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Original Article

Antipsychotic drugs and the risk of recurrent venous thromboembolism: A prospective cohort study

L.M. Mollard[a], R. Le Mao[a,b], C. Tromeur[a,b], E. Le Moigne[a,b], M. Gouillou[c], B. Pan-Petesch[b,d], A. Delluc[a,b], F. Couturaud[a,b,c], K. Lacut[b,c,*]

[a] Département de médecine interne et pneumologie, CHU Brest – Brest, France
[b] EA3878, Université de Bretagne Occidentale – Brest, France
[c] CIC1412, INSERM – Brest, France
[d] Centre de traitement de l'hémophilie, Hématologie, CHU Brest – Brest, France

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ABSTRACT

Background: Numerous studies have suggested that antipsychotic drugs are associated with an increased risk for a first episode of venous thromboembolism (VTE). However, after anticoagulation discontinuation, the impact of antipsychotic drugs on the risk of recurrent VTE (rVTE) remains unknown.
Objective: To estimate the risk of rVTE in association with antipsychotic drugs.
Methods: Between May 2000 and December 2012, we included all consecutive patients with a first unprovoked symptomatic VTE and who discontinued anticoagulation. During follow-up, exposure to antipsychotic drugs was systematically assessed.
Results: A total of 736 patients with a first unprovoked symptomatic VTE were followed-up during a median period of 27.0 months (interquartile range (IQR) 6.2–60.0). Patients' median age was 66.0 years (IQR 49.0–76.0), 404 (54.9%) were men, and 61 (8.3%) were exposed to antipsychotics during follow-up. The incidence rate of r VTE was 12.1% person-year (95% CI 7.2–20.5) in antipsychotics users compared with 8.3% person-year (95% CI 7.1–9.8) in non-users ($p = 0.20$). Multivariate analysis showed a significant increased risk of recurrence associated with antipsychotic exposure (adjusted hazard ratio 1.9, 95% CI 1.1–3.3).
Conclusions: In this cohort study, exposure to antipsychotic drugs was found to be associated with an increased risk of rVTE among patients with a previous first unprovoked symptomatic VTE and who discontinued anticoagulation. Larger studies are needed to confirm and further explore this association.

1. Introduction

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease and a leading cause of patient morbidity and death. At least three months of anticoagulation are recommended for the treatment of the acute episode of VTE. After discontinuation of anticoagulation, the risk of recurrent VTE (rVTE) varies depending on the circumstances of the first VTE event. In case of VTE due to a major transient risk factor, such as surgery, the annual risk of recurrence is very low (< 1%), and discontinuing anticoagulant treatment appears safe [1,2]. In contrast, patients with an unprovoked VTE have a high risk of a recurrence within the first year after discontinuation of anticoagulation (from 5 to 27%) and extending the period of anticoagulation beyond the initial 3 month period has been recommended [3–6]. However, assessing the individual risk of recurrence in patients with first unprovoked VTE is complex. Despite the identification of many risk factors for VTE recurrence, such as cancer, increasing age, male sex, antithrombin deficiency, or lupus anticoagulant, there is a high proportion of patients with recurrent events in whom no risk factor has been found, suggesting the existence of other unsuspected risk factors [7,8].

Numerous studies have suggested that antipsychotic drugs could be associated with an increased risk for a first episode of VTE [9,10]. Several hypotheses (sedation, weight gain, enhanced platelet aggregation, or increased levels of antiphospholipid antibodies) have been proposed to explain this association, but no clear pathophysiological mechanism prevails [11]. It has also been suggested that VTE risk could be more related to the underlying psychiatric disease rather than the medication. Antipsychotic drugs are primarily used to treat schizophrenia as well as other mental health conditions such as agitation, anxiety, mania, and aggression. These diseases can require long term antipsychotic treatment. Antipsychotics maintenance should not be an

* Corresponding author at: CIC 1412, Hôpital de la Cavale Blanche, Bd Tanguy Prigent, F-29609 Brest Cedex, France.
E-mail address: karine.lacut@chu-brest.fr (K. Lacut).

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issue when anticoagulation is ongoing. However, when anticoagulant therapy is stopped, exposure to antipsychotics may influence the risk for VTE recurrence.

In this prospective cohort study, we sought to determine the potential association between antipsychotic drugs exposure and the risk of rVTE in patients with a first episode of symptomatic unprovoked VTE after discontinuation of anticoagulation therapy.

2. Materials and methods

2.1. Study population

All consecutive patients aged 18 and over seen between May 2000 and December 2012 in Brest University Hospital with a first symptomatic VTE event were enrolled in the study [12]. Diagnosis of DVT was established by the absence of full compressibility of a proximal or distal vein of the lower limb on compression ultrasonography (CUS). Diagnosis of PE was established by 1) a segmental or larger artery filling defect on chest computed tomography (CT) scan; 2) the combination of high pre-test clinical probability of PE with high probability ventilation–perfusion (V/Q) lung scan according to the PIOPED criteria; or 3) proximal DVT on CUS in a patient with suspected PE.

Patients were eligible for the present study if they had a first unprovoked VTE and had no indication for indefinite anticoagulation (e.g. atrial fibrillation or recurrent VTE while on anticoagulation or major thrombophilia). A first unprovoked VTE was defined as VTE occurring in the absence of surgery or plaster cast, pregnancy or post-partum in the 3 months prior to the index VTE event, VTE not associated with contraception or hormone replacement therapy, and VTE occurring without diagnosis of active malignancy in the prior five years to the enrolment.

All patients were treated in accordance with the available recommendations. Anticoagulant treatment was given for at least 6 weeks for isolated distal DVT and at least 6 months for proximal DVT and/or PE. Patients who stopped anticoagulant treatment and who completed the scheduled period of anticoagulation without experiencing rVTE were eligible for a prospective follow-up. However, patients resuming anticoagulant treatment within 3 months for another reason than rVTE were excluded from follow-up.

2.2. Follow-up

Regular visits were planned during the follow-up. The first visit was scheduled 3 or 6 months after acute VTE, and then annually. The day of oral anticoagulant discontinuation was defined as the follow-up onset, and the end of follow-up was set at a maximum of five years after the initial VTE. At each visit, patients were asked on possible rVTE. For all suspected outcome events, the results of any diagnostic test, patient's charts and clinical notes were collected. The rVTE had to be clinically suspected. The diagnosis of recurrent DVT by CUS was based on either a previously compressible venous segment that could no longer be compressed or an extension of 4.0 mm or more of the thrombosis in the case of a previously abnormal venous segment [13]. The diagnosis of recurrent PE was based on 1) a high probability lung scan, with the presence of new or enlarged segmental perfusion defect, or 2) a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery previously visualised on a chest CT-scan.

2.3. Drug exposure

At inclusion, all drugs taken before VTE index event were collected. Drugs regularly taken prior to admission but discontinued more than one week before admission were not recorded. During the follow-up, at each visit or contact, information on drugs exposure was collected. Furthermore, databases of Brest University Hospital were used to search for hospitalization's and/or visit's reports from all units (medicine, surgery or psychiatry). We assessed the exposure to antipsychotic drugs after the end of anticoagulation treatment and until rVTE, death, or date of last visit.

We classified patients as non-users if no antipsychotic drugs were prescribed during the follow-up. Exposure was defined as at least one prescription of antipsychotic drugs after the end of anticoagulation treatment. Therefore, exposure to antipsychotic drugs included both cases of continuation of therapy (current users) and new users of antipsychotic drugs during follow-up. We recorded calendar dates of the first and last days of drug intake to calculate the duration of drug exposure. However, for current users, because the real date of first prescription of antipsychotic was usually unknown, we used the date of follow-up onset as the first date of drug intake to calculate the duration of drug exposure. We recorded also on the basis of prescription, drug name and diagnosis of psychiatric disease. Antipsychotic agents were classified as conventional or atypical. Atypical antipsychotic drugs available in France during the study period included aripiprazole, clozapine, olanzapine, and risperidone.

2.4. Statistical analysis

Baseline data were summarised using frequency (percentage) for categorical variables and mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and were compared between users and non-users of antipsychotic drugs using the Chi-square or Fisher's exact test for categorical data or Student *t*-test or Mann-Whitney for continuous data as appropriate. Survival analysis was used to analyze the association between antipsychotic drugs exposure and the risk of VTE recurrence. Antipsychotic drugs use was included as a time-dependent variable. Probability of rVTE was assessed using the Kaplan-Meier method and survival curves were compared using the Logrank test. Multivariate Cox proportional hazard regression was used to identify the potential confounders between antipsychotic drug use and the risk of recurrence. Age, sex, BMI, duration of anticoagulant therapy, initial presentation of VTE, and family history of VTE were entered as covariates into a multivariate Cox proportional model. Using a backward elimination process, variables significant to $p < 0.05$ were retained in the final model. Hazard ratios and their 95% confidence interval (CI) were calculated and reported. All statistical calculations were performed with SAS version 9.4.

The study protocol was approved by our hospital scientific and ethics board. All patients gave informed consent.

3. Results

3.1. Study population

Between May 2000 and December 2012, 2959 patients with objectively confirmed symptomatic DVT and/or PE were included in our prospective cohort. Of them, 1341 had a first unprovoked VTE event. A total of 605 patients were secondarily excluded because of death before the end of anticoagulation treatment, diagnosis of cancer during follow-up, no anticoagulation discontinuation or lost to follow-up. Therefore, 736 patients were available for analysis (Fig. 1).

Baseline characteristics are shown in Table 1. The median age was 66.0 years (IQR 49.0 to 76.0). Clinical presentation of initial VTE was 290 (39.4%) isolated DVT and 446 (60.6%) PE ± DVT. Factor V Leiden mutation was found in 92 patients (12.8%) and G20210A prothrombin gene mutation was found in 33 patients (4.6%). Mean body mass index was 26.9 kg/m^2 (SD, 5.24). Median duration of anticoagulation treatment was 6.4 months (IQR, 5.8 to 12.0). Baseline demographics were not different between users and non-users of antipsychotic drugs, with the exception of family history of VTE and long-distance travels less frequent in antipsychotic users (Table 1).

At the time of the first unprovoked VTE, 49 patients were current