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Original Article

Bleeding and asymptomatic overdose in patients under Vitamin K antagonist therapy: Frequency and risk factors

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ABSTRACT

Background: Vitamin K antagonists are widely used in the treatment and prevention of thromboembolic disease. However, these drugs can cause serious side effects, especially bleeding. This study aims to evaluate frequency and risk factors of both bleeding and asymptomatic overdose in North African patients undergoing Vitamin K antagonist therapy.

Methods: We performed a cross-sectional study in patients undergoing Vitamin K antagonist therapy. A statistical analysis has been conducted to identify overdose and bleeding risk factors by using chi-square test ($p < .05$).

Results: One hundred and eleven patients were included. We recorded 14 cases of bleeding and 26 cases of asymptomatic overdose. Advanced age, poor adherence, concomitant use of paracetamol and history of previous bleeding are significant risk factors of over-anticoagulation. An INR value over 6 at admission, a high therapeutic target range for INR, concomitant use of acetylsalicylic acid, lack of information on overdose signs and measures to be taken in case of bleeding were identified as risk factors for bleeding.

Conclusion: Most of the risk factors identified in our study seem to be related to patients lack of information and education. These results highlight the importance of creating a therapeutic patient education program.

1. Background

Vitamin K antagonists (VKA) (acenocoumarol, warfarin, fluindione) are widely prescribed for the prevention and treatment of thromboembolic complications of cardiovascular diseases. Bleeding is a frequent side effect of this treatment and it can limit its use substantially. A great number of studies have evaluated bleeding prevalence in patients under VKA therapy. In nationally representative emergencies departments in the United States in 2002, 2004, and 2005, warfarin was identified as the drug most commonly associated with adverse events.[1,2] In France, two national studies in 1998 and 2007 conducted by pharmacovigilance centers revealed that 13% of hospital admissions for adverse events are related to hemorrhage with VKA, with about 17,000 hospitalizations and 5000 deaths per year.[3] In Tunisia, a study carried out in an university hospital in 2009 showed an incidence of hospitalization for severe hemorrhage under VKA of 0.8%.[4] A number of studies have evaluated factors that are associated with bleeding such us advanced age, recent initiation of VKA therapy and intensity of anticoagulation with an International Normalized Ratio (INR) v alue > 4.5.[5–8] In 15 to 30% of cases, VKA overdose is asymptomatic,[3] an asymptomatic overdose is defined by an INR value outside of the therapeutic range without any clinical sign of hemorrhage. It is a risky situation that needs to be quickly managed to avoid bleeding complications. This study aims to evaluate the frequency and risk factors of both bleeding and asymptomatic overdose in a sample of North African patients undergoing VKA therapy.

2. Methods

We performed a cross-sectional study in a Tunisian university hospital. The study enrolled inpatients and outpatients followed up in cardiology and internal medicine departments for VKA therapy. The only exclusion criteria were the absence of patient's consent and the presence of a cognitive impairment that affects the patient's comprehension.

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As a first step, patients' medical records were reviewed for individual clinical characteristics including sex, age, indication of oral anticoagulant therapy, co-treatment and previous history of oral anticoagulant therapy-related bleeding.

Second, we collected detailed information on VKA therapy such as: dosage of acenocoumarol, age of oral anticoagulant therapy, INR value on admission and possible signs of bleeding. To evaluate bleeding risk, the HAS BLED score was calculated for all patients. Finally, interviews with patients allowed us to collect information on:

- Knowledge about VKA therapy and pathology using a 19-item survey; knowledge level was considered insufficient if the patient did not correctly answer at least one question among the 5 questions that were considered most relevant to the risk of over-anticoagulation (regular time of intake, drug interaction, action to be taken in case of a missing dose, INR monitoring and frequency).
- Medication adherence which was assessed with the "Compliance assessment test" developed by Girerd et al.
- Compliance to INR monitoring.
- Social background and level of education.
- Hand function disability or vision impairment.

Patients were divided into 3 groups:

- Group 1: Patients with a therapeutic INR value on admission and without any sign of bleeding.
- Group 2: Patients with overdose with or without bleeding signs. Overdose was defined by an INR value that is outside the therapeutic range (between 2 and 3 or 3 and 4.5, depending on the therapeutic indication).
- Group 3: Patients with bleeding signs on admission.

A statistical analysis has been conducted to identify overdose and bleeding risk factors. Statistical analyses were conducted using IBM SPSS version 19. The chi-square test was applied and a significance threshold of 0.05 was adopted in the statistical analysis.

3. Results

One hundred and eleven patients at an average age of 56.5 years (54 men and 57 women) were included. Atrial fibrillation was the most common indication for VKA therapy (47.7%). Most of the patients were under anticoagulant treatment for more than 5 years (37.8%). The clinical characteristics of the study population are indicated in Table 1.

During the study, we reported14 cases of bleeding (12.6%) and 26 cases of asymptomatic overdose (23.4%). Bleeding complications were mainly minor: bleeding gums (4 patients), bruising (4 patients), epistaxis (3 patients) and hemoptysis (2 patients). A single case of thalamic hematoma with intraventricular hemorrhage was recorded.

The main INR value in the population was 4,5. Among the 14 patients having experienced bleeding complications, 10 (71.4%) had INR values over 6.0.

The comparison between patients in group 1 and group 2 shows, as described in Tables 2 and 3, that advanced age (p = .001), poor adherence to treatment (p = .003) and to INR monitoring (p = .028), history of previous bleeding (p = .014) and concomitant use of paracetamol (p = .033) are significant factors correlated with an increased risk of over-anticoagulation. Lack of knowledge about VKA therapy, the risk of drug interactions and precautions before invasive procedure, was also correlated with a higher risk of over-anticoagulation.

Table 1
Patients characteristics.

	Group 1 (n = 71)	Group 2 (n = 40)
Median age	55 years [20–84]	58 years [26–82]
Sex	30 Male 41 Female	25 Male 15 Female
Department		
Internal medecine		
Inpatients	5	1
Outpatients	18	1
Cardiology		
Inpatients	26	28
Outpatients	22	10
VKA indication		
Secondary prevention of deep vein thrombosis	20	1
Secondary prevention of pulmonary embolism	1	0
Atrial fibrillation	31	32
Valvular cardiopathy	10	0
Valvular prothesis	6	7
Superficial thrombophlebitis	1	0
Intraventricular thrombus	2	0
Age of VKA therapy		
[3 months–1 year]	14 (20%)	6 (16%)
[1 year–5 years]	17 (24%)	10 (23%)
≤3 months	11 (15%)	4 (10%)
≥5 years	29 (41%)	20 (51%)

The comparison between group 1 and group 3 patients shows that concomitant use of acetylsalicylic acid (p = .034), lack of information on overdose signs (p = .002), an INR value over 6 at admission (p = .002) and a high therapeutic target range for INR (between 3 and 4.5) (p = .031) were correlated with an increased risk of bleeding (Tables 4 and 5).

4. Analysis and discussion

This study allowed us to evaluate the prevalence of bleeding complication and asymptomatic overdose under VKA therapy in a representative sample of North African patients. Among 111 random patients, the prevalence of bleeding was estimated at 12.6% and that of asymptomatic overdose at 23.4%. The bleedings observed were mainly minor such us bleeding gums, bruising, epistaxis and haemoptysis. Only one case of thalamic hematoma with intraventricular bleeding was reported. In a French case-control study conducted in 2009, authors estimated bleeding prevalence under VKA therapy at 31.5%, this rate seems to be higher than our findings but it can be explained by the fact that this study was conducted in the emergency department.[9]

In Dakar, in a study that included 154 patients, Khadidiatou Dia et al. reported 8,4% of asymptomatic overdose, but this cannot be compared to our findings since they only included patients with INR values upper than 5.[10] Another study evaluating overdose frequency established that 1.19% of patients presented oral-anticoagulant-related over-anticoagulation but this rate cannot be compared to our result since they defined over-anticoagulation as an INR value greater than or ranging from 4 to 6 and complicated with bleeding.[11] In a similar study, this rate was estimated at 9.7% of all included patients.[12]

In a prospective and observational study enrolling 1019 patients in New York, the rate of asymptomatic overdose (INR values greater than 3) was estimated at 29%.[13]

In our study population, we found that advanced age (over 65 years) was strongly associated with VKA-related overdose and bleeding (P = .001). Our finding is strongly supported by several studies that have shown that patients older than 65 years are the

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