



An association between benzodiazepine use and occurrence of benign brain tumors

Tomor Harnod^{a,b}, Cheng-Li Lin^{c,d}, Fung-Chang Sung^{c,d}, Chia-Hung Kao^{e,f,*}

^a Department of Neurosurgery, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

^b College of Medicine, Tzu Chi University, Hualien, Taiwan

^c Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

^d Department of Public Health, China Medical University, Taichung, Taiwan

^e Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

^f Graduate Institute of Clinical Medical Science, School of Medicine, College of Medicine, China Medical University, Taiwan

ARTICLE INFO

Article history:

Received 20 September 2013

Received in revised form 6 November 2013

Accepted 8 November 2013

Available online 16 November 2013

Keywords:

Benzodiazepine

Benign brain tumor (BBT)

Malignant brain tumor (MBT)

Population-based

Cohort study

National Health Insurance System

ABSTRACT

Objective: This study was designed to evaluate the impact of long-term benzodiazepine use on the subsequent risk of benign brain tumor (BBT) or malignant brain tumor (MBT) development.

Method: We used data from the National Health Insurance System of Taiwan. For the study cohort, we identified 62,186 patients who had been prescribed benzodiazepine for at least 2 months between January 1, 2000 and December, 31, 2009. For each of the benzodiazepine cases, we randomly selected one insured person from the non-benzodiazepine cohort with frequency matching sex, age, and year of index date. The non-benzodiazepine cohort comprised 62,050 patients. The related hazard ratios (HRs) and 95% confidence intervals (CIs) of developing brain tumors were investigated.

Results: The overall BBT incidence rate was 3.33-fold higher in the benzodiazepine cohort than the non-benzodiazepine cohort (46.3 vs 13.9 per 100,000 person-years) with an adjusted HR of 3.15 (95% CI = 2.37–4.20). Similarly, the MBT incidence rate was 84% higher in the benzodiazepine cohort (3.71 vs 2.02 per 1000 person-years), and the adjusted HR of 1.21 (95% CI = 0.52–2.81) was not statistically significant. When compared with the non-benzodiazepine cohort, the adjusted HRs of BBTs increased with benzodiazepine dosage (adjusted HR = 2.12, 95% CI = 1.45–3.10, for 36–150 mg/year; adjusted HR = 7.03, 95% CI = 5.19–9.51, for ≥151 mg/year).

Conclusion: In this population-based study, we found a significant increase in the risk of benign brain tumor development in a cohort of long-term BZD users.

© 2013 Elsevier B.V. All rights reserved.

1. Introduction

Benzodiazepines are a category of drug that is widely used to treat various neurological and psychiatric conditions such as seizures, agitation, insomnia, anxiety, alcohol dependence, and panic. The prevalence of benzodiazepine use ranges from 10% to 43% worldwide among the aged population [1–5]. Meanwhile, benzodiazepines are also known to have some adverse effects, such as nausea, vertigo, amnesia, ataxia, headache, drowsiness, confusion, or even tremor, which imply the possible neuro-toxicity in long-term or high-dose use of benzodiazepines. Previous animal studies have revealed that benzodiazepine might increase the risk of liver and breast cancer [6,7]. A survey conducted in the United States found that the use of sleeping pills (most of which are benzodiazepines) increased the risk of developing cancer [8]. We published similar results from a retrospective cohort study conducted

in Taiwan in 2012 [9]. However, although there is a long history of human beings modulating the central nervous system, the potential link between benzodiazepine use and subsequent brain tumor development remains unclear. This study was conducted using the Taiwan nationwide population-based database.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program was initiated in Taiwan on March 1, 1995. By the end of 2009, approximately 99% of Taiwan's 23.74 million people were enrolled in the National Health Insurance Research Database (NHIRD) [10]. The National Health Research Institute maintains and updates the NHIRD. The data used in this study was obtained from a NHIRD sub-data set, which contains the longitudinal claim data of a cohort of 1,000,000 insurance enrollees randomly selected from all of the insured beneficiaries. The NHIRD is one of the largest insurance databases in the world, and previous studies have shown the accuracy and high validity of ICD-9 codes' diagnoses

* Corresponding author at: Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan. Tel.: +886 4 22052121x7412; fax: +886 4 22336174.

E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

stored in the database [11,12]. We used three data files: the registry of beneficiaries, ambulatory care claims, and inpatient claims. The database provided confidential information such as patient identification number, birthdate, sex, occupation, residential area, medications, and diagnostic codes in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). With approval from NHI and China Medical University, this study was exempted by the Institutional Review Board (CMU-REC-101-012).

2.2. Study participants

For the benzodiazepine cohort, we identified 62,186 patients (mean age = 47.4 years, SD = 14.1 years) who had been prescribed benzodiazepine for at least 2 months between January 1, 2000 and December 31, 2009. We defined the index date as the initial date of benzodiazepine treatment. We excluded patients with a history of benign brain tumors and malignant brain tumors diagnosed before the index date. We also excluded patients for whom we could not determine the sex or age. For each benzodiazepine case, we randomly selected one insured person from the non-benzodiazepine cohort who had no history of benign brain tumors, malignant brain tumors, or benzodiazepine treatment. Moreover, each person selected was of the same sex, age (every 5 years), and index date year. The non-benzodiazepine cohort totaled 62,050 patients (mean age = 45.7 years, SD = 14.3 years).

2.3. Outcome measures

The person-years of follow-up were estimated for the study participants from the index date until the diagnosis of benign brain tumors (BBTs) (ICD-9-CM code 225) or malignant brain tumors (MBTs) (ICD-9-CM codes 191, 192, 194.3 and 194.4) or censored because of death, loss to follow-up, withdrawal from the insurance system, or December 31, 2010.

The baseline comorbidities and treatment that may be associated with BBTs and MBTs were identified before the end dates (the date of BBT or MBT diagnosis, date the patient was lost to follow-up, date of death, date of withdrawal from insurance, or final day of 2010) for the participants in both cohorts. Comorbidities and treatments that were considered in the data analysis included stroke (ICD-9-CM code 430–438), dementia (ICD-9-CM code 290.0–290.4, and 331.0), epilepsy (ICD-9-CM code 345), head injuries (ICD-9-CM 850–854, and 959.01), and brain CT/MRI examinations (ICD-9-OP procedure code 870.3 and 889.1).

For further analysis, we divided the benzodiazepine cohort into 4 groups, according to their disease status, as follows: (1) those with sleep disorders (ICD-9-CM codes 370.4 and 780.5 [except for sleep apnea syndrome: codes 780.51, 780.53, and 780.57]); (2) those with anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 309.81); (3) those with both sleep disorders and anxiety; and (4) those with neither.

2.4. Statistical analysis

Demographic factors, including age, sex, residential status, comorbidities and treatment, were compared between the benzodiazepine cohort and non-benzodiazepine cohort by using the χ^2 test. The incidence densities of BBTs and MBTs in both cohorts were calculated. Poisson regression models were used to evaluate the benzodiazepine cohort to non-benzodiazepine cohort incidence rate ratio (IRR) with 95% confidence intervals (CIs). Univariable and multivariable Cox proportional hazard regression analyses were performed to assess the risk of developing BBTs and MBTs associated with benzodiazepine use, compared with non-benzodiazepine cohort. The multivariate models were simultaneously adjusted for demographic characteristics, comorbidities and brain CT, or MRI examinations. Hazard ratio (HR) and 95% CI were estimated in the Cox model. We further stratified benzodiazepine

according to annual dosage taken to estimate the risk of BBT and MBT development associated with benzodiazepine use. All of the analyses were performed using the SAS statistical package (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA). A two-tailed p-value lower than 0.05 suggests statistical significance.

3. Results

3.1. Characteristics of the study participants

Table 1 lists the characteristics of all of the 124,236 study participants in both the benzodiazepine and non-benzodiazepine cohorts. Approximately 31.9% of the patients were young, between 20 and 39 years of age. There were more women than men in both cohorts (52.8% vs 47.2% and 52.1% vs 47.9%, respectively). In both cohorts, more patients were living in urban areas (59.8% and 61.6%, respectively). Compared to the non-benzodiazepine cohort, the benzodiazepine patients were more likely to have a stroke (2.82% vs 8.28%), dementia (0.49% vs 2.05%), epilepsy (0.35% vs 2.05%), head injury (3.37% vs 8.06%), and brain CT or MRI examinations (2.38% and 7.59%).

3.2. Incidence rate ratios of BBTs and MBTs

The overall incidence of BBTs was 3.33-fold higher in the benzodiazepine cohort than in the non-benzodiazepine cohort (46.3 vs 13.9 per 100,000 person-years, IRR = 3.33, 95% CI = 3.17–3.50) (Table 2). The overall incidence of MBTs was also significantly higher in the benzodiazepine cohort than in the non-benzodiazepine cohort (3.71 vs 2.02 per 1000 person-years, IRR = 1.84, 95% CI = 1.75–1.93). The age-specific analyses showed that BBTs were significantly highest for those aged 50–59 years in the benzodiazepine cohort than the non-benzodiazepine cohort (IRR = 4.30, 95% CI = 3.84–4.81). Age-specific benzodiazepine cohort-to-non-benzodiazepine cohort incidence densities of MBTs increased with age in both cohorts and comparison of benzodiazepine cohort with non-benzodiazepine cohort showed that the IRR of MBTs decreased with age (from IRR = 3.82, 95% CI = 3.44–4.25 in the ≤ 39 -year-old age group to IRR = 1.28, 95% CI = 1.16–1.40 in the ≥ 60 -year-old age group).

Table 1
Baseline characteristics between BZD group and non-BZD group in 2000–2009.

Variables	BZD				p-Value
	No N = 62,050		Yes N = 62,186		
	n	%	n	%	
Age, years					0.91
20–39	19,838	32.0	19,838	31.9	
40–49	15,819	25.5	15,819	25.4	
50–59	12,815	20.7	12,815	20.6	
≥ 60	13,578	21.9	13,714	22.1	
Sex					0.02
Women	32,335	52.1	32,812	52.8	
Men	29,715	47.9	29,374	47.2	
Urban status ^a					<0.0001
Level 1	21,179	32.1	20,947	31.3	
Level 2	19,451	29.5	19,033	28.5	
Level 3	11,968	18.1	11,566	17.3	
Level 4	13,455	20.4	15,323	22.9	
Comorbidity					
Stroke	1747	2.82	5147	8.28	<0.0001
Dementia	307	0.49	1277	2.05	<0.0001
Epilepsy	217	0.35	1277	2.05	<0.0001
Head injury	2089	3.37	5010	8.06	<0.0001
Treatment					
Brain CT or MRI examinations	1478	2.38	4717	7.59	<0.0001

Chi-square test.

^a Level = 1 highest urban area; level 7 = lowest urban areas. Levels 4, 5, 6 and 7 were grouped together because of low populations in these areas.

Download English Version:

<https://daneshyari.com/en/article/8278405>

Download Persian Version:

<https://daneshyari.com/article/8278405>

[Daneshyari.com](https://daneshyari.com)