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Original Research Article

Frequency of bleeding complications in Algerian patients treated with the vitamin K antagonist acenocoumarol and associated factors

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ABSTRACT

Background: The major complication of vitamin K antagonist (VKA) therapy is bleeding. This study aimed to estimate the rate of hemorrhagic accidents and identify the hemorrhagic factors in Algerian patients treated by the VKA, acenocoumarol.
Methods: We performed a cross-sectional study in patients undergoing VKA therapy, followed in the cardiology department of the University Hospital of Sidi Bel Abbes.
Results: One hundred patients were included. We recorded 22 cases of bleeding. Overdose and concomitant use of drugs that interfere with the acenocoumarol effect are significant risk factors of bleeding.
Conclusions: Knowledge of predictive factors for VKA-related excessive anticoagulation seems to be of the utmost importance for improving patient management. There is a need for a national registry to assess the efficacy and safety of drug use in the short and long term. This pilot study is a cornerstone in the development of oral anticoagulation therapy monitoring in our region.

Keywords: Vitamin K antagonist, Acenocoumarol, Bleeding, Oral anticoagulant

INTRODUCTION

Vitamin K antagonists (VKA) have been the most widely used oral anticoagulant since their introduction in 1954.[1] Warfarin is the only VKA licensed in the United States. In contrast, the other VKAs, such as acenocoumarol, fluindione, or phenprocoumon, are frequently used in Europe. The anticoagulant effect consists in the inhibition of the enzyme vitamin K epoxide reductase, which catalyzes the γ-carboxylation of the so-called vitamin K–dependent coagulation factors (II, VII, IX, and X).[2] Inhibition of this enzyme results in the production of functionally deficient factors, thereby leading to impaired hemostasis. VKAs are mainly used as long-term anticoagulant therapy. Their prescription does not cease the prevention and treatment of thromboembolic events.[3] However, its most common complication is bleeding, which may be life-threatening.[4] Thus, the clinical use of AVK is complex. It requires dose adjustments, routine patient monitoring, and international normalized ratio (INR) measurements. It is also dependent on food-drug interactions. Besides, VKAs differ in their chemical structure, come in various strengths, and are substrates of cytochrome P450, all of which influence their pharmacokinetic and dynamic properties.[5] A great number of studies have assessed the occurrence of bleeding in patients receiving VKA therapy. However, there is a lack of data on haemorrhagic accidents related to VKA in the Algerian population. The treatment of anticoagulation in our country is based on knowledge from western countries. As far as we know, acenocoumarol (Sintrom) is the only VKA available in Algeria. Most of the published

information is related to warfarin and, there are few studies with acenocoumarol, which were performed in Europe. To respond to this lack of information, we decided to estimate the rate of haemorrhagic accidents and identify the haemorrhagic factors in patients treated by the VKA, acenocoumarol.

METHODS

Patients and method

We conducted a cross-sectional study at the Cardiology Department of Sidi Bel Abbes University Hospital. We performed this study for the period of three months, from February 2019 to April 2019. Inclusion criteria were male, female patients aged 18 or older treated with VAK. We excluded patients on heparins associated with VKA and who have hematocrit less than 30% from the present study. Data collection extracted from the medical record was on spreadsheets containing demographic data (age, sex, and educational level), Comorbidities and cardiovascular risk factors, medical history, VKA dose, treatment duration, associated treatments, bleeding complication, INR rate.

Data analysis

The D'Agostino-Pearson test for normality was used to analyse the values. As not all values were normally distributed, data were presented as either median (range) or mean ±SD. Paired and unpaired data were compared using the Wilcoxon test and the U Whitney test, respectively. The t-test was used to compare the mean between the groups. Either the Chi-square test or Fisher test checked differences in frequencies. Statistical analysis was performed with the Statistical package for social sciences (SPSS) statistical package. We also used binary logistic regression modelling to determine the impact of some factors on hemorrhagic accidents related to acenocoumarol. For all statistical tests, $p<0.05$ was considered statistically significant.

RESULTS

We included one hundred hospitalized patients in this study. The sex ratio was 1.7. Baseline data for all patients, men and women, are shown in Table 1, in which we can observe that there was a similar distribution between the genders. Acenocoumarol was the only VKA prescribed. The posology varied between 1 and 4mg, and the most prescribed dose was 2 mg Figure1. The average treatment duration was nine years (with extremes ranging from 6 months to 33 years). All patients have a target INR between 2 and 3. However, 34 have overdosed, and 20 were underdosed Figure 2. A drug interaction increasing the anticoagulant effect of acenocoumarol was observed in 19 % of patients (Table 2). Results illustrated in Table 3 show the comparison of the bleeding rate between the current study and other reports. Among the 100 patients, 22 had a hemorrhagic stroke. The factors related to hemorrhagic accidents in these patients are shown in Table 4.

Table 1: Baseline data for all patients, men and women.

	Total	Male	Female	P value
Age years	62.70 (14.24)	64.15 (14.26)	61.77 (14.27)	NS
Sex	100	39	61	
Educational level	50	21	29	NS
Arterial hypertension	55	25	30	NS
Diabetes mellitus	21	8	13	NS
Renal failure	8	5	3	NS
Stroke	4	1	3	NS
Anaemia	16	4	12	NS
Polymedication	77	32	45	NS

NS: nonsignificant difference

Table 2: Drug-drug interactions.

Drug	%
Aspirin	9
Anti-inflammatory drug	2
Antiplatelet agent	3
Statins	2
Amiodarone	1
Propranolol	2

Table 3: Comparison of the bleeding rate between the current study and those of the other reports.

Reference	Country	Number of patient	Rate of bleeding (%)	P value
Belkacemi et al 2021	Algeria	100	22	
Chetoui et al 2016	Maroco	200	15	NS
Ben Mbarka et al 2018	Tunisia	101	12.8	NS
Tremey et al 2009	France	1700	13	NS
Sjögren et al 2015	Sweden	77 423	2.24	<0.0001
Gomes et al 2013	Canada	125 195	3.8	=0.0001
Palareti et al 2017	Italy	5707	1.38	=0.0002

NS: nonsignificant difference

Table 4: The factors related to hemorrhagic accidents in patients treated with acenocoumarol.

Variable	OR	IC 95%	P value
Age >65 ans	1.176	0.450- 3.070	NS
Sex	0.671	0.246- 1.831	NS
Illiterate patients	1.263	0.489-3.26	NS
Duration >9 ans	0.6111	0.236-1.583	NS
Overdose	6.220	1.944-19.904	0.002*
Arterial Hypertension	1.294	0.501- 3.340	NS
Diabetes Mellitus	1.254	0.374- 4.203	NS
Renal failure	0.434	0.095- 1.979	NS
Myocardial infarction	1.438	0.159-12.997	NS
Stroke	0.182	0.019- 1.787	NS*
Anaemia	0.558	0.171- 1.823	NS
Drug-Drug interaction	7.435	2.101-26.304	0.004*

*Adjusted OR NS: nonsignificant difference

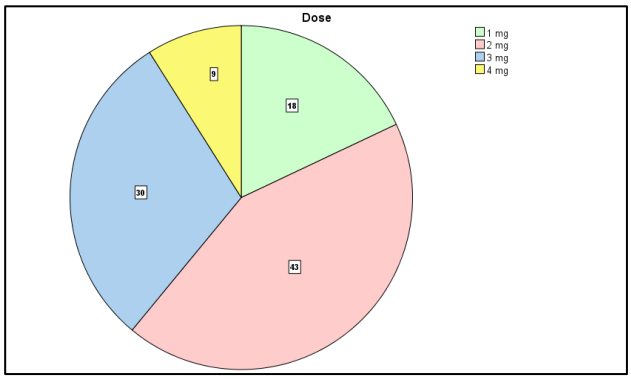

Figure 1: Acenocoumarol posology.

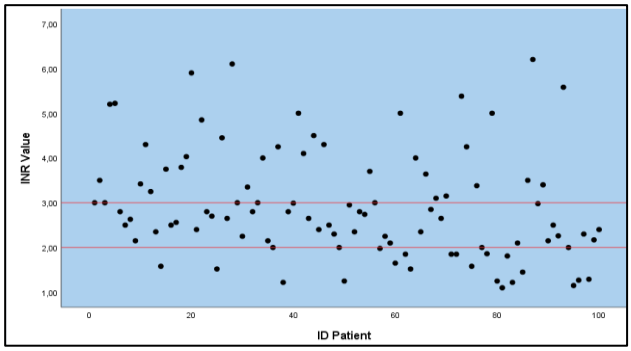

Figure 2: Conformity of prescription.

Among the factors examined (age, sex, educational level, duration of treatment, overdose, diabetes, arterial hypertension, chronic kidney failure, myocardial infarction, stroke, anaemia, associated drugs), only overdose and drug interaction were significantly linked with bleeding associated with VKA therapy.

DISCUSSION

This study permitted us to estimate the prevalence of bleeding complications during acenocoumarol treatment in the Algerian patient sample. The global rate of bleeding with the VKA acenocoumarol recorded in this study was comparable to those previously described in some neighbouring and some European countries.[6-8] However, this rate was significantly higher than the incidence reported in most Western countries.[9-11] This discrepancy in prevalence between countries within a region may be ascribed to differences in socioeconomic status, in management of VKA therapy and differences between experimental and observational studies.

There was no notable difference in the bleeding rate that we found between males and females. We confirmed the previous finding that the patient's gender has no effect on accidents due to VKAs.[12,13] Furthermore, we found no age differences between patients who showed a hemorrhagic accident related to VKA. However, some studies described

an increased risk of hemorrhagic complications in older patients, while others found that age is not an independent risk factor.[14-18] For various reasons, Bleeding is more common in the aged population. The existence of one or more comorbidities was considered as a risk indicator.[19] Elderly patients have more frequent indications for oral anticoagulants. Thus, VKAs are widely prescribed for them.

Regarding age, one of the reasons could be that we have few patients over 70 years. Furthermore, Illiterate patients were not at significant risk of a bleeding complication. A number of studies and reviews showed that increased anticoagulation risk is related to patients lacking oral anticoagulation information.[20,21] Education of the patient was effective in promoting better anticoagulation control.[22] These findings highlight the importance of creating a therapeutic patient education program.

We found no link between duration treatment and bleeding complications. Many authors have reported that the risk of bleeding decreases during therapy because patients on long-term treatment had oral anticoagulation knowledge higher than that of the new patients. A lack of information and education among African patients has been reported.[23] Hence, these findings may not apply to our population. The higher risk at the start of treatment may be explained by the longer half-life of AVK and the use of a loading dose. In contrast, some authors disagree with this observation. They found a greater predisposition for bleeding in the patients with longer courses of treatment.[24, 25]

It, therefore, appears that overdose is an important factor in terms of bleeding related to VKA. An international normalized ratio (INR) ≥of 4.0 was associated with an increased risk of an accident hemorrhagic. The findings of our study confirm previous observations that the rate of bleeding depends on the INR target range.[26,27] AVK overdoses are the leading cause of iatrogenic hospitalization in France and pose a real public health problem. In the United Kingdom, they are ranked in the third position. Hence, monitoring the deviation of INR may help predict patients at higher risk for bleeding.

Several studies have shown that hypertension, even when treated, is associated with an increased risk of bleeding during anticoagulation therapy.[28,29] Although, some studies have not supported this finding.[30,31] Moreover, in our study, the risk of bleeding does not increase in the presence of hypertension. Thus, hypertension may not be an independent risk factor for anticoagulant-related bleeding.

There are no previous reports in the literature that bleeding complications are higher in patients with diabetes than in those without diabetes. Consistent with previous studies, we showed that a history of diabetes was not associated with an increased risk of bleeding complications.[32,33] Most studies have shown that patients with renal insufficiency have an increased risk of major bleeding during VKA treatment.[34-36] However, there is a lack of this association in our study; this could be that we have a few patients with Renal Insufficiency.

Multiple studies have confirmed that either myocardial infarction (Ml) or ischaemic heart disease (IHD) is not associated with an increased risk of bleeding.[33] We found no other statistically significant relationship between bleeding complications and the presence of a previous stroke. These results are in full agreement with previous studies.[37]

In most studies, severe anaemia (hematocrit 0.30 or less) unrelated to acute bleeding has been associated with major anticoagulant-related bleeding.[38,39] However, there is a lack of this association in our study; this could be that all patients have hematocrit higher than 30%.

Our findings confirm that drug interactions have an increased risk of bleeding.[40,41] Several drugs may influence the anticoagulant' effect of AVK, mainly anti-platelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and amiodarone. Patients on anti-vitamin K therapy need to be aware that the anticoagulant effect is sensitive to various drugs. Hence, they must inform any health care provider they consult about their anti-vitamin K therapy to take the risk of drug interactions into account.

A new class of anticoagulants has been developed in recent years that is easy to use for follow-up patients. These drugs called ''new oral anticoagulants'' (NOACs) are ximelagatran, dabigatran, etexilate, rivaroxaban, edoxaban, and apixaban; their mechanism of action consists of the direct inhibition of the coagulation factor Xa, or IIa.[42] NOACs have some advantages to standard therapy with VKA, such as the rapid onset of action, low interactions with food and drugs, and a predictable anticoagulant effect; this latter effect eliminates the requirement for monitoring blood coagulation. A meta-analysis of randomized clinical trials revealed an incidence of 1.08 versus 1.75 % in patients treated with NOACs and warfarin, respectively.[43] Compared to AVK, treatment with NOACs showed a significant reduction in major bleeding.[44] New oral anticoagulants (NOACs) may represent an alternative to standard therapy with VKA.[45,46]

There are some strengths and limitations to this research. One of the major strengths of this survey is that it gives the first data on the rate of bleeding during the VKA acenocoumarol treatment as well as risk factors in Algerian patients. This study has all of the limitations that come with a retrospective study. The main weakness stems from a nonrandomized selection of the sample. Despite this weakness, the findings of our survey provide solid observations on how these frail patients were treated and what factors influenced their outcomes in the short and long term.

CONCLUSION

VKAs are the current gold standard of long-term antithrombotic therapy. However, their use is complex.

The risk of hemorrhagic complications is high, so VKA therapy must be used with caution. The knowledge of predictive factors of VKA-related excessive anticoagulation seems of utmost importance to improve patients' management. Our study highlights that overdose and drug interactions are the most consistent risk factors for bleeding with oral anticoagulant therapy. There is the need to expand national studies, as the factors that influence treatment may have their local characteristics. In some cases, given the severity of bleeding caused by VKA, new direct oral anticoagulants may be a good option. Therefore, a national registry for oral anticoagulant follow-up is needed to assess the efficacy and safety of drug use in the short and long term. The current pilot study is a cornerstone to develop monitoring oral anticoagulation therapy in our region.

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