ASSOCIATION BETWEEN BENZODIAZEPINES AND RECURRENT FALLS: A CROSS-SECTIONAL ELDERLY POPULATION-BASED STUDY

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Abstract: Background: While the association between benzodiazepines (BZD) and single fall is long-known, the association between BZD and recurrent falls has been few studied. Objective: The aims of this study were 1) to examine whether BZD were associated with recurrent falls while taking into account the effect of potential confounders, and 2) to determine whether there was an interaction in terms of risk of falls between BZD and balance impairment in a community-dwelling population-based adults aged 65 and older. Study design: Cross-sectional. Setting: Three health centers in North-East of France. Population: 7643 community-dwelling volunteers aged 65 and older. Outcome measures: The use of BZD, the Mini Mental State Examination (MMSE) score, the Clock Drawing Test (CDT), the One Leg Balance (OLB) test, the Five Times Sit-To-Stand test (FTSS), and a history of falls were recorded. Subjects were separated into 4 groups based on the number of falls: 0, 1, 2 and ≥ 3 falls. Results: Among the 1456 (19.2%) fallers, 994 (13.0%) were single fallers and 462 (6.1%) were recurrent fallers (i.e., > 2 falls). The number of falls increased significantly with age (Incident Rate Ratio (IRR)=1.04, P<0.001), female gender (IRR=2.24, P<0.001), the use of benzodiazepine (IRR=1.65 P<0.001) and especially while subjects used bromazepam (IRR=1.44, P<0.001), clobazam (IRR=3.01, P=0.014) and prazepam (IRR=2.29, P<0.001). A low MMSE score (IRR=0.96, P<0.001), an impaired CDT (IRR=0.91, P<0.001), and a bad performance at OLB and FTSS (respectively IRR=1.85, P<0.001 and IRR=1.26, P<0.001) were related to the recurrence of falls. After adjustment only the advance in age (IRR=1.02, P<0.001), female gender (IRR=2.15, P<0.001), clobazam (IRR=2.54, P=0.04), prazepam (IRR=1.63, P=0.03) and OLB (IRR=1.55, P<0.001) were still significantly related to the number of falls. Conclusion: The current study shows that the age, the female gender, the use of clobazam or prazepam and a low score at OLB are related to the recurrence of falls.

Key words: Benzodiazepines, recurrent falls, balance impairment.

Introduction

Falls are adverse events in older adults because they lead to injuries, loss of independence, institutionalization and social isolation that imposes high costs to public health and social services (1, 2). Benzodiazepines (BZD) are the most common used psychotropic medication in general population (3). Recently, a systematic review showed that BZD were one of the most important risk factors of falls and fractures in older adults (4).

While the association between BZD and single falls is long-known, the association between BZD and recurrent falls has been few studied (5-7). Previous studies have been limited by the low sample size of studied subjects and failed to control for potential confounders such as the advance in age, female gender, balance impairment and cognitive decline (4-7). It has been shown that BZD may directly increase the risk of falls by causing attention and balance impairment (1, 2). They may also be a marker of comorbidities like cognitive decline or depression which are both independent risk factors for falls (4).

Only one study has explored the association between BZD and recurrent falls in a large cohort of subjects and showed that the use of BZD was significantly related to recurrent falls (5). In this study, the studied sample was only composed of women. In addition, although it has been show that BZD may provoke balance impairment, interaction between BZD and comorbid-related balance impairment has not been examined. Therefore, finding out more about the association of BZD with recurrent falls may improve our understanding of the role of BZD in the mechanism of recurrent falls. The aims of this study were 1) to examine whether BZD were associated with recurrent falls while taking into account the effect of potential confounders, and 2) to determine whether there was an interaction in terms of risk of falls between BZD and balance impairment in a community-dwelling population-based sample of adults aged 65 and older.

Methods

Study population

Between January 2005 and December 2008, 7643 consecutive voluntary subjects aged 65 and older (mean age 70.9±4.6 years; 50.5% women) were examined in 3 health centers localized in North-East France (Lorraine). Participants were recruited from the electoral lists and were invited to a free medical examination. No participants were excluded from the study.
Assessment

During the full medical examination, the use of drugs was recorded. A computerized dictionary was used to categorize type of drugs from product brand and generic names obtained from participants report. Subsequently, a physician blinded to outcome status reviewed the computerized drug data and classified medications using the Anatomic Therapeutic Classification (ACT) (8). Participants or their proxies were especially questioned about the use of BZD during the last two days. Based on the plasma half-life of single molecules and metabolites, BZD were classified in short half-life (< 12 hours) BZD medications which included oxazepam, intermediate half-life (between 12 and 24 hours) BZD medications which included bromazepam, clobazam, estrazolam, nitrazepam and flunitrazepam , and long half-life (> 24 hours) BZD medications which included prazepam, clorazepate, chlordiazepoxide, diazepam, lorfazepate and nordazepam. Furthermore, all included subjects performed two clinical tests which were the One-Leg Balance (OLB) test and the Five Times Sit-To-Stand test (FTSS) (9, 10). Before testing, a trained evaluator gave standardized verbal instructions regarding the test procedure. Subjects were instructed to stand unassisted on his freely chosen one leg for 5 second during the OLB, and then to stand up from a chair five times as quickly as possible without pushing off. OLB was considered abnormal when the subject was unable to stand on his leg during 5 seconds (9), whereas the threshold of an abnormal score for the FTSS was fixed at 15 seconds (10). Cognitive performance was examined using Folstein’s Mini Mental State Examination (MMSE) and the Clock Drawing Test (CDT) (11, 12). A score of 30 and 7 indicates normal cognitive function, respectively.

Information on falls including their number and dates were collected based on a standardized questionnaire. A fall was defined as unintentionally coming to rest on the ground, floor, or other lower level. In case of moderate cognitive impairment (16 < MMSE score < 25), information on falls were confirmed by a person living with the subject. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki (1983).

Statistical Analysis

The subject’s baseline characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Subjects were firstly separated into four groups based on the number of falls reported during the past 12 months (i.e., 0, 1, 2 and > 3 falls). Firstly, comparisons between groups were performed using ANOVA, Chi-square test, Kruskal-Wallis test or Cuzick test, as appropriate. Secondly, uni and multivariate Poisson regression analyses were performed to specify the association between the number of falls and the use and type of BZD. Thirdly, four groups of subjects were defined according to the performance at OLB and the use of prazepam or clobazam (see the group definition, Figures 1 and 2). Prazepam, clobazam and OLB were chosen because they were the three variables significantly related to the number of falls in the stepwise backward Poisson regression model. Lastly, multivariate Poisson regression was performed separately with the 4 possible interactions between prazepam and OLB, and clobazam and OLB, recoded as 3 dummy variables, and was run as described by Melin et al. (13). For the analysis, the reference group consisted of subjects who did not take Prazepam or Clobazam and who had normal OLB. P-values less than 0.05 were considered as statistically significant. All statistics were performed using SPSS (version 16.0; SPSS, Inc., Chicago, IL).

Results

As shown in Table 1, 1456 (19.2%) participants were fallers. Nine hundred ninety four (13.0%) were single fallers and 462 (6.1%) were recurrent fallers (i.e., > 2 falls). Being older and a women, and using BZD were significantly more prevalent in participants with a higher number of falls (P <0.001). Amongst the BZD, bromazepam was the most consumed medication and represented 52.3% of prescriptions. The use of bromazepam increased significantly with the number of fall (P trend=0.020) and subjects who failed at least one time used bromazepam more frequently than non-fallers (P=0.027). Similar results