No association between losartan use and acute pancreatitis in hypertensive patients

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ABSTRACT

Background and objective Clinical evidence is scarce about the relationship between losartan use and acute pancreatitis. We therefore conducted a population-based case–control study using the database from the Taiwan National Health Insurance Program to investigate this question.

Methods The study consisted of 1449 hypertensive subjects aged 20–84 years with a first episode of acute pancreatitis during the period 2000–2011 as the case group and 2479 hypertensive subjects without acute pancreatitis as the control group. Both the case and control groups were matched for sex, age, comorbidities and index year of acute pancreatitis diagnosis. According to the history of losartan prescription before the date of diagnosis of acute pancreatitis, subjects who had never received a prescription for losartan were defined as 'never use of losartan', those whose last remaining losartan tablet was detected within 7 days before the date of diagnosis of acute pancreatitis were defined as 'current use of losartan' and those whose last remaining tablet of losartan was detected ≥8 days before the date of diagnosis of acute pancreatitis were defined as 'late use of losartan'. ORs and 95% CIs were measured to investigate the risk of acute pancreatitis associated with losartan use by the multivariable unconditional logistic regression model.

Results After adjustment for potentially confounding factors, the adjusted OR of acute pancreatitis was 0.96 (95% CI 0.68 to 1.37) for subjects with current use of losartan compared with those with never use of losartan, but the difference was not statistically significant. For subjects with late use of losartan the adjusted OR of acute pancreatitis was 1.05 (95% CI 0.80 to 1.37), which also was not statistically significant.

Conclusions No significant association can be detected between losartan use and acute pancreatitis in hypertensive patients. More research is required to determine the potential role of losartan in the risk of acute pancreatitis.

INTRODUCTION

Losartan, the first angiotensin II antagonist available in the market, is mainly prescribed for the treatment of hypertension, with good efficacy and tolerability.[1 2] Clinically, very few adverse events of losartan use have been reported; those reported include hepatotoxicity, bullous pemphigoid and angioedema.[3–5] Additionally, three cases of acute pancreatitis have been reported to be potentially related to losartan use.[6–8] The US Food and Drug Administration has shown that, among 13173 people reporting side effects when taking losartan since 2001–2012, 20 (0.15%) had acute pancreatitis, but the causal effect was not elucidated.[9]

Although numerous factors have been found to be related to acute pancreatitis including alcohol, biliary stones and type 2 diabetes mellitus,[10 11] about 0.1–2% of acute pancreatitis cases were potentially related to medication use.[12 13] However, clinical evidence on the relationship between losartan use and acute pancreatitis based on systematic population-based research is scarce. If losartan use might be associated with acute pancreatitis, clinicians should take this drug into consideration in search of the aetiologies of acute pancreatitis. We therefore conducted a population-based case–control study to investigate this question.

METHODS

Design and study population

We conducted a population-based case–control study using the database from the Taiwan National Health Insurance Program. This programme launched on 1 March 1995 and covers about 99% of the 23 million citizens living in Taiwan.[14] The details of the programme have been well documented in previous papers.[15–21] This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Cases and controls

Hypertensive subjects aged 20–84 years with a first episode of acute pancreatitis according to the International Classification of Diseases 9th Revision Clinical Modification (ICD-9 code 577.0) during the period 2000–2011 were selected as the case group. The index date for each case was defined as the date on which acute pancreatitis was diagnosed. Hypertensive subjects without a diagnosis of acute pancreatitis were randomly selected from the same database as the control group. Both case and control groups were matched for sex, age (every 5 years), comorbidities and the index year of diagnosing acute pancreatitis. To decrease biased results, subjects who had chronic pancreatitis (ICD-9 code 577.1) or pancreatic cancer (ICD-9 code 157) before the date acute pancreatitis was diagnosed were excluded from the study. Subjects who had prescriptions for other angiotensin II receptor antagonists available in Taiwan were also excluded from the study.

Comorbidities

Comorbidities potentially associated with acute pancreatitis before the index date were included as follows: alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3 and V11.3), biliary stone (ICD-9 code 574),

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cardiovascular disease 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 hypertriglyceridaemia (ICD-9 code 272.1). The ICD-9 code accuracy of these comorbidities has been well reviewed in previous studies.[22–32] A prescription history of other antihypertensive agents available in Taiwan was also included in the study.

Definition of losartan exposure

According to the history of losartan prescription before the date of diagnosis of acute pancreatitis, we could estimate the last remaining tablet for losartan. The definition of losartan use was adapted from previous studies.[27 33–35] Subjects whose last remaining tablet of losartan was detected within 7 days before the date of diagnosis of acute pancreatitis or who still had losartan tablets at the date on which acute pancreatitis was diagnosed were defined as 'current use of losartan'. Subjects whose last remaining losartan tablet was detected ≥8 days before the date of diagnosis of acute pancreatitis were defined as 'late use of losartan'. Subjects who had never received a prescription for losartan were defined as 'never use of losartan'.

Statistical analysis

The distributions of sex, age, use of losartan, use of other antihypertensive agents and comorbidities were compared between the case and control groups using the χ^2 test and Fisher exact test for categorised variables and the t test for continuous variables. All variables were first included in the univariable unconditional logistic regression model and those found to be significant were further examined in the multivariable unconditional logistic regression model. ORs and 95% CIs were measured to investigate the risk of acute pancreatitis associated with losartan use. All data processing and statistical analyses were performed with SAS software V.9.2 (SAS Institute, Cary, North Carolina, USA). A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 shows the distributions of sex, age, use of losartan, use of other antihypertensive agents and comorbidities between the case and control groups. This study consisted of 1449 cases with acute pancreatitis and 2479 controls without acute pancreatitis, with a similar sex and age distribution. The mean±SD ages of the study subjects were 59.4±14.3 years for the case group and 59.0±14.6 years for the control group, without statistical significance (t test, p=0.47). There was no significant difference in current use or late use of losartan between the case and control groups (χ^2 test, p=0.75). The case group had higher proportions of ever use of other antihypertensive agents (94.41% vs 92.05%), alcohol-related disease (10.6% vs 7.70%), biliary stone (26.4% vs 22.7%), chronic kidney disease (6.42% vs 4.03%), hepatitis B (4.69% vs 2.22%), hepatitis C (4.00% vs 1.82%), hyperparathyroidism (0.48% vs 0.04%) and hypertriglyceridaemia (2.83% vs 1.13%) than the control group, which was statistically significant (χ^2 test and Fisher exact test, p<0.05).

Table 1 Characteristics of cases with acute pancreatitis and controls from 2000 to 2011

	Cases (N=1449)		Controls (N=2479)		
Variable	**n**	**(%)**	**n**	**(%)**	**p Value***
Sex					0.89
Female	549	(37.9)	945	(38.1)	
Male	900	(62.1)	1534	(61.9)	
Age group (years)					0.80
20–39	159	(11.0)	257	(10.4)	
40–64	723	(49.9)	1234	(49.8)	
65–84	567	(39.1)	988	(39.9)	
Age (years), mean (SD)†	59.4	(14.3)	59.0	(14.6)	0.47
Losartan					0.75
Never use	1300	(89.7)	2238	(90.3)	
Current use	52	(3.6)	90	(3.6)	
Late use	97	(6.7)	151	(6.1)	
Other antihypertensive agents					0.006
Never use	81	(5.59)	197	(7.95)	
Ever use	1368	(94.41)	2282	(92.05)	
Comorbidities before index date					
Alcohol-related disease	154	(10.6)	191	(7.70)	0.002
Biliary stone	383	(26.4)	563	(22.7)	0.009
Cardiovascular disease	623	(43.0)	1048	(42.3)	0.66
Chronic kidney disease	93	(6.42)	100	(4.03)	<0.001
Chronic obstructive pulmonary disease	364	(25.1)	596	(24.0)	0.45
Diabetes mellitus	367	(25.3)	567	(22.9)	0.08
Hepatitis B	68	(4.69)	55	(2.22)	<0.001
Hepatitis C	58	(4.00)	45	(1.82)	<0.001
Hyperparathyroidism‡	7	(0.48)	1	(0.04)	0.005
Hypertriglyceridaemia	41	(2.83)	28	(1.13)	<0.001

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with SD given in parentheses.
*χ^2 test.
†t test comparing subjects with and without acute pancreatitis.
‡Fisher exact test.

Acute pancreatitis associated with losartan use

After adjusting for other antihypertensive agents, alcohol-related disease, biliary stone, chronic kidney disease, hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridaemia, the multivariable unconditional logistic regression model demonstrated that the adjusted OR of acute pancreatitis was 0.96 (95% CI 0.68 to 1.37) for subjects with current use of losartan compared with subjects with never use of losartan, which was not statistically significant. The adjusted OR of acute pancreatitis was 1.05 (95% CI 0.80 to 1.37) for subjects with late use of losartan, which also was not statistically significant (table 2).

DISCUSSION

Although more than 90% of patients had used other antihypertensive agents in both groups, to date, three case reports of acute pancreatitis have been found to be potentially related to losartan use.[6–8] That is why we focus on the relationship between losartan use and acute pancreatitis in hypertensive patients by using population-based claims data. In this well-matched case–control study we observed no significant association between losartan use and acute pancreatitis, irrespective of whether patients were current users or late users of losartan.

Table 2 ORs and 95% CIs for acute pancreatitis associated with losartan use from 2000 to 2011

	Crude		Adjusted*	
Variable	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Losartan use (never use as reference)				
Current use	1.00	(0.70 to 1.41)	0.96	(0.68 to 1.37)
Late use	1.11	(0.85 to 1.44)	1.05	(0.80 to 1.37)

*Controlled for other antihypertensive agents, alcohol-related disease, biliary stone, chronic kidney disease, hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridaemia.

Previous studies in Europe have reported the possibility of a protective effect of angiotensin II antagonists in acute pancreatitis, but they did not reach statistical significance.[36 37] There seems to be a conflicting result between case reports and epidemiological data on the association between losartan use and acute pancreatitis.

We have reviewed and summarised the current knowledge on this question. First, the local renin-angiotensin system in the pancreas plays an important role in regulation of pancreatic acinar cell digestive enzyme secretion and pancreatic ducts.[38–40] In animal models, losartan may decrease pancreatic parenchymal necrosis and neutrophil infiltration, inhibit acinar digestive enzyme secretion and further ameliorate the pancreatic injury in experimental acute pancreatitis.[38 41 42] These data suggest that losartan may protect against acute pancreatitis, which can partially explain why previous epidemiological studies have shown that losartan use is associated with a non-significantly reduced risk of acute pancreatitis.[36 37] Second, losartan may induce angioedema and rash.[3 43] We think that losartan may also induce hypersensitivity of the pancreas, which leads to the onset of acute pancreatitis. This can partially explain the mechanism of case reports. Therefore, the literature is somewhat ambivalent about potential mechanisms by which losartan may promote or protect against acute pancreatitis. Further research is needed to elucidate the underlying mechanism.

Limitations and strengths of the study

This study has some limitations. First, the underlying causes of acute pancreatitis were not recorded in the database, so there is no knowing how many patients of acute pancreatitis were really caused by losartan. Second, we were not sure whether the patients actually took losartan. This is an almost universal limitation of administrative databases. Instead, we used losartan prescriptions for analysis. There could be a small gap between use of medication and prescription of medication. Third, some known risk factors for acute pancreatitis were not recorded in the database such as alcohol, smoking and body mass index. We included alcohol-related disease instead of alcohol and included chronic obstructive pulmonary disease instead of smoking. Alcohol-related disease does not necessarily indicate similar consumption of alcohol (quantity, frequency, pattern (binge vs daily use)) among cases and controls. Thus, it cannot be inferred that both groups had similar exposure to alcohol. Fourth, it is very difficult to include all potentially concurrent medications for analysis. We focus on losartan use only and acute pancreatitis. Fifth, a retrospective case–control study design can only demonstrate a statistical association with no conclusion about causation. Such a design is not sufficiently robust for the inference made.

Some strengths of this study should also be mentioned. Losartan is the first angiotensin II antagonist available in the market. It has more research to be reviewed, which is why we selected losartan for study. This is a potentially important report on a retrospective case–control study examining the association of losartan use with acute pancreatitis after excluding those with use of other angiotensin II receptor antagonists. The methodology, data and interpretation are fairly appropriate. The findings of this study are of interest, given the scarcity of clinical data around this question.

CONCLUSION

We conclude that no significant association can be detected between losartan use and acute pancreatitis in hypertensive patients. More research is required to illustrate the potential role of losartan in the risk of acute pancreatitis.

Key messages

What is already known on this subject

- A few cases with acute pancreatitis have been reported to be potentially related to losartan use.
- Clinical evidence based on systematic research is scarce about the relationship between losartan use and acute pancreatitis.

What this study adds

- This systematic population-based case–control study demonstrates that no significant association can be detected between losartan use and acute pancreatitis in hypertensive patients.

Contributors S-WL planned and conducted the study, substantially contributed to the conception of the article, initiated the draft of the article and critically revised it. H-FL and C-LL conducted the data analysis and critically revised the article. K-FL planned and conducted the study, participated in the data interpretation and critically revised the article.

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Competing interests None declared.

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