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Opinion paper

Flunarizine and the risk of parkinsonism in a newly diagnosed type 2 diabetic population in Taiwan: A nested case-control study

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ABSTRACT

Previous studies demonstrated that both diabetes and flunarizine use can increase the risk of parkinsonism. The aim of the current study was to investigate the risk of developing parkinsonism after flunarizine treatment, in a cohort of patients newly diagnosed with type 2 diabetes. We conducted a nested case-control study of a type 2 diabetic cohort from the Taiwan Longitudinal Health Insurance Database 2005 (LHID 2005). Each incident case of parkinsonism, during the period from 2001 to 2013, was randomly matched with 3–10 controls, according to age, sex, calendar year of cohort entry, and the duration of follow-up. Conditional logistic regression was used to estimate the odds ratio (OR) of parkinsonism associated with flunarizine use. The cohort consisted of 44,644 patients with newly diagnosed type 2 diabetes from 2001 to 2013, of whom 464 patients had a parkinsonism event during the follow-up period. The adjusted OR of parkinsonism with relation to flunarizine use was 2.75 (95% confidence interval: 2.26–3.36). There were also duration- and dose–response effects. Compared to those who had not used it, the OR for developing parkinsonism was 1.77 for patients who used flunarizine for less than 1 month. When the exposure period expanded over 3 months, the OR increased to 7.03. Our findings suggested that flunarizine use is a potential risk factor for parkinsonism in patients with newly diagnosed type 2 diabetes, especially when the drug is persistently used for over 3 months.

1. Introduction

European, American, and Asian patients with type 2 diabetes are at an increased risk of developing Parkinson's disease [1–5], although some reports have presented conflicting results [6–10].

Flunarizine is a calcium channel blocker, which also has antihistamine properties [11]. It is widely used for migraine prophylaxis and vertigo treatment [12,13]. Common side effects include drowsiness, weight gain, weakness, depression, and extrapyramidal symptoms [11]. Flunarizine-induced parkinsonism (FIP) was first introduced by De Melo-Souza et al. in Brazil in 1984 [14], with several subsequent studies describing similar conditions [15–20]. However, large-scale epidemiological studies for FIP are still limited.

In 2013, Yamanaka et al. [21] reported that metabolic syndrome might be a risk factor for vertigo in Japanese men. Although flunarizine can be used to treat vestibular vertigo [22,23], its use in patients with diabetes could pose an extraordinarily high risk of parkinsonism, and is thus potentially harmful rather than beneficial to these patients.

There is currently a lack of studies on FIP among patients with type 2 diabetes. To investigate the risk of developing parkinsonism owing to flunarizine use in a more homogeneous population, we conducted a nested case-control study in a population of patients who were newly diagnosed with type 2 diabetes in Taiwan.

2. Materials and methods

2.1. Data source

In 2014, approximately 99.9% of the Taiwanese population was enrolled in the National Health Insurance (NHI) program, which was launched in Taiwan in 1995. The National Health Insurance Research Database (NHIRD) contains information on outpatient services, inpatient care, dental care, Chinese medicine, and all other medically-relevant services that were claimed by the

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enrolled citizens. The NHIRD contains demographic information, as well as information of diagnoses, examinations, drug prescriptions, and operations. However, it does not provide personal information such as body weight, body height, family history, laboratory data, and examination results.

In the present study, we used the longitudinal health insurance database 2005 (LHID 2005), a subset of the NHIRD. Following de-identification and encryption, the LHID 2005 was made available to investigators in Taiwan for research purposes; it contained all original claimed data of one million beneficiaries enrolled in 2005, which were randomly sampled from the 2005 Registry for Beneficiaries of NHIRD. There is no significant difference in the sex distribution ($\chi^2 = 0.008$, df = 1, p-value = .931) between the patients in the LHID 2005 and the original NHIRD [24]. The institutional review board of Changhua Christian Hospital approved this study. Informed consent was waived since this study used de-identified data.

2.2. Study cohort

The source population consisted of subjects who were newly diagnosed with diabetes (ICD-9-CM code 250), aged 45–79 years. All subjects had at least three outpatient-visit records within 1 year or one admission record, and received oral antidiabetic prescription for more than 7 days within half a year. Patients who had diabetes since before 2000 were excluded. To prevent enrolling subjects with advanced diabetes or type 1 diabetes, we excluded patients who received insulin treatment for daily glucose control within 1 year after diabetes diagnosis (n = 0). Cohort entry was defined by the date of diabetes diagnosis. We also excluded patients who were dispensed dopamine depleting agents within 1 year before cohort entry. We excluded patients who had type 1 diabetes, ischemic/haemorrhagic strokes, schizophrenic disorders, severe mood disorders, and cancers before cohort entry. We further excluded patients who had been diagnosed with parkinsonism before cohort entry or within 1 year after cohort entry to ensure at least 1 year of follow-up. A nested case-control analysis was conducted within the foregoing newly diagnosed type 2 diabetic cohort.

2.3. Parkinsonism cases and controls

All patients with parkinsonism (ICD-9-CM code 332) in the type 2 diabetic cohort during the study period were assigned to the 'parkinsonism' group. These patients had at least three records of neurology outpatient visits or one neurology admission diagnosis. The index dates of cases were defined as the dates of parkinsonism diagnoses. Patients with old age have a higher incidence of parkinsoinism, and gender is also a confounder. Therefore, each incident case was matched with 3–10 controls from risk set, according to age, sex, calendar year of diabetes diagnosis, and duration of follow-up. Approximately 64% of parkinsonism cases were matched with 10 controls. In addition, the index dates of controls were the same as their matched cases.

2.4. Flunarizine exposure

We obtained drug information from the NHI website to determine the dose of flunarizine used from 2001 to 2013 in the aforementioned type 2 diabetic cohort. We also calculated the continuous duration of flunarizine use and estimated the maximum duration by year to describe the trend of flunarizine use in the diabetic population. We identified all flunarizine exposure within 2 years before the index date, which defined as diagnostic date of parkinsonism for the case group and the comparable date for control subjects. We defined at least 50 mg of cumulative flunarizine dose as 'ever use of flunarizine' and less than 50 mg as 'never use', within 2 years before the index date. We also examined whether there was a linear duration-response effect between the use of flunarizine and incidence of parkinsonism. For this analysis, the cumulative duration of use was obtained by adding up each individual drug day, within 2 years before the index date. In addition, we examined a linear dose–response effect by examining the cumulative dose of flunarizine use. Moreover, we calculated the continuous duration of flunarizine use within 2 years prior to the index date. We then estimated the maximum duration for each flunarizine user within 2 years. We stratified the maximum duration into less than 1 month, 1–3 months, and over 3 months to estimate the risk for continuous use of flunarizine in medical practice.

2.5. Potential confounders

We considered several confounders, such as sex, age at index date, comorbidities, and co-medications. Comorbidities included hypertension, hyperlipidaemia, mood disorder, anxiety, and schizophrenic disorders, which were identified as present if at least three outpatient visits or one admission record within 2 years before the index date were present. Co-medications consisted of prescriptions of metoclopramide, antipsychotics (i.e. chlorpromazine, clozapine, flupentixol, haloperidol, perphenazine, prochlorperazine, sulpiride, and trifluoperazine), antidepressants, insulin, biguanides, sulfonylureas, and other blood glucose lowering drugs, and statin, diuretics, beta-blockers, calcium antagonists, and renin-angiotensin-system, within 2 years before cohort entry. The definition of disorders and the co-medication list are provided in the Supplementary material (Tables S1 and S2, respectively).

2.6. Statistical analyses

We used descriptive statistics to summarize the characteristics of cases and matched controls. Conditional logistic regression was used to calculate odds ratios (ORs), with 95% confidence intervals (CIs), of the incidence for parkinsonism, comparing 'ever use of flunarizine' with 'never use'. In trend test analyses, we entered the duration-response variables and dose–response variables as continuous variables to test its linear trend. Sensitivity analyses were conducted by stratifying the diagnostic code of 332 into Parkinson's disease (332.0) and parkinsonism (332.1) to assess the reliability of the definition of the outcome in our study. All statistical analyses were performed with R version 3.2.3 [25,26]. Statistical significant was set at P < .05.

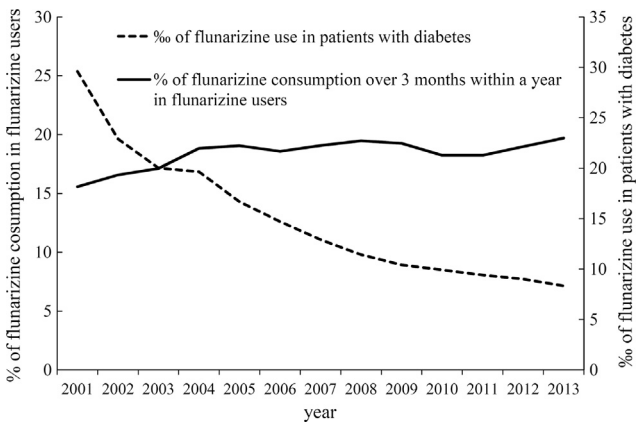

Fig. 1. The trend of flunarizine use in the type 2 diabetic cohorts from 2001 to 2013.

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