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Original article

Epistaxis complicating treatment by anti-vitamin K and new oral anticoagulants

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ABSTRACT

Objectives: To assess any differences in severity and management of epistaxis when complicating treatment by anti-vitamin K (AVK) or by new oral anticoagulants (NOAC).
Materials and method: All patients admitted to the ENT department of a University Hospital Center for epistaxis under oral anticoagulation therapy between January 2010 and June 2015 were included in a retrospective study. Severity was assessed in terms of management and of hemoglobin level at admission. Two groups were distinguished: treatment by AVK or by NOAC.
Results: One hundred and thirty-four patients were included: 126 under AVK and 8 under NOAC. There was a significant difference in mean hospital stay: 4.5 days for AVK versus 3.5 days for NOAC ($P = 0.019$; 95% CI [0.1921; 0.8907]). There were no significant differences for the other severity criteria. None of the patients died.
Conclusion: Admission rates for epistaxis complicating NOAC therapy was low, and much lower than in case of AVK. Bleeding severity was equivalent with both treatments. NOACs significantly reduce hospital stay. Contrary to the study hypothesis, epistaxis is less serious when complicating NOAC than AVK therapy.

1. Introduction

Treatment and prevention of thromboembolic events are major public health issues in view of the risk of excess mortality, the medical and socioeconomic impact and the increasing number of patients concerned by such pathology [1]. Anti-vitamin K (AVK) is the reference treatment, especially in case of non-valvular atrial fibrillation [2].

Since 2008, there has been an alternative to AVK: new oral anticoagulants (NOAC). These are direct coagulation inhibitors, acting on thrombin (anti-factor IIa) or factor X. The first class comprises only dabigatran etexilate (Pradaxa®), and the second rivaroxaban (Xarelto®) and apixaban (Eliquis®), marketed since 2008, 2009 and 2012, respectively. French national health insurance statistics show that almost half (48%) of patients beginning oral anticoagulation therapy between October 2012 and September 2013 were prescribed a NOAC; the study revealed prescription beyond the Health Authority guidelines [3]. Sales have soared since their introduction, with 1 million defined daily doses (DDD) in 2009 and 117 million in 2013 [1]. This increase and overprescription can be explained by the ease of use for patients: unlike AVK, no biological monitoring or dose adaption is required [4]. Nor do NOACs display the numerous drug and food interactions complicating treatment found with AVKs [5,6].

The French National Drug Safety Agency (*Agence nationale de sécurité du médicament*: ANSM), however, warned physicians of the bleeding risks associated with all classes of anticoagulant. Epistaxis is one such hemorrhagic complication, consisting in frequent and potentially dangerous bleeding, and was the second most frequent cause of minor hemorrhage in a study by the French National Health Insurance Scheme (*Caisse nationale d'assurance maladie*) [3].

Given the increase in the number of NOAC prescriptions, it can be assumed that the rate of epistaxis under NOAC is also rising. The absence of biological monitoring, with dose modulation according to clinical context, lack of antagonists and of guidelines in case of hemorrhage suggest that epistaxis may be more serious than under AVK. To our knowledge, since NOACs received market authorization, there have been no French studies assessing their impact on the rate and severity of epistaxis complicating oral anticoagulation treatment.

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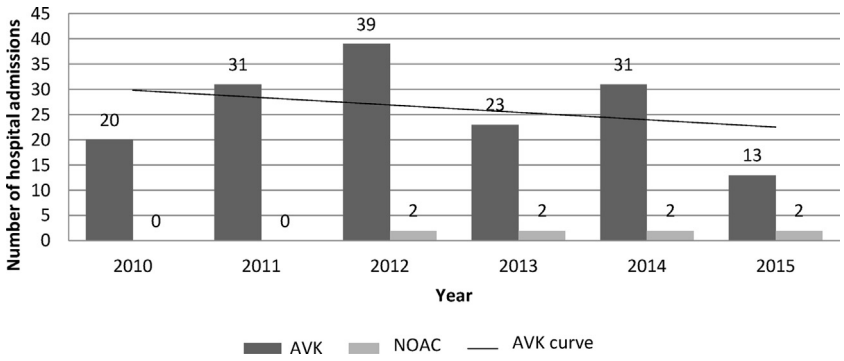

Fig. 1. Progression of admissions for epistaxis during anticoagulation therapy in the ENT department of Besançon Regional University Hospital Center between 2010 and 2015. The curve shows a trend for admission for epistaxis during AVK therapy only. AVK: anti-vitamin K; NOAC: new oral anticoagulants.

The main aim of the present study was therefore to investigate possible differences in the severity of epistaxis under AVK compared to NOACs.

2. Materials and method

A retrospective descriptive study included all patients aged > 18 years admitted to the ENT department of a Regional University Hospital Center for spontaneous epistaxis under oral anticoagulation therapy by AVK or NOAC between January 1, 2010 And June 30, 2015.

Data comprised demographic variables (age and gender), type of treatment and indication, biological work-up at admission (hemostasis, urea and creatinemia), aggravating bleeding risk factors (high blood pressure and/or concomitant antiplatelet therapy), and comorbidities such as known kidney or liver failure.

After clearing the nose and aspirating clots, first-line treatment in our center consists in uni- or bilateral anterior packing with calcium alginate. In case of failure, anteroposterior packing is performed using double-balloon probes, in which case admission is systematic. Other criteria for admission comprise duration and/or abundance of bleeding, iterative epistaxis, and diathesis. Endoscopic surgical treatment is indicated for recurrence of bleeding, whether during or on removal of packing. Embolization is indicated in case of contraindications to surgery: local obstacle, or contraindications to general anesthesia. In case of AVK overdose, antagonists are administered in line with Health Authority guidelines.

Severity was assessed on 4 criteria:

- hemoglobin concentration at admission;
- need for transfusion;
- type of treatment (need for heavy treatment such as surgical hemostasis and/or embolization);
- in-hospital progression (hospital stay, transfer to continuous surveillance or intensive care, death).

Two treatment groups were distinguished: AVK (fluindione, warfarin or acenocoumarol), and NOAC (dabigatran etexilate, rivaroxaban or apixaban).

Statistical analysis used the BiostaTGV application [Pierre-Louis Epidemiology and Public Health Institute, affiliated to the National Institute of Health and Medical Research (Inserm) and Pierre-and-Marie-Curie University, Paris). Fisher or Student tests were used as appropriate. The significance threshold was set at $P = 0.05$.

3. Results

Between January 1, 2010 and June 30, 2015, 134 patients were admitted for spontaneous epistaxis complicating oral anticoagulation therapy: 126 under AVK and 8 under NOAC. Molecules comprised fluindione, 84.2% ($n = 139$); acenocoumarol, 6.1% ($n = 10$); warfarin, 4.9% ($n = 8$); rivaroxaban, 3% ($n = 5$); and dabigatran, 1.8% ($n = 3$). None of the NOAC patients received apixaban.

Fig. 1 shows mean annual admission distributions: 26.1 for epistaxis under AVK, with a decreasing trend, and 2 for epistaxis under NOAC (as of 2012). Admission for epistaxis under NOAC did not increase over the study period.

Table 1 shows epidemiological data.

Results for severity of bleeding as endpoint are shown in Table 2. Only mean hospital stay showed a significant inter-group difference, with 4.5 days for AVK versus 3.5 days for NOAC ($P = 0.019$; 95% CI [0.1921; 0.8907]).

4. Discussion

In almost 80% of the present series, oral anticoagulants were prescribed for atrial fibrillation, with the objective of preventing secondary stroke. According to European Society of Cardiology guidelines, indications for effective anticoagulation are based on the CHA_2DS_2-VASc score (Table 3) [7]. When anticoagulation therapy is required, the choice between AVK and NOAC is left up to the prescriber [7], although the French Health Authority (HAS) systematically recommends AVK in first line [2]. Three major studies assessed non-inferiority of NOACs to warfarin in this indication: RE-LY for dabigatran [8], ROCKET-AF for rivaroxaban [9] and ARISTOTLE for apixaban [10]. The ROCKET-AF results were later extrapolated to study treatment of major hemorrhage in the two treatment arms [11]. Only severe epistaxis on the International Society on Thrombosis and Haemostasis (ISTH) criteria was included: i.e., epistaxis leading to death, with ≥ 2 g/dL fall in hemoglobin concentration, or requiring transfusion of ≥ 2 PRBCs [12]. There was no difference in epistaxis rate according to treatment. Comparison of major hemorrhage rates under warfarin versus apixaban was significantly in favor of the NOAC: 2.13% per year for apixaban versus 3.09% for warfarin ($P < 0.001$). Comparison of rates of hemorrhage of whatever severity also favored the NOAC: 28.5% per year for warfarin versus 18.1% for apixaban; however, epistaxis rates per bleeding location were not specified [13]. According to the literature, the risk of bleeding is equivalent between AVK and NOACs, with a trend in favor of NOACs.

The data from the RE-LY study, which included 18,113 patients, were used to study the interaction between age and bleeding risk. Intra- and extracranial bleeding risk was equivalent between treatments up to the age of 75 years; at more advanced age, the risk of intracranial bleeding was less under dabigatran, but the risk of extracranial bleeding was greater in certain locations. Data for epistaxis were not analyzed specifically but rather included in a

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