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The risk of ischemic cerebrovascular disease associated with benzbromarone use in gout people

A retrospective cohort study in Taiwan

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Abstract

Epidemiological studies have shown that people having hyperuricemia are at increased risk of ischemic cerebrovascular disease. This research aimed to study the relation of ischemic cerebrovascular disease with benzbromarone use among persons with gout-related disorders. This was a retrospective cohort design utilizing a 2003 to 2015 national health insurance database in Taiwan. Subjects aged 20 to 99 years who already had suffered from gout-related disorders were included as eligible subjects. Eligible persons who had the benzbromarone prescription alone were selected into the benzbromarone group. Sex-matched and age-matched eligible persons who never used any urate-lowering agents were selected into the control group. An index date was set as a date of benzbromarone being prescribed. The end-point was defined as ischemic cerebrovascular disease being newly diagnosed. A hazard ratio was applied to measure the association strength between benzbromarone use and ischemic cerebrovascular disease. Totally, there were 13,398 persons in the benzbromarone group and 13,398 persons in the control group. The incidence rate of ischemic cerebrovascular disease seemed to be modestly higher in the benzbromarone group than the control group, but it did not achieve statistical significance (0.78 vs 0.75 every 100 person-years, incidence rate ratio = 1.05, 95% confidence interval = 0.94–1.16). A crude hazard ratio of ischemic cerebrovascular disease showed 1.05 in the benzbromarone group (95% confidence interval = 0.94–1.17, *P* = .373) comparing with the control group. No significant association can be detected between benzbromarone use and the probability of ischemic cerebrovascular disease among persons with gout-related disorders. We think that reduction of the serum uric acid by use of benzbromarone could not be related to the probability of ischemic cerebrovascular disease. Further research is suggested to clarify this issue.

Abbreviations: 95%CI = 95% confidence interval, ICD-9 = international classification of diseases 9th revision clinical modification.

Keywords: benzbromarone, cohort study, gout, ischemic cerebrovascular disease

1. Introduction

Despite of no consensus on hyperuricemia definition, hyperuricemia is commonly defined as uric acid in blood ≥ 6.8 mg/dL.[1,2] The prevalence of hyperuricemia demonstrates a worldwide variation owing to different definition of hyperuricemia. For example, the prevalence of hyperuricemia among US adults was 14.6% in 2015 to 2016 (uric acid in blood > 6.8 mg/dL).[3] The prevalence of hyperuricemia in Taiwan was 21.6% in male persons and 9.57% in female persons in 2005 to 2008 (uric acid in blood > 7.7 mg/dL among male persons and > 6.6 mg/dL among female persons).[4]

Hyperuricemia not only is the major etiological factor for gout flares,[5] but also correlates with higher risks of cardiometabolic disease and cerebrovascular disease.[6,7] Two cross-sectional studies disclosed that the prevalence of hyperuricemia was high among persons with ischemic cerebrovascular disease (30%–47.3%).[8,9] Two case-control studies demonstrated that there was a significant relation between ischemic cerebrovascular disease and hyperuricemia (odds ratio range 1.25–2.95).[10,11]One cohort study in Netherlands showed that a high uric acid level correlated with a 1.77-fold probability of ischemic cerebrovascular disease as comparing with a low

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S-WL and K-FL contributed equally to this work.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

All methods were carried out in accordance with relevant guidelines and regulations. Insurance reimbursement claims data used in this research were available for public access. Patient identification numbers had been scrambled to ensure confidentiality. Patient informed consent was not required. The study was approved by the Research. Ethics Committee at Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation in Taiwan (REC109-35).

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Significance

1. No significant association can be detected between benzbromarone use and the probability of ischemic cerebrovascular disease among persons with gout-related disorders.
2. Reduction of the serum uric acid by use of benzbromarone could not be related to the probability of ischemic cerebrovascular disease.

uric acid level (≧6.35 mg/dL vs <4.18 mg/dL, hazard ratio = 1.77).[12] One cohort study in US revealed that a high uric acid level showed a 1.49-fold probability of ischemic cerebrovascular disease when comparing with a low uric acid level among study persons not using diuretics (≧6.9 mg/dL vs ≦ 4.8 mg/dL, relative hazard = 1.49).[13]

Given that people having hyperuricemia are at risk of ischemic cerebrovascular disease, it is a rational hypothesis that reduction of serum uric acid might lower the probability of ischemic cerebrovascular disease. Benzbromarone is a potent uricosuric agent which has been withdrawn from many countries in 2003 because of its fatal liver toxicity,[14] but it remains to be available in some markets including Taiwan. At present, no available study explored the association of benzbromarone use with the probability of ischemic cerebrovascular disease. Therefore, a retrospective cohort design was conducted to explore the relation of ischemic cerebrovascular disease and benzbromarone use among persons with gout-related disorders.

2. Methods

2.1. Design and data source of study

It was a retrospective cohort design. The data source was from a 2003 to 2015 national health insurance database in Taiwan.

2.2. Research subjects

Subjects aged 20 to 99 years who already had experienced gout-associated disorders (including joint gout flare, gouty tophi, gouty urolithiasis, gouty nephropathy, and gout with other manifestations) were included as eligible subjects. An index date was set as a date of benzbromarone being prescribed. Eligible persons who had a cumulative duration of benzbromarone use alone ≥ 90 days were assigned into a benzbromarone group. The control group included eligible persons who had never used any urate-lowering agents. Both benzbromarone and control groups were matched by sex and age.

2.3. Exclusion criteria

Subjects who had the following conditions were excluded: people who had any type of cerebrovascular disease before an index date; people who developed ischemic cerebrovascular disease within 90 days after the index date; people who had any type of cancers before an index date and during the follow-up period; people who concomitantly took benzbromarone and other uric acid-lowering agents during the follow-up period (Fig. 1).

2.4. Medications and comorbidities

Uric acid-lowering agents in the study included allopurinol, febuxostat, benzbromarone, probenecid and sulfinpyrazone. Anticoagulants included heparin, warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban. Antiplatelets included aspirin, clopidogrel, and ticlopidine.

Comorbidities which could correlate with ischemic cerebrovascular disease were selected as following: alcohol-related disease, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes mellitus (DM), hyperlipidemia, and hypertension. The definition of these comorbidities was validated by the codes of international classification of diseases 9th revision clinical modification (ICD-9 codes).

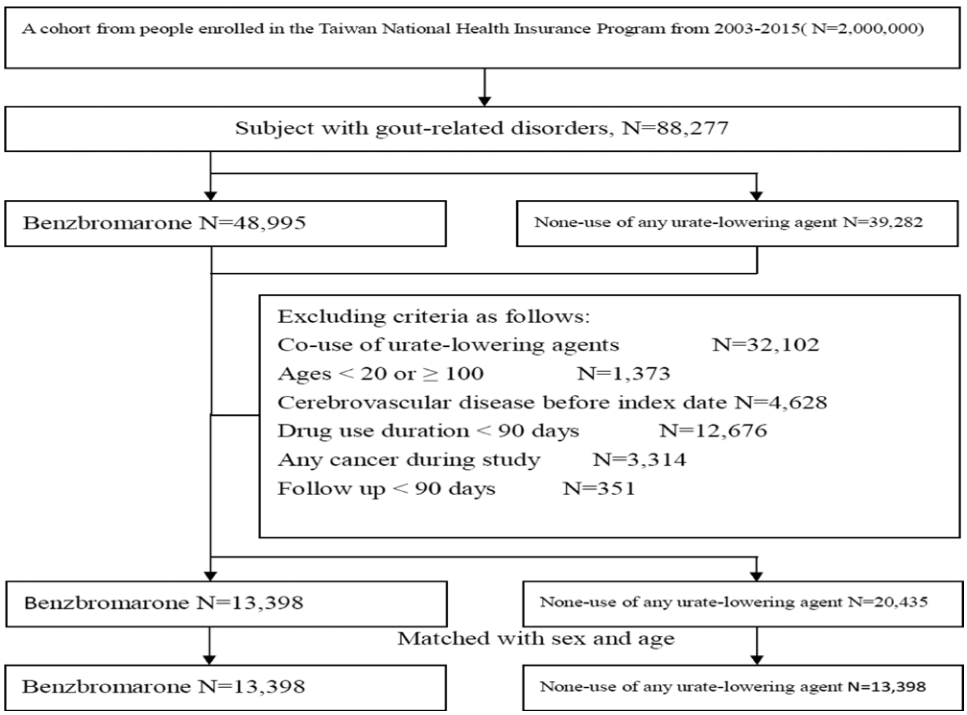

Figure 1. Flow chart depicting selection process of study subjects.

2.5. Main outcome

Ischemic cerebrovascular disease had 2 conditions including ischemic stroke and transient ischemic attack (according to the ICD-9 codes 433, 434, and 435).The main outcome was set as persons who had a new diagnosis of ischemic stroke or transient ischemic attack. The diagnosis accuracy of ischemic cerebrovascular disease in Taiwan based-on ICD-9 codes was 94%.[15]

2.6. Statistical analyses

The number with percentage was presented among the categorical variables. A mean with standard deviation was shown among the continuous variables. The categorical variables were assessed by applying a Chi-square test. The continuous variables were assessed by applying a *t* test. The incidence density of ischemic cerebrovascular disease was shown with person-years in a benzbromarone group and a control group. A Cox proportional hazard regression model was applied to explore a hazard ratio with 95% confidence interval (95%CI) for the relation of ischemic cerebrovascular disease with demographics, medications as well as related comorbidities. A proportional hazard assumption was evaluated by the Kolmogorov-type Supremum Test. That was not violated. All analyses were run by the SAS software (version 9.4 for Windows; SAS Institute Inc., Cary, North Carolina). A *P* value < .05 was regarded as having statistical significance.

3. Results

3.1. Baseline information of the study subjects

Table 1 presents the baseline data of the study population. Totally, there were 13,398 persons in a benzbromarone group and 13,398 persons in a control group. The benzbromarone group and the control group had similar proportions of sex and age, with 75.6% being male persons. The mean age was 50.8 years old in these 2 groups (standard deviation 15.0). The benzbromarone group had higher proportions of antiplatelets use, chronic kidney disease, coronary artery disease, hyperlipidemia and hypertension as comparing with the control group (*P* < .001for Chi-square test).

3.2. Incidence density of ischemic cerebrovascular disease

Table 2 presents that the incidence rate of ischemic cerebrovascular disease seemed to be modestly higher in a benzbromarone group than that in a control group, but it did not achieve statistical significance (0.78 vs 0.75 every 100 person-years, incidence rate ratio = 1.05, 95%CI = 0.94–1.16). As stratification with sex and age, the difference in the incidence rate of ischemic cerebrovascular disease between a benzbromarone group and a control group did not reach statistical significance.

3.3. Hazard ratio of ischemic cerebrovascular disease with medications and related comorbidities

In Table 3, the crude analysis disclosed that a hazard ratio of ischemic cerebrovascular disease was modestly higher in a benzbromarone group as comparing with a control group, but without reaching statistical significance (crude hazard ratio = 1.05, 95%CI = 0.94–1.17 and *P* = .373). Because of not reaching statistical significance, a multivariable regression analysis was not run.

4. Discussion

In our retrospective cohort study, no significant association was noted between benzbromarone use and the probability of ischemic cerebrovascular disease among persons with gout-related disorders. Because benzbromarone has been withdrawn from some nations since 2003 owing to the hepatic toxicity,[14] little research was available for comparison with our study.

Although the biological mechanisms underlying ischemic cerebrovascular disease associated with hyperuricemia have not been fully explored, we reviewed the literature as follows. Clinical studies demonstrated that the high level of uric

Table 1

Baseline characteristics of study subjects.

	Benzbromarone group N = 13398		Control group N = 13398		
Variable	n	(%)	n	(%)	*P* value*
Sex					1.000
Male	10134	(75.6)	10134	(75.6)	
Female	3264	(24.4)	3264	(24.4)	
Age group (yr)					
20–39	3321	(24.8)	3321	(24.8)	.975
40–64	7474	(55.8)	7488	(55.9)	
65–99	2603	(19.4)	2589	(19.3)	
Mean age ± SD †	50.8 ± 15.0		50.8 ± 15.0		.937
Medications					
Anticoagulants use	853	(6.4)	836	(6.2)	.669
Antiplatelets use	3453	(25.8)	2872	(21.4)	<.001
Baseline comorbidities					
Alcohol-related disease	106	(0.8)	104	(0.8)	.889
Atrial fibrillation	99	(0.7)	76	(0.6)	.081
Chronic kidney disease	414	(3.1)	310	(2.3)	<.001
Chronic obstructive pulmonary disease	723	(5.4)	679	(5.1)	.227
Coronary artery disease	1114	(8.3)	774	(5.8)	<.001
Diabetes mellitus	1673	(12.5)	1667	(12.4)	.912
Hyperlipidemia	3337	(24.9)	2458	(18.4)	<.001
Hypertension	5427	(40.5)	3488	(26.0)	<.001

SD = standard deviation.

* Chi-square test;

† *t*-test comparing the benzbromarone group and the control group.

Table 2

Incidence density of ischemic cerebrovascular disease between benzbromarone group and control group.

	Benzbromarone				Control group				
Variable	N	Event	Person-yr	Incidence rate	N	Event	Person-years	Incidence rate	Incidence rate ratio (95%CI)†
All	13398	697	89415	0.78	13398	674	90426	0.75	1.05 (0.94–1.16)
Sex									
Male	10134	464	67383	0.69	10134	446	68672	0.65	1.06 (0.93–1.21)
Female	3264	233	22032	1.06	3264	228	21754	1.05	1.01 (0.84–1.21)
Age group (yr)									
20–39	3321	30	23821	0.13	3321	20	24721	0.08	1.56 (0.88–2.74)
40–64	7474	332	50052	0.66	7488	325	50681	0.64	1.03 (0.89–1.21)
65–99	2603	335	15542	2.16	2589	329	15024	2.19	0.98 (0.85–1.15)

Incidence rate: 100 person-years.

95%CI = 95% confidence interval.

† Incidence rate ratio: benzbromarone group versus control group (95% confidence interval).

Table 3

Hazard ratio and 95% confidence interval of ischemic cerebrovascular disease associated with medications and comorbidities.

		Crude	
Variable	HR	(95%CI)	
Sex (male vs female)	0.64	(0.57–0.72)	<.001
Age (every 1 yr)	1.06	(1.06–1.07)	<.001
Medications			
Benzbromarone use (controls as a reference)	1.05	(0.94–1.17)	0.373
Anticoagulants use (nonuse as a reference)	1.89	(1.57–2.28)	<.001
Antiplatelets use (nonuse as a reference)	2.39	(2.14–2.66)	<.001
Baseline comorbidities (yes vs no)			
Alcohol-related disease	0.61	(0.27–1.36)	0.225
Atrial fibrillation	3.69	(2.46–5.54)	<.001
Chronic kidney disease	2.34	(1.82–3.02)	<.001
Chronic obstructive pulmonary disease	1.90	(1.59–2.28)	<.001
Coronary artery disease	2.74	(2.37–3.17)	<.001
Diabetes mellitus	2.28	(2.01–2.60)	<.001
Hyperlipidemia	1.39	(1.22–1.57)	<.001
Hypertension	2.65	(2.38–2.94)	<.001

Because benzbromarone use did not reach statistical significance in a crude analysis, a multivariable Cox proportional hazards regression model was not performed.

95%CI = 95% confidence interval, HR = hazard ratio.

acid in blood correlates with endothelial dysfunction.[16,17] As well known, xanthine oxidase plays a key enzyme which can catalyze the oxidation processes of hypoxanthine into xanthine and xanthine into uric acid during the metabolism of human purine.[18] During these processes, both uric acid and reactive oxygen species could be produced concomitantly.[19] Reactive oxygen species seems to be deleterious to endothelial function.[19,20] The other postulated mechanism is that the uric acid can enter the endothelial cells through the help of uric acid transporters and in turn might cause inflammation and increased oxidative stress, which might lead to damage to endothelial function.[19,20] Epidemiological studies demonstrated that endothelial dysfunction might play an important factor which correlates with an increased probability of ischemic cerebrovascular disease.[21,22] One meta analysis of 29 studies demonstrated that endothelial dysfunction could be involved in a pathogenesis of ischemic cerebrovascular disease.[23] Therefore, there could be a rational link that a high uric acid level increases the risk of a person's endothelial dysfunction, which in turn increases his or her risk of ischemic cerebrovascular disease. Endothelial dysfunction might be a mediator in the causal chain between a high level of uric acid and a high risk of ischemic cerebrovascular disease. Based on the above review, theoretically reducing the uric acid level or inhibiting xanthine oxidase might decrease the probability of ischemic cerebrovascular disease. Benzbromarone is a potent uricosuric drug, which can diminish the uric acid level through the step of inhibiting urate transporter 1 in kidney (URAT1).[24] Our findings indicate that reduction of uric acid by use of benzbromarone does not correlate with the probability of ischemic cerebrovascular disease. Many risk factors shown in Table 3 were found to be associated with a higher probability of ischemic cerebrovascular disease. These risk factors included atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hyperlipidemia, and hypertension. We think that only reducing serum uric acid but without ameliorating these risk factors could not change the natural course of developing ischemic cerebrovascular disease.

5. Limitation

This present study has some limitations. First, owing to the inherent limitation of the database, there was no information on the status of cigarette smoking and alcohol use. But chronic obstructive pulmonary disease was selected for a surrogate of smoking and alcohol-related disease was selected for a surrogate of alcohol use. Such a replacement has been found in previous studies.[25,26] Second, owing to the same limitation, there was no data on the uric acid level. Our study could not assess the relation between the baseline uric acid, post-treatment uric acid and the probability of ischemic cerebrovascular disease. This limitation points out a further study direction.

6. Conclusions

No significant association can be detected between benzbromarone use and the probability of ischemic cerebrovascular disease among persons with gout-related disorders. We think that reduction of the serum uric acid by use of benzbromarone could not be associated with the probability of ischemic cerebrovascular disease. Further research is suggested to clarify this issue.

Author contributions

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Investigation: Shih-Wei Lai.
Methodology: Shih-Wei Lai.
Writing – original draft: Shih-Wei Lai.
Writing – review & editing: Shih-Wei Lai, Kuan-Fu Liao.

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