Association between the use of benzodiazepines and the occurrence of acute angle-closure glaucoma in the elderly: a population-based study

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Directed by Professor Kee Namkoong

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This certifies that the Doctoral Dissertation of Woo Jung Kim is approved.

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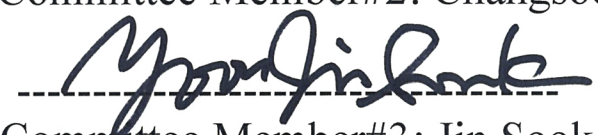

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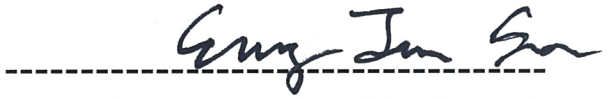

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Woo Jung Kim

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ABSTRACT

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INTRODUCTION: Because benzodiazepines (BZDs) can affect pupillae muscles, their use could be a risk factor for acute angle-closure glaucoma (AACG), which is an ophthalmic emergency. However, there is no research evidence for the association between BZDs and AACG, except two case reports. We aimed to investigate whether BZDs increase the risk of AACG in a geriatric population.

MATERIALS AND METHODS: We performed a case-control study using

a geriatric cohort from the National Health Insurance database (2002–2013) in Korea. Case subjects (n = 1,117) were patients diagnosed with AACG. Controls, people who have not been diagnosed with AACG, were randomly matched with the case group according to age, sex, and index year (n = 4,468). To examine the risk of BZD use for AACG, we performed multiple logistic regression analyses with potential confounders including antidepressant use at index date and histories of medical comorbidities.

RESULTS: The use of BZD within a 1-month period was not associated with a risk of AACG (adjusted odds ratio [aOR] = 1.01, 95% confidence interval [CI] = 0.84–1.22). The subgroup analysis showed that, unlike non-immediate BZD use (aOR = 0.89, 95% CI = 0.72–1.09), immediate BZD use (within 1–7 days) had a significant aOR for the development of AACG (aOR = 1.70, 95% CI = 1.17–2.41).

CONCLUSION: We found that BZDs increase the risk of AACG at the beginning of its use among the Korean elderly. Clinicians should monitor visual disturbance in the elderly during the early period after prescription of BZD.

Key Words: benzodiazepines, acute angle-closure glaucoma, population-based study, pharmaco-epidemiology, case-control design.

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I. INTRODUCTION

Glaucoma is a progressive optic neuropathy accompanied by a visual field defect, and is categorized as either an open angle or angle-closure glaucoma.[1] Globally, glaucoma accounts for 12% of the causes of blindness, and its prevalence is still increasing among the aging population worldwide.[2,3] For angle-closure glaucoma, the increasing prevalence with age is more evident in Asia than in Europe.[2] Angle-closure glaucoma is characterized by impairment in the outflow of the aqueous humor due to obstruction of the

anterior chamber angle. Patients with "acute" angle-closure glaucoma (AACG) have severe eye pain, headache, and visual changes because of the sudden and high increase in intraocular pressure.[4] AACG is an emergent sight-threatening condition, which may cause moderate visual disturbance or even blindness with only a single occurrence.[1,5] Specifically, the Asian ethnicity and old age are known to be risk factors of AACG.[5]

Benzodiazepines (BZDs) are frequently prescribed to a large number of patients with depression, insomnia, anxiety disorder, and alcohol withdrawals or seizures. Although BZD prescription to the elderly is not recommended,[6] its use among the elderly is common in real practice.[7-9] BZDs have muscle relaxant effects, which can affect the sphincter pupillae muscle of the iris. This muscle determines the irido-corneal angle.[10] Knowing that the sensitivity of the elderly to drugs is generally increased, the use of BZDs among Asian elderly can be enough a risk factor for AACG.

Although the drug manuals of most BZDs specify that they are contraindicated in patients with AACG, there has been no definitive research evidence showing that BZD increase the risk of AACG. There has been only a few case reports describing a risk of AACG in relation to the concurrent use of BZDs with other psychotropic medications.[11,12] The current study aimed to investigate whether BZDs increase the risk of AACG in the elderly. To do this, we performed a population-based study using a nationwide-claims database (DB) in Korea.

II. MATERIALS AND METHODS

1. Data source

We used the elderly cohort database (DB) for research (2002–2013), which was established by the National Health Insurance Service (NHIS) and covers the whole population in South Korea, for the study. This cohort was randomly sampled from people ≥ 60 years old (n = 558,147). The method for data construction in the elderly cohort DB is similar to that used in the NHIS-National Sample Cohort.[13] These claims data have been accepted to be representative of the medical use status of the entire Korean population. Using the established NHIS-National Sample Cohort, we previously observed that the rate of incidence among the aged (≥ 60 years old) was 69.4% of total incidence of AACG. Thus, we considered that the use of the elderly cohort DB of the NHIS will be relevant for our study. The elderly cohort DB contains demographic and economic variables, and medical information including diagnoses and details of treatment. The diagnostic codes in the DB of the NHIS are based on the International Classification of Diseases, 10th edition (ICD-10). This study was approved by the Institutional Review Board of Myongji Hospital (IRB No. MJH-16-01-046).

2. Case definition and study design

The data from the first year (2002) was only used to identify whether the diagnosis of AACG was new. We defined the diagnosis of AACG as

following: first identified the diagnostic code for angle-closure glaucoma (ACG; H40.2); and then, to detect "acute" ACG, we verified the claims code for laser iridotomy (S5030 or S5041) within three days from the date of ACG diagnosis. Laser iridotomy is known to be a definitive treatment for AACG. Index date was defined as the date of ACG diagnosis.

In this case-control study, we selected subjects who were newly diagnosed with AACG between 2003 and 2013 (n = 1,117). These subjects were assigned to the case group in the analysis. The control group comprised people without AACG diagnosis until 2013. Subjects in the control group were randomly selected with 1:4 matching to those in the case group according to sex, age (5-year span), and the year of the index date. **Figure 1** shows a flow chart of the study.

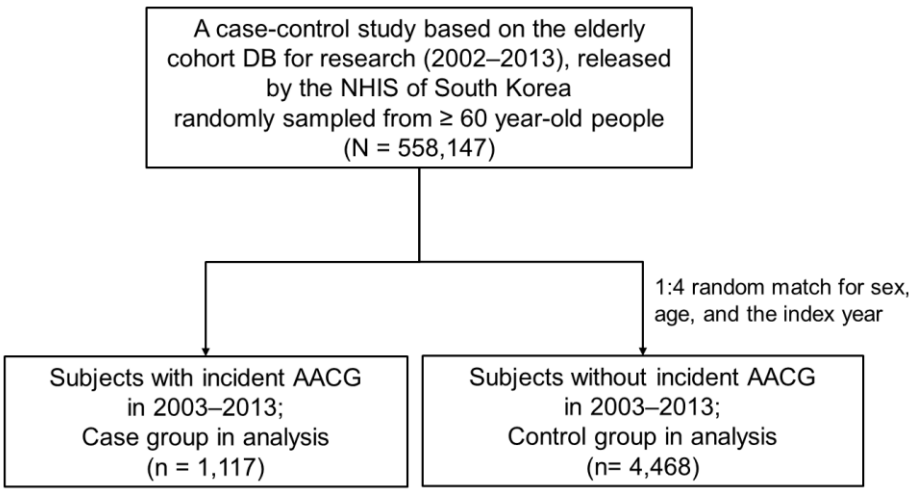

Figure 1. Study flowchart. DB, database; NHIS, National Health Insurance System; AACG, acute angle-closure glaucoma.

3. Exposure to BZD

We considered a time window within 1–30 days before the index date. We defined exposure to BZD according to the following three criteria: (1) the use of at least one BZD prescription within 1–30 days; (2) a time point of exposure which comprised immediate and non-immediate users; and (3) the elimination half-life of the BZD, which was categorized as either short- or long-acting. Immediate users were defined as those who received any BZD prescription 1–7 days before the index date. Non-immediate users were defined as those who received no BZD prescription within seven days of the index date but received at least one BZD prescription 8–30 days before the index date. We grouped all BZDs by their elimination half-life as either short-acting (half-life of < 24 hours) or long-acting (half-life of ≥ 24 hours)(**Table 1**). Subjects with concurrent use of short and long-acting BZDs were assigned to the long-acting group. Subjects without any BZD prescription during the 30-day time window were categorized as non-users.

4. Potential confounders of AACG

Antidepressants are often prescribed together with BZDs.[14] According to previous pharmacoepidemiological studies,[15,16] some antidepressants can increase the risk of AACG. We considered the use of antidepressants as potential confounders with other medical comorbidities such as hypertension (I10–I15), diabetes (E10–E14), hyperlipidemia (E78.0–

E78.5), ischemic heart disease (I20–I25), cerebrovascular disease (G46, I60–I69), and insomnia (F51.0, G47.0). **Table 2** shows the list of included antidepressants.

Table 1. List of number of subjects with benzodiazepines use in the study

Benzodiazepines use	(N = 1,045)
Short half-life	(n = 550)
Alprazolam	231
Bromazepam	23
Brotizolam	2
Clotiazepam	40
Etizolam	71
Lorazepam	42
Tofisopam	98
Triazolam	43
Long half-life	(n = 495)
Clobazam	3
Clonazepam	27
Clorazepate	6
Chlordiazepoxide	3
Clidinium	2
Diazepam	427
Flunitrazepam	6
Flurazepam	7
Loflazepate	4
Mexazolam	5
Pinazepam	5

Table 2. List of antidepressants included in the study

Class	Generic drug name
TCA	Amitriptyline, amoxapine, clomipramine, imipramine, nortryptiline
SSRI	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Others	Bupropion, duloxetine, milnacipran, mirtazapine, moclobemide, tianeptine, trazodone, venlafaxine

TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors.

5. Statistical analysis

Descriptive statistics were used to describe the characteristics of case and control groups. To examine the association between the use of BZDs and the risk of AACG, we performed logistic regression analyses, which yielded the odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analyses were conducted to adjust for potential confounders. Two-sided P values < 0.05 were considered statistically significant. We conducted statistical analyses using the R (www.R-project.org) software.

III. RESULTS

Table 3 shows the baseline characteristics of the AACG case group and non-AACG control group in the study. The mean age for subjects was 71.8 ± 5.7 years with a female predominance (female, 77.4%). With the exception of cerebrovascular diseases, the other medical comorbidities and the use of antidepressants were not significantly different between the case and control groups.

During the study period, 171 cases (15.3% of 1,117 cases) with AACG and 684 controls (15.3% of 4,468 controls) received BZD prescriptions. **Table 4** presents the crude and adjusted ORs for AACG associated with BZD use. BZD use did not significantly increase the risk of AACG (adjusted OR = 1.01, 95% CI = 0.84–1.22). Unlike non-immediate BZD users (adjusted OR = 0.89, 95% CI = 0.72–1.09), immediate BZD users were at a higher risk of AACG (adjusted OR = 1.70, 95% CI = 1.17–2.41). Regardless of the half-life of the BZD, short- and long-acting BZD users were not significantly associated with a risk of AACG (short-acting users, adjusted OR = 0.91, 95% CI = 0.69–1.18; long-acting users, adjusted OR = 1.11, 95% CI = 0.87–1.40). Among all comorbidities, only cerebrovascular diseases were associated with a higher risk of AACG (crude OR = 1.34, 95% CI = 1.09–1.63) (data was not shown).

Table 3. Characteristics of subjects in the study

	Non-AACG controls (N = 4,468)		AACG cases (N = 1,117)		P value
Sex, n (%)					Matched
Male	1,012	(22.6)	253	(22.6)	
Female	3,456	(77.4)	864	(77.4)	
Age group, n (%)					Matched
60–64 years	348	(7.8)	87	(7.8)	
65–69 years	1,440	(32.2)	360	(32.2)	
70–74 years	1,388	(31.1)	347	(31.1)	
75–79 years	832	(18.6)	208	(18.6)	
≥ 80 years	460	(10.3)	115	(10.3)	
Age (years), mean ± SD	71.8	± 5.7	71.8	± 5.7	Matched
Antidepressant use, n (%)	116	(2.6)	28	(2.5)	0.950
Comorbidities, n (%)					
Hypertension	2,327	(52.1)	559	(50.0)	0.236
Diabetes	894	(20.0)	221	(19.8)	0.900
Hyperlipidemia	540	(12.1)	138	(12.4)	0.846
Ischemic heart disease	429	(9.6)	101	(9.0)	0.607
Cerebrovascular disease	449	(10.0)	145	(13.0)	0.005
Insomnia	145	(3.2)	26	(2.3)	0.135

AACG, acute angle-closure glaucoma; SD, standard deviation.

Table 4. Crude and adjusted odds ratio and 95% confidence interval for acute angle-closure glaucoma associated with benzodiazepine use

	Controls (N = 4,468)		Cases (N = 1,117)		Crude		Adjusted[1]	
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
Benzodiazepines use								
Non-users	3,784	(84.7)	946	(84.7)	1	(reference)	1	(reference)
Users (1–30 days)	684	(15.3)	171	(15.3)	1.00	(0.83–1.20)	1.01	(0.84–1.22)
Benzodiazepines exposure time point								
Non-users	3,784	(84.7)	946	(84.7)	1	(reference)	1	(reference)
Immediate user (1–7 days)	105	(2.3)	44	(3.9)	1.68	(1.16–2.38)	1.70	(1.17–2.41)
Non-immediate user (8–30 days)	579	(13.0)	127	(11.4)	0.88	(0.71–1.07)	0.89	(0.72–1.09)
Benzodiazepines elimination half-life								
Non-users	3,784	(84.7)	946	(84.7)	1	(reference)	1	(reference)
Short-acting users	326	(7.3)	73	(6.5)	0.90	(0.68–1.16)	0.91	(0.69–1.18)
Long-acting users	358	(8.0)	98	(8.8)	1.09	(0.86–1.38)	1.11	(0.87–1.40)

OR, odds ratio; CI, confidence interval. [1]Adjusted for sex, age, antidepressant use, hypertension, diabetes, hyperlipidemia, ischemic heart disease, cerebrovascular disease, and insomnia.

IV. DISCUSSION

In this population-based case-control study, we examined the association between the use of BZDs and the occurrence of AACG. We found that the use of BZD was associated with a high risk of AACG within 7 days after prescription among Korean elderly. Two previous case reports[11,12] showed a possible association between BZDs and AACG. However, it was uncertain whether BZD itself was associated with the incidence of AACG, because in the case reports[11,12] other psychotropic drugs and BZDs (diazepam and phenobarbital;[11] alprazolam, clotiazepam, and maprotiline[12]) were administered to the case patients at the time of AACG occurrence. As there was no research evidence on the association between BZDs and the incidence of AACG,[17,18] we aimed to provide a more solid evidence of their association using this study.

According to our results among the Korean elderly, BZDs can cause AACG during the early period after their use. While there was no increase in the incidence of AACG among non-immediate BZD users, immediate BZD users were associated with a high risk of AACG. The risk of AACG does not correlate with the elimination half-life of BZDs. Since BZDs can induce relaxation of the sphincter pupillae muscle of the iris and also have a mild anticholinergic effect, their use can affect the development of AACG, theoretically.[10] Nevertheless, in earlier related reviews, BZDs were not

included in the AACG-inducible drug list.[19-22] Because of both pharmacokinetics and pharmacodynamics, the elderly may be more sensitive to the effects of BZDs.[23] We could not conclude that BZDs cause AACG in any age group other than the elderly. In addition, lipid solubility and protein binding affinity are factors which influence the penetration of systemic drugs such as BZDs into the ocular tissue.[24] Even within the BZDs, their lipid solubility or protein binding affinity are different each other.[25] Hence, we need to investigate the actual change in the irido-corneal angle in patients using BZDs according to the type of BZD in ophthalmology clinics.

Other recent population-based studies[15,16] demonstrated that the use of antidepressants is associated with an increased risk of AACG. Our study showed that the use of antidepressants, which was used as a covariate in the multiple regression model, did not affect the incidence of AACG. Among antidepressants, especially tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) are known to be able to influence the development of AACG through their anticholinergic, noradrenergic, and serotonergic properties.[5,17-20,22,26] Because we considered all antidepressants, regardless of the class, as covariates in the multivariate analysis, the different antidepressants might have offset each other's effects. Further study is therefore needed to determine whether the risk of AACG is different for different classes of antidepressants.

Although systemic diseases such as hypertension, diabetes, and hyperlipidemia are risk factors for open angle glaucoma,[5,27,28] they were not associated with the incidence of AACG in this study. In fact, unlike open angle glaucoma, known risk factors for AACG have a close relation to anatomical factors of individual subjects, including narrowness of the angle of the anterior chamber, shallowness of the anterior chamber, hyperopia, and nanophthalmos.[5,26] Known risk factors for AACG have also been related with ethnicity (Asian, Eskimo, and Hispanic). Females have more narrow angles than males, and aging reduces the width of the anterior chamber progressively.[26] The reason why the female sex and age of subjects were not associated with AACG in our study might be because we performed the study, from the start, in a geriatric population, which already displayed some degree of anatomical change.

On the other hand, cerebrovascular diseases increased the risk of AACG in our study. We defined cerebrovascular diseases as varied conditions that affect blood vessels of the brain and cerebral circulation (e.g., intracerebral hemorrhage, cerebrovascular accident, and occlusion of cerebral arteries) in accordance with the ICD. Since one of the manifestations of AACG is headache, it can be assumed that cerebrovascular diseases are correlated with AACG. Indeed, further research might help to identify the pathophysiology of AACG associated with cerebrovascular diseases.

Apart from the relationship between BZDs and AACG, the prescription of BZDs should be minimized to the geriatric population. BZD is potentially an inappropriate medication for the elderly,[29] as it is known to increase the risk of cognitive impairment, delirium, falls, fractures, and car accidents in older adults.[8] A previous study[9] reported that there is a high prevalence of BZD prescription (42.5%) among older adults in Korea. The prevalence in Korea is higher than that in Canada (less than 25%), where an effort was made to improve this potentially inappropriate medication.[30,31] A vigorous clinical intervention will be needed to decrease the rate of BZD use in older adults.

The strength of this study is that we used a large, population-based sample composed of the elderly who are at a greater risk of AACG. This study, which uses claims data, will work as a part of a post-marketing drug surveillance system, specifically in the geriatric or pediatric population. Subjects in these populations are usually not recruited for clinical trials. Moreover, we provided evidence for the adverse effect of BZDs in the elderly. Indeed, to examine the impact of a drug on a rare disease such as AACG in the field of epidemiology, the case only study will be more needed, which can focus the effect of medication to the "susceptible" individuals. Nonetheless, this study emphasizes that not only should clinicians not prescribe BZD when a patient has AACG as is well known, and should also closely monitor the early period after BZD prescription to the elderly, who have a high risk of

developing narrow angles in the anterior chamber.

The current study has some limitations. First, because of the characteristics of the claims data study, the diagnostic coding used in this study may contain inaccuracies. However, AACG is a typical emergent disease for which unnecessary or erroneous coding might have been minimized in ophthalmology. Additionally, a validation study compared the diagnosis in the claims database with the actual diagnosis in medical records of patients. They reported that the overall positive predictive value of the diagnoses was 83.4%.[32] Second, we could not consider the effects of the dosage of BZDs and could not include all AACG-inducible drugs (e.g., antihistamines, [anti-]cholinergics, adrenergics, anticoagulants, and sulfa-based drugs)[19-22] as covariates. Further studies are needed to clarify the effect of different dosages of medication on AACG and the risk of concurrent use of BZDs with other AACG-inducible drugs. Third, our results may not be generalizable to younger-aged groups and other countries or ethnicities. Nevertheless, our study is significant, in that it was conducted among a vulnerable group (the elderly Asian population).

V. CONCLUSION

This study showed that BZDs increase the risk of AACG at the early

stages of their use among the Korean elderly. This result adds to evidence demonstrating that the use of BZDs is a risk factor for AACG. Clinicians should pay more attention to the monitoring of visual disturbance in the elderly during the early period after BZD prescription. The knowledge of the potentially harmful effects of BZDs and their rational use can improve the quality of life of the elderly.

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ABSTRACT (IN KOREAN)

노인 인구에서 벤조다이아제핀 사용과 급성 폐쇄각녹내장 발생의 연관성: 인구집단 기반 연구

<지도교수 남궁 기>

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서론: 급성 폐쇄각녹내장은 심한 안통, 두통, 시야 변화를 동반한 안과적 응급질환이다. 벤조다이아제핀은 연령과 적응을 불문하고 정신적, 신체적 질환에 널리 사용되어왔다. 벤조다이아제핀은 항콜린성 작용이 있어 안구의 동공산대근육에 영향을 미칠 수 있으므로, 이론적으로는 벤조다이아제핀이 급성 폐쇄각녹내장의 위험요인이다. 그러나, 벤조다이아제핀이 실제로 급성 폐쇄각녹내장의 위험을 높이는지는 명확하지 않다. 현재까지 벤조다이아제핀과 급성 폐쇄각녹내장의 관계에 대한 임상연구는 없었다. 우리는 노인 인구에서 벤조다이아제핀이 급성 폐쇄각녹내장 발생의 위험을 높이는지 알아보고자 하였다.

재료 및 방법: 건강보험공단 노인코호트 구축자료(2002-2013)를 이

용한 환자-대조군 연구를 시행하였다. 환자군은 급성 폐쇄각녹내장의 표준치료인 레이저 홍채 절개술 청구 여부를 통해 진단을 확정하였다.(n = 1,117) 급성 폐쇄각녹내장을 진단받지 않은 대조군은 연령, 성별, 기준연도에 따라 1:4의 비율로 무작위 매칭되었다.(n = 4,468) 급성 폐쇄각녹내장에 대한 벤조다이아제핀의 위험성을 평가하기 위해, 급성 폐쇄각녹내장 진단시점의 항우울제 사용 여부 및 주요 내과적 질환의 과거력 등의 잠재적 혼란변수를 감안하여 다중 로지스틱 회귀분석을 시행하였다.

결과: 30일 이내에 벤조다이아제핀을 복용한 적이 있더라도 급성 폐쇄각녹내장 발생에는 영향이 없었다.(adjusted odds ratio [OR] = 1.01, 95% confidence interval [CI] = 0.84-1.22) 하위그룹 분석 결과, 비즉각적으로 사용한 경우와는 달리,(adjusted OR = 0.89, 95% CI = 0.72-1.09) 기준일 7일 이내에 벤조다이아제핀을 사용한 경우 급성 폐쇄각녹내장 발생의 오즈비가 유의하게 높게 나타났다.(adjusted OR = 1.70, 95% CI = 1.17-2.41).

결론: 우리는 노인 인구에서 벤조다이아제핀이 사용 초기에 급성 폐쇄각녹내장 발생 위험을 높일 수 있다는 점을 발견하였다. 임상가들은 벤조다이아제핀 처방 초기에 노인에서 시야 장애가 발생하는지 등에 대해 보다 충분히 주의를 기울여야 할 것이다.

핵심되는 말: 벤조다이아제핀, 급성 폐쇄각 녹내장, 인구집단 기반 연구, 약물역학, 환자-대조군 설계