Original Paper

Epidemiology of Intracranial Haemorrhages Associated with Vitamin K Antagonist Oral Anticoagulants in Spain: TAC Registry

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Key Words

Intracranial haemorrhage · Vitamin K antagonists · Oral anticoagulants · Neuroepidemiology · Incidence

Abstract

Background: Vitamin K antagonist oral anticoagulants (VKA-OACs) are effective for primary and secondary prevention of embolic events. The rate of haemorrhagic neurological complications in patients admitted to neurology departments in Spain is not yet known. **Aims:** We aimed to determine the clinical and epidemiological characteristics of patients with intracranial haemorrhage secondary to VKA-OACs as well as the incidence of this severe complication. **Methods:** We conducted a retrospective, descriptive, multi-centre study using information from the medical records of all patients admitted to neurology departments, diagnosed with

Researchers in the TAC (Traditional Anticoagulation Complications) Registry study are listed in the Appendix.

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spontaneous intracranial haemorrhage, and treated with VKA-OACs within a 1-year period. We collected demographic and care data from centres, patients' medical records [demographic data, medical history, haemorrhage origin, vascular risk factors, concomitant treatment, and National Institutes of Health Stroke Scale (NIHSS) scores], and patients' outcome at 3 months [independence (modified Rankin Scale score <3) and mortality rate]. **Results:** Twenty-one hospitals serving a population of 8,155,628 inhabitants participated in the study. The total number of cases was 235, the mean age was 78.2 (SD 9.4) years, and the baseline NIHSS score was 11.6 (SD 9.5; median 9; interquartile range 14). The VKA-OACs used were acenocoumarol in 95.3% (224 patients) and warfarin in 4.7% (11 patients). The haemorrhage origin was deep in 29.8%, lobar in 25.5%, intraventricular in 11.5%, extensive in 17.4% (>100 ml), cerebellar in 12.3%, and in the brainstem in 3.4%. The international normalised ratio was within therapeutic ranges at admission (according to indication) in 29.4% (69 patients). The global incidence (cases per 100,000 inhabitants per year) is 2.88. The in-hospital mortality rate was 40%, and 24.3% of the patients were independent at 3 months, while the mortality at 3 months was 42.6%. **Conclusion:** VKA-OAC treatment is associated with a large percentage of all cases of spontaneous intracranial haemorrhage, an event leading to high dependence and mortality rates.

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Introduction

Oral anticoagulants (OACs) are the most effective treatment for embolism prevention in patients presenting with atrial fibrillation (AF) and vascular risk factors. This widely used treatment is also indicated for a number of other diseases (i.e. pulmonary embolism and deep venous thrombosis). As the population ages, incidence rates of AF and OAC use are likely to grow [1]. It would, therefore, make sense to expect an increase in the incidence of complications related to OACs. The most frequent adverse events during treatment with OACs are haemorrhages; approximately 8% of them are severe, and among all life-threatening haemorrhages, most are intracranial haemorrhages (ICHs) [2]. Patients with OAC-associated ICH (OAC-ICH) exhibit larger haematomas than patients not receiving OACs [3] and mortality rates of approximately 40%, depending on the patient series and the duration of the follow-up period [4–7]. Current management of acute-phase OAC-ICH involves patient hospitalisation in stroke units or intensive care units (depending on clinical severity), monitoring of vital signs, anticoagulation reversal, and surgery. However, no specific treatments have been proven to effectively reduce the high dependence and mortality rates associated with these haemorrhages [8–12]. In Spain, 2 previous registry-based studies have determined certain general epidemiological characteristics of stroke at the national level. The EPICES prospective study [13] showed that OAC-ICH represents 8.4% of all haemorrhagic strokes, and the IBER-ICTUS study [14] reported an adjusted incidence of haemorrhagic stroke of 26 per 100,000 inhabitants per year. The main objective of this study was to determine the epidemiological and clinical characteristics and the real incidence of OAC-ICH in Spain.

Materials and Methods

We conducted an observational, retrospective, multi-centre study representing the whole of Spain, based on registries and databases containing prospective data on stroke patients in consecutive order. All patients were admitted to neurology departments (mainly stroke units) between September 1, 2012, and August 31, 2013. Selecting a 1-year period allowed us to calculate annual rates and thereby avoid the potential effect of seasonal variations. Our main purpose was to determine the incidence of ICH associated with vitamin

K antagonist OACs (VKA-OACs) and the percentage of the total patients treated for ICH who were taking VKAs. Our secondary aim was to identify the clinical characteristics of patients with OAC-ICH. In order to participate, health centres had to meet the following inclusion criteria: (1) being a general hospital; (2) having a well-defined reference population; (3) providing 24-hour emergency care 365 days a year; (4) 24-hour availability of brain CT or MRI 365 days a year; (5) treating patients in the acute phase of stroke; (6) having a neurology department/unit; (7) providing all stroke patients with specialised care (admission to the neurology department or to another department under supervision of a neurologist), and (8) agreeing to participate in the study. Patients, in turn, had to meet the following inclusion criteria: (1) being 18 years or older; (2) having been admitted to a hospital during the study period, and (3) having been diagnosed with spontaneous haemorrhagic stroke associated with VKA-OACs. Patients diagnosed with subarachnoid haemorrhage, cerebral infarction with haemorrhagic transformation, epidural or subdural haematoma, or traumatic haemorrhage were excluded.

We designed an electronic form that each hospital had to complete with the following data corresponding to the study period: (1) reference population; (2) total number of patients admitted to the neurology department; (3) number of admitted patients diagnosed with acute stroke (either ischaemic or haemorrhagic); (4) number of admitted patients diagnosed with spontaneous ICH, and (5) number of admitted patients diagnosed with transient ischaemic attack or ischaemic stroke. Another electronic form was used to gather clinical data on the participants: demographic data; vascular risk factors; type of OAC prescribed; reason for OAC prescription; international normalised ratio (INR) at admission; concomitant treatment; concomitant presence of other haemorrhagic, neurological, or systemic complications; presence of associated structural lesions; in-hospital death; stroke severity at admission and discharge [measured with the National Institutes of Health Stroke Scale (NIHSS)], and outcome at 3 months [measured with the modified Rankin Scale (mRS)]. Haemorrhage origin was classified into the following categories: lobar, deep (basal ganglia or thalamus), brainstem, cerebellar, extensive hemispheric supratentorial (volume >100 ml regardless of the apparent source of bleeding, calculated using the ABC/2 formula), and intraventricular (either primary or secondary to hemispheric or brainstem haemorrhages). INRs within the therapeutic range were defined as 2.5–3.5 for patients with a metallic prosthetic valve and 2.0–3.0 for the rest of the patients.

Since this study is retrospective, we gathered no data which could be used to identify patients. Informed consent forms were therefore not necessary. The study was approved by the ethics committee at the promoting hospital and was classified by the Spanish Agency for Medicines and Medical Devices as EPA-OD (post-authorisation study with a design other than prospective follow-up). Data were analysed using epidemiology and descriptive statistics programs: SPSS® version 13.0, Microsoft Excel® 2003, EpiDat® 4.0, R v3.0.1, and OpenEpi (online version).

Results

The study period covered 1 full year from September 1, 2012, to August 31, 2013. A total of 21 health care centres participated, representing a total reference population of 8,155,628 inhabitants; these data represent the sum of the reference population covered by each centre. The total population of Spain as of January 1, 2013, was calculated at 46,727,890 inhabitants [15]. We therefore calculated that the participating centres provide health care to approximately 17.45% of the national population.

A total of 235 patients with OAC-ICH were identified during the study period. Thus, we calculated a crude incidence rate (not adjusted for age) of 2.881 per 100,000 inhabitants per year (exact 95% mid-p CI 2.53–3.27). OAC-ICH accounted for 1.94% of all stroke cases and 13.6% of all cases of spontaneous ICH (95% CI 12.06–15.31). These and other related data are listed in online supplementary table 1 (see www.karger.com/doi/10.1159/000437150 for all online suppl. material). Online supplementary table 2 provides a summary of the demographic and clinical data of the sample. Regarding the details of the anticoagulant treatment (online suppl. table 3), most patients (95.3%) had been on treatment with acenocoumarol, and only a third presented INRs within the therapeutic range at admission. AF was the most frequent indication for prescribing VKA-OACs. Online supplementary table 4 shows the different origins of

Fig. 1. Functional outcome at 3 months of follow-up (in percent of patients) after stroke measured by the mRS. The missing 5.1% of patients correspond to follow-up losses.

haemorrhage. Haemorrhages were more frequently located in the supratentorial region. We also found a significant number of extensive (17.4%) and ventricular (11.5%) haemorrhages.

The mean hospital stay duration was 11.3 (SD 14.2) days. The in-hospital mortality rate was 40%, reaching 42.6% at 3 months of follow-up. We gathered follow-up data from 95% (223) of the patients. Figure 1 shows the distribution of mRS scores at 3 months of follow-up. The percentage of independent patients (mRS score <3) at 3 months was 25%.

Discussion

The main findings of this study are as follows: (1) the incidence of VKA-associated ICH was 2.9 cases per 100,000 inhabitants per year, and (2) 13.6% of the patients with ICH were undergoing treatment with VKA. As far as we know, no prior studies have addressed the incidence of this complication in Spain. The IBERICTUS study mentioned above provides global incidence rates of haemorrhagic stroke but does not present a breakdown by stroke aetiology. The study performed by Rodríguez-Campello et al. [7] in Catalonia analysed 401 patients diagnosed with ICH and hospitalised between 1995 and 2003. They identified 26 cases of OAC-ICH (6.5%). The multi-centre EPICES study [13], conducted between 2008 and 2009, reported that 8.4% of the ICH cases were due to OACs. Although the EPICES study and our own are not comparable because of their differences in methodology, these findings point toward an increasing incidence of OAC-ICH, which is consistent with findings from other studies [6, 8, 16]. This increase is thought to be caused by an increase in OAC prescription. Although this hypothesis is plausible, we do not have data on anticoagulant prescription in the general population, and our study therefore cannot confirm this to be the cause.

Our results show that OAC-ICH is a severe complication associated with high rates of mortality and long-term disability. Besides anticoagulation reversal, an effective treatment specific to this type of haemorrhage is lacking, and this may be one of the main factors contributing to the fatal outcome. We did not gather data regarding withdrawal of care, which could have influenced the mortality rates. Some clinical trials [17–21] have found that patients treated with dabigatran, rivaroxaban, apixaban, or edoxaban showed ICH incidence rates equal to or lower than patients receiving warfarin. These findings suggest that the recent launch of new anticoagulants may reduce the incidence rate of OAC-ICH. We did not analyse

the incidence of haemorrhages associated with new OACs, since they are seldom used at present in our setting. Once prescription of these drugs becomes more generalised, we will require a simultaneous analysis of the incidence of haemorrhages associated with each of the two drug groups (OACs vs. new OACs) in order to establish and compare their clinical and epidemiological characteristics.

Our study has a number of limitations. The retrospective design may have failed to include patients who had not been registered correctly. Although most patients in Spain choose to be treated by the public health care system, any patients with OAC-ICH who attended private hospitals would not have been included in the TAC Registry. We have not had access to autopsy findings from patients with an initial diagnosis other than OAC-ICH, patients who died before reaching the hospital, and patients admitted to departments other than the neurology department. Nevertheless, we estimate that these situations are rare. We lack data on the age distribution of the populations of the areas covered by each health care centre and, therefore, cannot provide an incidence rate adjusted for age. This approach would be more correct from a methodological perspective and would also allow us to compare the incidence rate with incidence rates in other countries or in our own over time. Anticoagulant prescription rates in the Spanish general population are not known, which limits the calculation of specific haemorrhage rates in people at risk. Furthermore, our study is limited to a specific population with a particular ethnic composition, and our results may not be representative of the situation in other regions or countries.

According to our results, approximately a third of the sample presented an INR above the therapeutic range. Although the risk of OAC-ICH depends on the intensity of the anticoagulation treatment, it has been proved to increase 7- to 10-fold even when the INR is kept within the therapeutic range [22]. Furthermore, we only had one INR score for each patient, corresponding to the sample taken at admission, but we do not know how much time elapsed between VKA administration, haemorrhage onset, and INR measurement. In any case, this lapse was supposedly always shorter than 24 h. Cases with INR scores below the therapeutic range may still reflect haemorrhage directly associated with medication, combined with a longer time lapse between haemorrhage onset and INR measurement. We cannot attribute the aetiology of haemorrhage exclusively to the use of VKA treatment. The significant number of hypertensive patients with deep haemorrhage in our study suggests that arterial hypertension contributes to the pathophysiology of these haemorrhages. This is why we use the term 'VKA-associated bleeding'. Additionally, we could not find a relationship between a higher INR and haemorrhage volume, but this could be due to our relatively small sample.

In light of these results, we can conclude that OACs constitute an important and relatively frequent cause of ICH. Severe outcomes are common, resulting in high dependence and mortality rates. Physicians must, therefore, be mindful of the type of adverse events associated with these drugs and be on the lookout for them when prescribing anticoagulants and monitoring patients on this treatment. These data may help in the design of future research studies as well as in the implementation of local health policies.

Appendix

Researchers in the TAC Registry Study

Asturias: Hospital Universitario Central de Asturias: Dr. Sergio Calleja. Castile-La Mancha: Hospital Universitario de Albacete: Dr. Eva Fernández and Dr. Tomás Segura. Castile-León: Hospital Universitario de León: Dr. Javier Tejada García and Dr. Noelia González Nafraía; Hospital Universitario de Salamanca: Dr. José Carlos Gómez. Catalonia: Hospital del Mar: Dr. Jaume Roquer; Hospital Universitari Arnau de Vilanova: Dr. Francisco Purroy; Hospital de la Santa Creu i Sant Pau: Dr. Alejandro Martínez Domeño and Dr. Joan Martí Fábregas. Extremadura: Hospital San Pedro de Alcántara: Dr. Ignacio Casado. Galicia: Hospital Clínico Univer-

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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