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Antipsychotic treatment is associated with risk of atrial fibrillation: A nationwide nested case-control study

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ABSTRACT

Background: Antipsychotic agents are well known for their arrhythmigenic effect on ventricular arrhythmia. Though a few case reports observed the occurrence of atrial fibrillation (AF) after antipsychotic exposure, information about their implication in AF is limited.
Methods: Based on the National Health Insurance Database in Taiwan, we conducted a nested case-control study to investigate the relationship between antipsychotics and AF. From 2001 to 2010, a total of 34,053 cases of AF and 34,919 matched controls were enrolled. Antipsychotic exposure was measured and binding affinity to neurotransmitter receptors was calculated. Both medical and psychiatric comorbidities were identified and adjusted in multivariate logistic regression analysis.
Results: Current antipsychotic use was associated with a 17% increased risk of AF relative to nonusers (adjusted OR: 1.17, 95% CI: 1.10–1.26). A dose-dependent relationship of antipsychotic exposure and AF risk was observed (P for trend <0.001). Antipsychotics with higher binding affinity to muscarinic M2 receptors were associated with a higher incidence of AF. In subgroup analysis, subjects with preexisting hypertension, diabetes, or coronary artery diseases were at greater risk of developing AF following antipsychotic exposure.
Conclusion: Antipsychotic exposure was associated with increased risk of AF, especially for agents with higher cardiac muscarinic receptor binding affinity. Physicians should monitor the occurrence of new-onset AF, and strictly control underlying medical risk factors while prescribing antipsychotic agents to high-risk populations.

1. Introduction

Antipsychotic agents have been applied in clinical practice for >60 years and are used in the treatment of chronic psychiatric diseases as well as acute mental disturbance. Due to the potential adverse effects, physicians carefully weigh the risks and benefits when prescribing antipsychotic agents to patients with cardiac risk factors, especially when prescribing atypical antipsychotics, which are notorious for their risk of QT interval prolongation and sudden cardiac death [1]. Though the arrhythmigenic effect of antipsychotics on ventricular arrhythmia has been recognized for decades, our understanding of their involvement in atrial arrhythmia is still very limited. Atrial fibrillation (AF) is one of the most common atrial arrhythmias, and is associated with an approximately 5-fold increased risk of stroke and a 2-fold increased risk of long-term mortality [2]. Several antipsychotics have been reported to induce AF in patients without previous heart diseases, including clozapine [3], olanzapine [4], and paliperidone [5]. But there have not yet been any studies to investigate the relationship between antipsychotic exposure and incidence of AF.

Herein, we conducted a nested case-control study to examine the association between antipsychotic exposure and the risk of AF occurrence using nationwide population-based medical claim data in Taiwan. Furthermore, we explored the effect of antipsychotics on the autonomic

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nervous system by calculating their binding affinity to the receptors of different neurotransmitters. The moderating effects of various medical and psychiatric comorbidities were also evaluated in our current study.

2. Methods

2.1. Database source

This population-based study was conducted using the National Health Insurance Research Database (NHIRD) released by the National Health Research Institutes (NHRI) in Miaoli, Taiwan. The Bureau of National Health Insurance (NHI) launched a single-payer NHI program in 1995, and enrolled nearly all of the inhabitants in Taiwan. The NHIRD is a cohort that contains all medical claim data, from 2000 to 2010, of 1 million randomly sampled subjects from the 23.32 million enrollees under the NHI program. Information that could be used to identify individual patients has been encrypted to protect their privacy. The encryption procedure was consistent, thus allowing the linkage of medical claims and continuous follow-up of the same patient. The dataset has been confirmed by the NHRI to be representative of the Taiwanese population. Because the selected dataset consisted of de-identified files released for research purposes, this study was exempt from full review by the Institutional Review Board of Taipei Veterans General Hospital.

2.2. Identification of AF cases and controls

From January 1st, 2000 to December 31st, 2010, the medical claim data of 1 million beneficiaries were analyzed. Case groups with AF were defined as patients with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis of AF (ICD-9-CM code: 427.31) in either outpatient or inpatient settings. The date of first AF claim in the dataset was recorded as the index date. The control group was defined as those who had received either electrocardiography (ECG) or 24-h Holter exam, but without subsequent diagnosis of AF during 2000–2010. The control subjects were matched with cases by age, gender, and cohort entry date. Each control subject was assigned the same index date as his or her matched case. The definition for AF cases and controls had been validated in our previous work [6]. Patients with an enrolled age younger than 18 years old or with an AF diagnosis before January 1st, 2001 were excluded from this study. The flowchart of patient enrollment is illustrated in Fig. 1.

2.3. Identification the exposure to antipsychotic agents

For each enrolled subject, the exposure to antipsychotic agents before the index date was retrieved from the claim data by accessing the codes of Anatomic Therapeutic Chemical (ATC) Classification System. A total of 22 oral antipsychotic agents were analyzed, including 14 first-generation antipsychotics (FGAs: chlorpromazine, clopenthixol, clotiapine, flupenthixol, fluphenazine, haloperidol, levomepromazine, loxapine, perphenazine, pimozide, prochlorperazine, sulpiride, trifluoperazine, and thioridazine) and 8 second generation antipsychotics (SGAs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, zotepine).

We classified antipsychotic exposure status according to the date and duration of drug prescription. Subjects who received at least 1 day of drug supply within 12 months prior to the index day was defined as antipsychotic "users," whereas others were regarded as "nonusers." Users were further categorized as either "current users" (any antipsychotic supply within 1 month prior to the index date) or "former users" (no prescription in the last 1 month prior to the index date). Finally, the current drug users were divided into "new users" (first prescription within 1 month prior to the index date and no exposure in the past 11 months) and "continuous users" (antipsychotic supply both within 1 month and 2–12 months before the index date). The same classification of drug exposure had been applied in another NHIRD-based study interpreting the thrombotic risk of antipsychotic agents [7].

2.4. Calculation of antipsychotic dosage and receptor occupancy

We calculated the daily dose of antipsychotic agents by dividing the cumulative prescribed doses into total supplied days. The daily doses of individual drugs were further transformed into the chlorpromazine-equivalent doses (CEDs) [8]. Comparison of AF incidence was performed between 3 groups of different daily exposure dosages: the nonusers, low-dose (CED ≤ 100) and high-dose group (CED > 100) [7].

To interpret the impact of each individual antipsychotic agent, we had separately analyzed the risk of AF for each antipsychotic drug, and classified it according to the pharmacological properties [9]. Then we

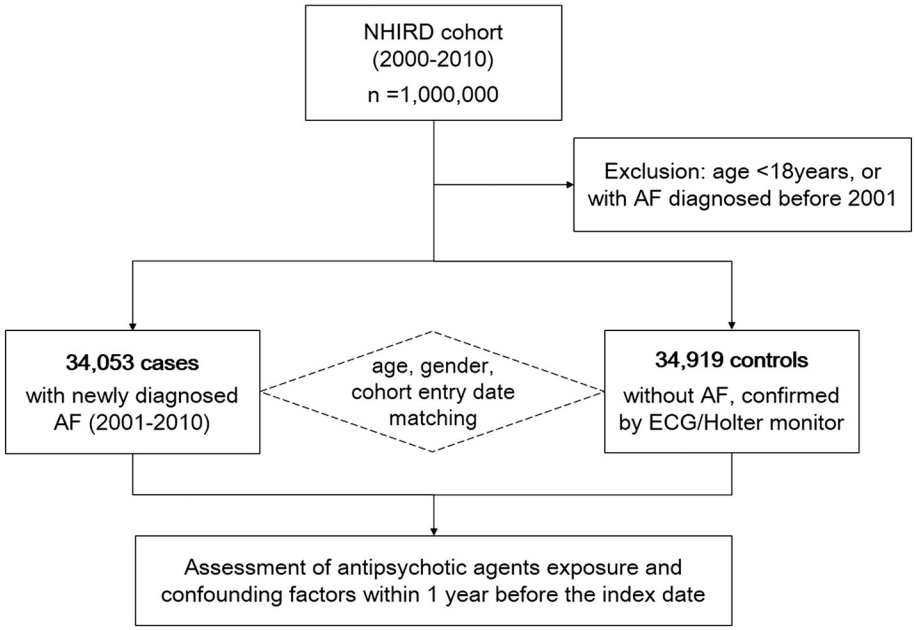

Fig. 1. Flowchart of patient enrollment. (NHIRD = national health insurance research database, AF = atrial fibrillation, ECG = electrocardiogram).