	22.24	<0.001
Cardiovascular disease	5118	22.67	1845	32.69	<0.001
Chronic obstructive pulmonary disease	3529	15.63	1230	21.79	<0.001
Diabetes mellitus	3257	14.43	1543	27.34	<0.001
Hepatitis B	835	3.70	442	7.83	<0.001
Hepatitis C	389	1.72	295	5.23	<0.001
Hypertriglyceridemia	5285	23.41	2078	36.82	<0.001

Data with percentages (under the "(%)" columns) are presented as the number of subjects in each group.
[a] Chi-square test comparing subjects with and without acute pancreatitis.
[b] We defined clopidogrel use as "actively using" if the final clopidogrel prescription was filled between 0 and 7 days before the date of diagnosing acute pancreatitis, or "not actively using" if the final clopidogrel prescription was filled ≧8 days before the date of diagnosing acute pancreatitis. Subjects who never used clopidogrel were defined as never used.
[c] The index date was defined as the date of diagnosing acute pancreatitis.