ORIGINAL ARTICLE

Effects of anticoagulation therapy with vitamin K antagonists on hospitalizations and emergency room accesses in Grosseto (Italy)

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Keywords

Warfarin • Hospitalization • Italy

Summary

Introduction. *A lot of drug groups are associated with preventable drug-related admissions. Coumarin derivatives, prescribed for the treatment and prevention of deep vein thrombosis or pulmonary embolism or prevention of systemic embolism or stroke in patients with prosthetic heart valves or atrial fibrillation, are often associated with bleeding. The aim of our study was to analyze how the anticoagulant therapy with VKAs could affects the hospitalizations and the visits to emergency room in the elderly population (> 65 years old).*
Methods. *In 2013 we conducted a cross sectional study analyzing the database of all pharmaceutical prescriptions, selecting patients living in Grosseto (Italy), which received at least two prescriptions of coumarin derivatives in 2012. We analyzed the admissions to hospital and the accesses to the emergency rooms (ERs) made by each patient, focusing especially on those related to bleeding. For each access to ER we recorded the date, time of stay, diagnosis and outcome. For each hospitalization the information we recorded were the date of admission and discharge diagnosis.*
Results. *3684 patients were included in our study. 261 (7.1%) patients visited the emergency room for bleeding; 37 (1%) for intracranial bleeding. The accesses made by men were higher than those made by women. The average time of stay in ER was 349 minutes. The admissions to hospital were 96 (2.6%); 42 (1.1%) were admitted to hospital with a diagnosis of major vascular event. 53 patients (20.3%), accessed to the ER more than one time. The 11.5% was admitted to the hospital more than one time.*
Conclusions. *Our study showed that VKAs are responsible of an increase of the accesses to ER and of the admissions to hospital. However, it would be interesting to enlarge the sample size including patients living in other provinces or in other regions, with a lower age and treated also with TSOACs, in order to evaluate the real cost-effectiveness of anticoagulant therapy.*

Introduction

The World Health Organization has defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems" [1]. Such "drug-related problems" include adverse drug reactions (ADRs), unintended injuries or complications that arise from iatrogenic drug related causes and which cause or prolong hospital admission and result in disability or death [2-4]. The risk of ADRs is necessarily an inherent risk of all drug therapy and is modulated by several factors, including dose and frequency of administration, genotype, and pharmacokinetic characteristics of special populations, such as pediatric and geriatric patients and those with hepatic or renal impairment. Due to the high frequency and potentially serious consequences, ADRs may have a dramatic impact in clinical practice both from a clinical and economic perspective [5]. As described by Formenti et al. in their study [6] the onset of adverse reactions (ADRs) represents a sentinel event and, in addition to diminishing the quality of life of the patient increases the number of medical visits, hospitalizations and even the deaths, resulting in an overall increase in health care costs. Containing the number of ADRs, therefore, would result in a cost reduction for the ADRs treatment, diagnostic examinations and differential diagnosis analysis [7-9].
Estimates from France suggest that up to 123,000 patients a year present to their general practitioner with an ADRs [10]. ADRs account for 4.2-30% of hospital admissions in the USA and Canada, 5.7-18.8% of admissions in Australia, and 2.5-10.6% of admissions in Europe [8].
A national study from the USA estimated that 11.4-35.5% of emergency department visits in older adults are due to drug-related causes [5, 11].
Howard et al. [8] showed in their systematic review that the drug groups most frequently associated with all types of preventable drug-related admissions were antiplatelets, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants.
Coumarin derivatives, such as warfarin, acenocoumarol and phenprocoumon are prescribed for different indications such as treatment and prevention of deep vein thrombosis or pulmonary embolism or prevention of

systemic embolism or stroke in patients with prosthetic heart valves or atrial fibrillation [12]. Because warfarin and other coumarin derivatives inhibit the vitamin K dependent synthesis of biologically active clotting factors, they are also called vitamin K antagonists (VKAs). The main adverse effect associated with coumarin derivatives is bleeding. Several studies have shown that the incidence of major bleeding in patients on warfarin ranges from 0.4%-7.2% per year [13]. Minor bleeding rates can be as high as 15.4% per year [14]. Fatal bleeding events occur at rates of 1.3 per 100 patient-years, according to a meta-analysis of 33 studies [15].
However in different studies is not always used the same definitions, methods, and consequently, the results vary a lot; moreover the follow-up time is variable and often the studies focus only on a category of patients. The aim of our study was to analyze the impact of the anticoagulant therapy with VKAs in the elderly population – over 65 years old, defined according to the World Health Organization definition of "elderly person" [16, 17] –, through the hospitalizations and the visits to emergency room, using only current data flows. This kind of analysis let us to analyze this phenomenon in a "real setting", in order to quantify the impact of the side effects in a not selected sample, with co-morbidities, with advanced age and with possible problems of compliance with therapy. This is particularly interesting for anticoagulants which are often used in old people with a lot of pathologies, and often living in not adequate domestic environments.

Methods

In 2013 we conducted a cross sectional study in the Demographic and Epidemiological System of the AUSL Toscana Sud Est. We analyzed the database of all pharmaceutical prescriptions: this is a database containing all the information about the loanable pharmaceutical prescriptions, derived from the flows directed to the National Health System.
We selected patients living in Grosseto – Italy, total resident population: 223,652 [18] –, which received at least two prescriptions of VKAs in 2012. This selection was chosen in order to identify patients subjected to long term therapy with anticoagulants. We collected information about age, gender, type of medication, city of residence. Then, through a unique identification code, we identified and analyzed the admissions to hospital (we considered the admissions to all Italian hospitals) and the accesses to the emergency rooms (ER – we considered the ERs of Grosseto, Castel del Piano, Orbetello, Pitigliano, Massa Marittima –) made by each patient. These data derived from the archives containing the flows of the hospital discharge records and accesses to ER, sent to the Region and then to the National Health System. We focused especially on the group of accesses to ER and hospitalizations related to bleeding, occurred within 4 months after the prescription of the anticoagulant. In fact, the daily dose of this kind of therapy varies a lot and could be interrupted for surgery (even for minor surgery). So we estimated, by default, the maximum time between two prescriptions (sometimes 2 packs for each prescription) in 4 months: so considered the time span was from January 2012 to April 2013.
For each hospitalization the information we recorded were the date of admission and discharge diagnosis. In the hospital discharge records all the diagnoses are codified with the code ICD IX, so we considered all the diagnoses containing the words "hemorrhage" and its derivatives and "anemia" and its derivatives.
For each access to ER we recorded the date, time of stay, diagnosis and outcome. Diagnoses related to the accesses to the ER are not codified using ICD IX, so we considered all the diagnoses related to bleedings in progress, previous or chronic.
The results were organized in a database and then exported for statistical analysis. The collected data were processed using the software Stata® SE, version 12.1 (StataCorp, College Station, Texas, USA). The level of significance was set at $p < 0.05$.

Results

From the pharmaceutical prescriptions database we extracted 4368 patients who received at least two prescriptions of VKAs in 2012; 2304 (52.74%) were men.
3684 patients (84.34% of the entire sample) were > 65 years old, 1889 were men (51.3%). The average age was 78.2 years (79.2 for women CI 95% 78.9-79.5; and 77.2 for men CI 95% 76.9-77.5).

Accesses to Emergency Rooms

261 (7.1%) patients visited the emergency room for bleeding; 37 (1%) for intracranial bleeding. Patients who accessed to ER were represented especially by men (7.9%): women were the 6.2%, and this difference was statistically different ($p < 0.05$). The average time of stay in ER was 349 minutes (CI 95% 296.1-402.2); for women 385 minutes (CI 95% 295.0-476.4); for men 325 minutes (CI 95% 260.5-389.8).
Table I shows the principal diagnoses recorded during the visits to ER.

Admissions to hospital

The admissions to hospital were 96 (2.6%); 42 (1.1%) were admitted to hospital with a diagnosis of major vas-

Tab. I. Accesses to ER.

Diagnosis	Percentage (%)
Epistaxis	24
Cerebral hemorrhage	11
Anemia	14
Conjunctival hemorrhage	9
Hematuria	11
Rectorragy	6
Other bleeding	25

cular event. There is not any statistically significant difference in the admission to hospital or in the accesses to ER due to the prescribed medication (warfarin or acenocoumarol).
53 patients (20.3%), accessed to the ER more than one time. The 11.5% was admitted to the hospital more than one time.
Figure 1 shows the principal diagnoses recorded during the admissions to hospital in the considered time-span.

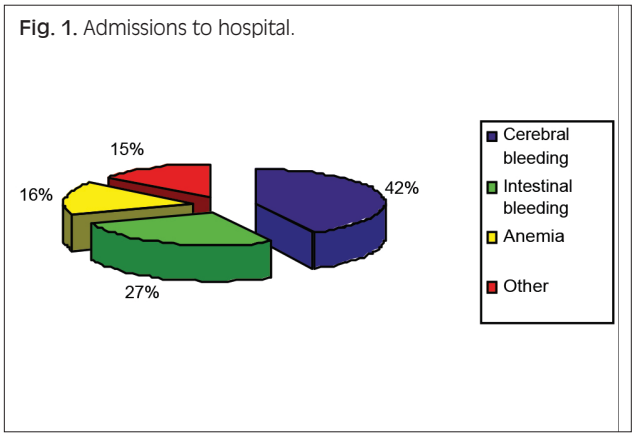

Fig. 1. Admissions to hospital.

Discussion and conclusions

The 84.34% of the sample analyzed in our study was > 65 years old, and was represented especially by men (51.3%) with an average age of 78.2 years. These data are partially in line with those found by Kim et al. in 2010: of the 2346 subjects enrolled in their study to evaluate the hospitalization costs associated with warfarin-related bleeding events, 1804 were females (77%) and about two-thirds of the subjects were over the age of 75 years (< 70 years: 12%, 71-75 years: 23%, 76-80 years: 28%, 81-85 years: 25%, ≥ 86 years: 12%) [19].
In our study the accesses to the emergency room for bleeding (7.1%) were higher than the admissions to hospital (2.6%). In a meta analysis conducted in 2012 [15] it was showed that during the initial 3 months of anticoagulation, the rate of major bleeding was 2.06% (CI 2.04% to 2.08%) and the rate of fatal bleeding was 0.37% (CI 0.36% to 0.38%). The rate of intracranial bleeding was 1.48% (CI 1.40% to 1.56%). Chai-Adisaksopha et al. in 2014 showed in their study that total bleeding occurred in 30.42% patients treated with vitamin K antagonists (VKAs), a lower percentage compared to the 24.86% of patients treated with Target-Specific Oral Anticoagulants (TSOACs); however, major gastrointestinal bleeding occurred in 2.09% of patients treated with TSOACs and 1.70% of patients treated with VKAs [20]. Dale et al. in fact showed that warfarin is associated with greater thrombin suppression in the brain and pathological thrombosis at sites of atherosclerotic plaque disruption [21].
The problem of bleeding after the therapy with VKAs is important for the costs that this phenomenon creates in the National Health System. Sameer R. Ghate et al. [22] showed that during the 12 months after the treatment there was a significantly higher increase of major gastrointestinal or intracranial bleeding event and consequently of hospitalizations, hospital days, and ER visits. In the 12 months after the warfarin start date, the mean adjusted annual costs obtained from the regression model were $42,574, $36,571, $22,824, and $22,507 for subjects with intracranial bleeding, major gastrointestinal bleeding, minor gastrointestinal bleeding, and no bleeding, respectively [22]. The mean length of stay was 7.8 days (SD: 7.1). For the entire cohort, warfarin-related bleeding resulted in an average increased cost of hospitalization of $508.30 per warfarin user [19].
The most important limit of our study is that the study sample is not representative of the Italian population: in fact our sample is composed by patients older than 65 years and treated with VKAs; furthermore, our sample is composed only by patients living in Grosseto Province. Our study is limited to 2013 because the organizational changes in the Local Health Units, led to the fusion of three Local Health Unit (Grosseto, Siena and Arezzo) in a unique Unit, with the following fusion of the databases, which is not totally finished yet. So the previous databases have not been implemented in the same way, therefore it is impossible to repeat the analysis with updated data, although we think that significant differences would not be found.
It could be interesting to complete our study enlarging the sample size, and enrolling patients living in other provinces or in other regions in Italy, with a lower age and treated also with TSOACs. We encourage other colleagues to conduct with us a multicentre study in order to identify significant differences that could influence the costs for the National Health System and evaluate the real cost-effectiveness of anticoagulant therapy. Moreover, it would be interesting to investigate the quality of life [23-25] of patients treated with the two classes of drugs and to evaluate the impact of these therapies on this non-economic aspect of healthcare.

Acknowledgments

The authors declare that there is no conflict of interest.

Authors' contributions

FN had the idea for the article, collaborated in performing the study, carried out the data analysis and collaborate in writing the article.
GT collaborated in writing the article and helped to conceptualize ideas.
NN collaborated in writing the article and helped to conceptualize ideas.
SD helped to conceptualize ideas.
PP collaborated in writing the article and helped to conceptualize ideas.

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