

Original article

Fluvastatin use and risk of acute pancreatitis: a population-based case-control study in Taiwan

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Received 24th of September, 2016 Accepted 20th of October, 2016

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Keywords:

Acute pancreatitis;
Alcohol;
Biliary stone;
Diabetes mellitus;
Fluvastatin

ABSTRACT

Objectives: This study aimed to examine the association between fluvastatin use and acute pancreatitis in Taiwan.

Methods: Using the database from the Taiwan National Health Insurance (NHI) Program, we designed a case-control study which consisted of 3501 individuals aged 20-84 with new at-the-time diagnoses acute pancreatitis as the case group and 8373 randomly selected individuals without acute pancreatitis as the control group during the period of 1998-2011. Both groups were matched for sex, age, and index year of being diagnosed with acute pancreatitis. "Current use" of fluvastatin was defined as individuals whose last remaining tablet of fluvastatin was noted ≤ 7 days before the date of their being diagnosed with acute pancreatitis. "Late use" of fluvastatin was defined as individuals whose last remaining tablet of fluvastatin was noted within 8-30 days before the date of their being diagnosed with acute pancreatitis. "No use" of fluvastatin was defined as individuals who had never had a fluvastatin prescription. The odds ratio (OR) and 95% confidence interval (CI) for acute pancreatitis associated with fluvastatin use was examined using a multivariable unconditional logistic regression analysis.

Results: After adjustment for potential confounders, the multivariable analysis showed that the adjusted ORs of acute pancreatitis were 1.17 for individuals with "current use" of fluvastatin (95% CI 0.69, 1.97) and 1.82 for individuals with "late use" of fluvastatin (95% CI 0.41, 8.19), but there was no statistical significance when compared with individuals with "no use" of fluvastatin.

Conclusions: In this study, no association was detected between fluvastatin use and acute pancreatitis.

1. Introduction

Fluvastatin, being a member of the statins, is the first fully synthetic HMG-CoA reductase inhibitor and is commonly used to treat patients with hypercholesterolemia and further to reduce the risk of cardiovascular disease [1, 2]. Clinically, fluvastatin has been used with relative efficacy, safety, and tolerability. Its few adverse effects include myopathy (including myositis and rhabdomyolysis), as well as asymptomatic, reversible elevations of serum creatine phosphokinase and serum hepatic transaminase [1, 3, 4]. However, one case regarding fluvastatin-related acute pancreatitis has been reported by Tysk *et al.* in Saudi-Arabia [5]. In addition, the U.S. Food and Drug Administration (FDA) has

also reported that during 2010, only 6 individuals (0.97%) had acute pancreatitis among the 617 individuals who reported having adverse effects when using fluvastatin [6].

Drug-induced acute pancreatitis contributes to approximately 2% of the cases of acute pancreatitis [7, 8]. To date, no population-based pharmacoepidemiological research is available on the association between fluvastatin use and acute pancreatitis. Given extensive use of fluvastatin clinically and on the basis of the above-mentioned case report and the U.S. FDA report, we made a plausible hypothesis that there is an association between fluvastatin use and acute pancreatitis. If this association is shown to really exist, physicians can then alert their patients as to the risk of acute pancreatitis when using fluvastatin. It is with this in

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mind that we conducted a population-based case-control study to examine this question.

2. Methods

2.1. Study design and study population

Taiwan is an independent country with more than 23 million people. Using the database of the Taiwan National Health Insurance (NHI) Program, we designed a population-based case-control study. Briefly, this insurance program started in March 1, 1995, and now covers approximately 99% of the 23 million people living in Taiwan [9]. Details of the NHI program have been well-reported previously [10-21]. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taichung, Taiwan (CMUH-104-REC2-115).

2.2. Inclusion criteria

Based on the International Classification of Diseases 9th Revision-Clinical Modification (ICD-9 code), we defined the cases of acute pancreatitis for our study as individuals aged 20-84 years at the date of their diagnosis, who were then newly diagnosed with acute pancreatitis (ICD-9 code 577.0) during the period of 1998-2011. We defined the index date for each case as the date of their being diagnosed acute pancreatitis. We randomly selected individuals without acute pancreatitis from the same database as controls, and matched them to those with acute pancreatitis according to sex, age (within 5 years), and the index year of the latter's being diagnosed with acute pancreatitis. Individuals with chronic pancreatitis (ICD-9 code 577.1) or pancreatic cancer (ICD-9 code 157) before the date of their being diagnosed with acute pancreatitis were excluded from this study. Individuals who received at least 1 prescription for other statins or non-statin lipid-lowering drugs were also excluded from the study.

2.3. Comorbidities potentially associated with acute pancreatitis

Comorbidities before the date of an individual being diagnosed with acute pancreatitis were included as follows: alcohol-related diseases (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0-571.3, 790.3 and V11.3), biliary stone (ICD-9 code 574), cardiovascular diseases including coronary artery disease, heart failure, cerebrovascular disease, and peripheral atherosclerosis (ICD-9 codes 410-414, 428, 430-438 and 440-448), chronic kidney disease (ICD-9 codes 585-586 and 588.8-588.9), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493 and 496), diabetes mellitus (ICD-9 code 250), hepatitis B (ICD-9 codes V02.61, 070.20, 070.22, 070.30 and 070.32), hepatitis C (ICD-9 codes V02.62, 070.41, 070.44, 070.51 and 070.54), hyperparathyroidism (ICD-9 code 252.0), and hypertriglyceridemia (ICD-9 codes 272.1, 272.2 and 272.4). The diagnostic accuracy of these comorbidities based on ICD-9 codes has been written about in previous studies [22-30].

2.4. Definition of fluvastatin exposure

According to its prescription date, the last remaining tablet of fluvastatin can be estimated. To decrease biased results, individuals whose last remaining tablet of fluvastatin was noted > 1 month

before the date of their being diagnosed with acute pancreatitis were excluded from the study. Therefore, only individuals whose last remaining tablet of fluvastatin was noted within 1 month prior to the date of their being diagnosed with acute pancreatitis were included in this study. The elimination half-life of fluvastatin ranges from approximately 30 minutes to 1.2 hours in healthy individuals [3, 31]. Thus, a period of 7 days was used as a cut-off point, something which we adopted from previous studies [27, 28, 32]. "Current use" of fluvastatin was defined as individuals whose last remaining tablet of fluvastatin was noted ≤ 7 days before the date of their being diagnosed with acute pancreatitis or those still having fluvastatin tablets at the date of their being diagnosed with acute pancreatitis. "Late use" of fluvastatin was defined as individuals whose last remaining tablet of fluvastatin was noted within 8-30 days before the date of their being diagnosed with acute pancreatitis. "No use" of fluvastatin was defined as individuals who never had a fluvastatin prescription.

2.5. Statistical Analysis

The differences in sex, age, fluvastatin use, and comorbidities between the cases and the controls were compared using a *Chi*-square test and a Fisher exact test for categorized variables, and a *t*-test for continuous variables. Initially, all variables were included in a univariable unconditional logistic regression model. Variables found to be significant in this univariable model were then included in a multivariable unconditional logistic regression model to measure the odds ratio (OR) and 95% confidence interval (CI) for acute pancreatitis risk associated with fluvastatin use and comorbidities. We used the SAS software for all data analysis (version 9.2 for Windows; SAS Institute Inc., Cary, North Carolina, USA). A *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic characteristics of the study population

In total, 3501 individuals with acute pancreatitis were selected as cases and 8373 individuals without acute pancreatitis were selected as controls. Table 1 presents the demographic characteristics between the cases and controls. The mean ages (standard deviation) were 49.2 (16.0) years in cases and 48.6 (15.8) years in controls (*t*-test, *P* = 0.03). The cases were more likely to have higher proportions of "current use" of fluvastatin and "late use" of fluvastatin than the controls, but that was without a statistical significance (0.66% vs. 0.49% for current use, and 0.09% vs. 0.05% for late use, respectively, *Chi*-square test, *P* = 0.39). The individuals in the cases group tended to have higher proportions of alcohol-related diseases, biliary stone, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism, and hypertriglyceridemia than the individuals in the controls (*Chi*-square test, *P* < 0.05 for all).

3.2. Association between acute pancreatitis and fluvastatin use

After adjusting for multiple confounders, the multivariable analysis showed that the adjusted ORs of acute pancreatitis were 1.17 for individuals with "current use" of fluvastatin (95%CI 0.69,

Table 1 – Demographic characteristics of cases with acute pancreatitis and controls in Taiwan during the period of 1998-2011.

Variable	Controls N = 8373		Cases N = 3501		P value*
	n	(%)	n	(%)	
Sex					0.99
Female	2679	(32.0)	1120	(32.0)	
Male	5694	(68.0)	2381	(68.0)	
Age group (years)					0.07
20-39	2979	(35.6)	1203	(34.4)	
40-64	3820	(45.6)	1578	(45.1)	
65-84	1574	(18.8)	720	(20.6)	
Age (years), mean (standard deviation)[†]	48.6	(15.8)	49.2	(16.0)	0.03
Fluvastatin					0.39
No use	8328	(99.46)	3475	(99.25)	
Current use	41	(0.49)	23	(0.66)	
Late use	4	(0.05)	3	(0.09)	
Comorbidities before index date					
Alcohol-related diseases	1148	(13.7)	545	(15.6)	0.008
Biliary stone	715	(8.54)	406	(11.6)	< 0.001
Cardiovascular diseases	1417	(16.9)	666	(19.0)	0.006
Chronic kidney disease	115	(1.37)	100	(2.86)	< 0.001
Chronic obstructive pulmonary disease	1123	(13.4)	519	(14.8)	0.04
Diabetes mellitus	623	(7.44)	365	(10.4)	< 0.001
Hepatitis B	185	(2.21)	146	(4.17)	< 0.001
Hepatitis C	79	(0.94)	93	(2.66)	< 0.001
Hyperparathyroidism ^{&}	1	(0.01)	9	(0.26)	< 0.001
Hypertriglyceridemia	658	(7.86)	336	(9.60)	0.002

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

*Chi-square test, [&]Fisher exact test, and [†]t test comparing subjects with and without acute pancreatitis.

1.97) and 1.82 for individuals with “late use” of fluvastatin (95% CI 0.41, 8.19), but there was no statistical significance when compared with individuals with “no use” of fluvastatin (Table 2).

4. Discussion

In this population-based case-control study, we observed that fluvastatin use was not associated with acute pancreatitis, no matter whether “current use” or “late use” of fluvastatin. To date, only one case regarding fluvastatin-related acute pancreatitis has been reported by Tysk *et al.* in Saudi-Arabia, a case which was definitely confirmed after receiving a re-challenge test [5]. The adverse effects of fluvastatin use published by the U.S. Food and Drug Administration (FDA) do not indicate a causal relationship between fluvastatin use and acute pancreatitis [6]. However, besides this study no other pharmacoepidemiological research on this issue is available. We cannot compare our research with anything. Therefore, this present study cannot support the hypothesis of fluvastatin-related acute pancreatitis raised in the one aforementioned case report and the adverse effect report issued by the U.S. FDA.

The relevant literature was reviewed to address the biological

plausibility of fluvastatin-related or -caused acute pancreatitis. Generally speaking, serious adverse effects of statin therapy are commonly associated with concomitant drugs affecting statin metabolism and are rarely associated with specific adverse responses to statin monotherapy [2, 33-35]. Fluvastatin is mainly metabolized by the cytochrome P-450 2C9 pathway, not by the cytochrome P-450 3A4 pathway [2, 33-35]. In theory, fluvastatin is less likely to provoke drug interaction than other statins [2, 33-35]. Whether some concomitant key drugs potentially inhibiting cytochrome P-450 2C9 might provoke drug interaction with fluvastatin should be considered. Despite serious adverse effects of statin therapy, such effects are rarely associated with statin monotherapy. Whether fluvastatin has an idiosyncratic effect or a direct toxic effect on the pancreas should also be considered. More research on this issue is needed to elucidate this issue.

Some concerns of this present study should be taken into consideration when interpreting our results. First, since the Taiwan NHI claims database is inherently restricted by a lack of laboratory results, diagnostic misclassification of acute pancreatitis is likely, which may have confounded our results. However, the diagnostic accuracy of acute pancreatitis based on ICD-9 codes has been examined in previous studies [36-39]. Second, due to the same limitation, some crucial confounders such as detrimental

Table 2 – Crude and adjusted odds ratio and 95% confidence interval for acute pancreatitis associated with fluvastatin use in Taiwan during the period of 1998-2011.

Variable	Crude		Adjusted [†]	
	OR	(95% CI)	OR	(95% CI)
Fluvastatin (no use as a reference)				
Current use	1.34	(0.81, 2.24)	1.17	(0.69, 1.97)
Late use	1.80	(0.40, 8.04)	1.82	(0.41, 8.19)

[†]Variables found to be significant in the univariable unconditional logistic regression model were further analyzed in the multivariable unconditional logistic regression model.

Additionally adjusted for age, alcohol-related diseases, biliary stone, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism, and hypertriglyceridemia.

life style or unhealthy habits are not documented in this database. Because of this, we used alcohol-related diseases instead of alcoholism and chronic obstructive pulmonary disease instead of cigarette smoking. Third, and also due to the same limitation, we are not sure how many individuals with acute pancreatitis had said acute pancreatitis caused by fluvastatin use in this study because the etiologies of acute pancreatitis are not documented in this database. In addition, only 0.75% of the cases in the database had been exposed to fluvastatin. Insufficient statistical power is a great concern. Fourth, only one case regarding fluvastatin-related acute pancreatitis has been reported in the extant literature [5], and only 6 cases of fluvastatin-related acute pancreatitis have been reported by the U.S. Food and Drug Administration [6]. The incidence of fluvastatin-related or -caused acute pancreatitis might be very low. Furthermore, no statistically significant findings have been disclosed. Whether the frequency of this adverse effect is really so low or only under-reported cannot be determined in this study. Fifth, we hope to show the original difference of comorbidities between the cases and controls. Only sex and age were matched between the cases and controls; the comorbidities were not matched. That is why the case group tended to have higher proportions of alcohol-related diseases, biliary stone, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism, and hypertriglyceridemia than the control group (*Chi-square test*, $P < 0.05$ for all). Last, although patients with acute pancreatitis may have recurrent attacks, only those with newly (at-the-time) diagnosed acute pancreatitis could be included in this study. Individuals with at-the-time current acute pancreatitis or chronic pancreatitis were not included.

Having said all of that, there are some advantages of this study. Individuals receiving at least 1 prescription for other statins or non-statin lipid-lowering drugs were excluded from this study. Therefore, this is the first population-based case-control study focusing on the association between only fluvastatin use and acute pancreatitis—it is not confounded by other lipid-lowering drugs. In addition, this topic is clinically relevant with a potential implication for practice. The methodology and the analysis were well-conducted. The results are of clinical importance. The study provides updated pharmacoepidemiological evidence on this issue.

All things considered, we have concluded that no association can be detected between fluvastatin use and acute pancreatitis, regardless of whether the case is “current use” or “late use” of fluvastatin. Of course, additional studies are needed to confirm

our findings.

Acknowledgments

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW106-TDU-B-212-113004). This funding agency did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Specific author contributions

Kuan-Fu Liao planned and conducted this study. He participated in the data interpretation and also critically revised the article. Po-Tsung Huang, Ching-Chun Lin, and Cheng-Li Lin conducted the data analysis and critically revised the article. Shih-Wei Lai planned and conducted this study. He substantially contributed to the conception of the article, initiated the draft of the article, and critically revised the article.

Conflicts of Interest Statement

The authors disclose no conflicts of interest.

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