ORIGINAL ARTICLE

Epistaxis and Dabigatran, a New Non-Vitamin K Antagonist Oral Anticoagulant

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Abstract

Objective: Dabigatran is a new non-vitamin K antagonist (VKA) anticoagulant with anti-thrombin action, with supposedly fewer haemorrhagic complications. However, there are actually no established agents to reverse its effect, nor specific coagulation time tests for monitoring it.

Materials and methods: An observational prospective study was developed, noting epidemiological, clinical and therapeutic features among subjects with epistaxis treated with dabigatran. Results were compared with a group of epistaxis cases of individuals under anticoagulant therapy with VKA (acenocoumarol) and a control group without anticoagulation.

Results: Since its inclusion in our health system almost 3 years ago, 19 patients with epistaxis and concomitant use of dabigatran have been attended at the Emergency Unit in our hospital, as against 59 under VKA therapy and 144 without anticoagulation, with a mean admittance rate of 26%, 28%, and 14%, respectively. In 3 out of 5 individuals admitted due to dabigatran treatment, previously unobserved renal failure was detected. Blood transfusion was needed in 80% of patients using dabigatran, 58% using VKA, and 23% without anticoagulation. Invasive procedures to control nosebleed were required in 80%, 35%, and 21%, respectively. Although haemorrhagic risk was lower in dabigatran cases, they showed the longest stay in the hospital when compared to the other groups.

Conclusions: With dabigatran, there are fewer cases of severe epistaxis than with acenocoumarol, but controlling them is more difficult.

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Epistaxis and Dabigatran

PALABRAS CLAVE
Epistaxis; Dabigatran; Efectos adversos

Epistaxis y dabigatran, nuevo anticoagulante oral no antagonista de la vitamina K

Resumen
Objetivo: Dabigatran es un nuevo anticoagulante no antivitamina K con efecto antitrombina. Se le atribuyen menos efectos secundarios hemorrágicos, pero no presenta antídoto que revierta su función ni tiempos de coagulación específicos que lo monitoricen.

Materiales y métodos: Estudio longitudinal observacional prospectivo anotando las características epidemiológicas, clínicas y terapéuticas más relevantes entre los sujetos tratados con dabigatran que manifestaron epistaxis. Se compararon resultados frente a un grupo de casos de epistaxis bajo terapia anticoagulante con acenocumarol y otro de epistaxis en controles no anticoagulados.

Resultados: Desde su inclusión en el Sistema Nacional de Salud hace casi 3 años dabigatran ha hecho acudir a urgencias de nuestro centro a 19 sujetos por epistaxis, frente a 59 por acenocumarol y 144 no anticoagulados, con ingresos hospitalarios del 26, 28 y 14%, respectivamente. En 3 de los 5 ingresados tratados con dabigatran se detectó insuficiencia renal, previamente no documentada. Precisaron transfusión de hemoderivados el 80% de los tratados con dabigatran, 58% con acenocumarol y 23% no anticoagulados, y procedimientos invasivos el 80, 35 y 21%, respectivamente. Aunque el riesgo hemorrágico fue menor para dabigatran, la estancia hospitalaria fue mayor frente a acenocumarol, y este frente a no anticoagulados.

Conclusiones: Dabigatran ofrece menos casos severos de epistaxis que acenocumarol, pero resultan más difíciles de controlar y revertir.

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Introduction

The thermoregulatory, protective, and respiratory functions of the nostrils justify their high output. Epistaxis thus constitutes a haemorrhagic manifestation of high incidence in both the healthy population and individuals with illnesses related to artery disease or haemostatic disorders. Epistaxis is also a frequent secondary effect among therapeutic agents, especially antithrombotic drugs. In the control of drug-induced epistaxis, results are affected by the skill of the practitioners in locating and blocking the active point, as well as by their appropriate knowledge of the mechanism of action of the agent involved. Consequently, the otolaryngology specialist has to be familiar with the medical actions that arise as derived from this.

Atrial fibrillation (AF) is estimated to affect 2% of the population,1 and up to 8.5% of the Spanish population more than 60 years old.2 This condition predisposes to ictus and systemic embolism up to 5 times more than in the general population. Ictus is the most important complication in AF in terms of frequency and impact on premature mortality and disability. Therefore, antithrombotic treatment should accompany the strategies of recovering sinus rhythm through electrical cardioversion and antarrhythmic agents.

For decades, vitamin K antagonists (VKA) were the only option available as oral anticoagulant therapy (OAT) in the prevention of thromboembolism from AF. However, in situations of contraindication or special-VKA associated risk, antiplaitelet agents were acceptable. Using VKA makes it necessary to monitor prothrombin time (PT), expressed as the international normalised ratio (INR). The risk of medicinal interactions and severe haemorrhage has consequently conditioned its use.

In the last few years, new anticoagulants have been developed, such as the direct thrombin inhibitor dabigatran etexilate (Pradaxa®, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany) and the direct factor Xa inhibitors rivaroxaban (Xarelto®) and apixaban (Eliquis®); these agents have shown a favourable risk–benefit ratio in various clinical conditions.3,4 Some autonomous communities are already carrying out projects aimed at assessing patients for whom the advantages of this OAT are greater, with a prudent increase in the number of individuals treated and under thorough control of the budget impact, especially focused on dabigatran.5,6

Dabigatran—the OAT alternative for acenocumarol most accepted in our country since it was included in the Spanish National Health Service (NHS, or SNS in Spanish) on 1 August 2011—shows a favourable profile for the prevention of ictus and systemic embolism in patients with non-valvular AF and at least 1 additional factor of risk for thromboembolic complications.7–8 Assuming the clinical situations that justify its use in the framework of the NHS (Table 1), it is an agent that is uninvolved with the extrinsic pathway of coagulation. This means that it is obligatory to carry out clinical considerations, especially when an excessive effect provokes haemorrage: the absence of monitoring through the normal clotting times, the lack of response to administering vitamin K or the factors dependent on the vitamin, and the slowness in reversing the antithrombotic and consequent pro-haemorrhagic effect.

Epistaxis represents a circumstance that could potentially cause anaemia and can seriously jeopardise the general conditions of the patient under anticoagulant management. We present the experience of this service in
managing such haemorrhages since the addition of dabigatran to the therapeutic OAT arsenal in Spain.

Patients and Methods

Between 1 August 2011 (the date of the first NHS, authorisation for dabigatran) and 31 December 2013, this centre followed up all the cases that consulted for epistaxis—both in the specialist centre and in emergency services—in the context of being submitted to OAT with dabigatran or acenocoumarol.

This revision consisted of recording the epidemiological features of the patients, treatment chosen in cases of hospital care, HAS-BLED bleeding risk score (Table 1), and specific needs for the cases requiring admission.

For the OAT with dabigatran, the indications of the Spanish Agency of Medicinal Products (Agencia Española del Medicamento) for preventing systemic embolism in subjects with non-valvular AF were followed (Table 2), with all of them on a dosage schedule of 220 or 300 mg every 12 h, without needing INR dose adjustment control. The patients treated with acenocoumarol received a dose of between 8 and 27 mg a week, adjusted according to the INR for the PT under documented indications for prevention of ictus and systemic embolism in subjects with non-valvular AF, valvular heart disease, valve replacements, pulmonary thromboembolism, deep vein thrombosis, and ischaemic heart disease. Knowing about the increase of the effect of non-VKA anti-coagulant in the face of renal function disorders, kidney function was measured using the Cockcroft–Gault equation to calculate creatinine clearance:

\[
\text{creatinine clearance} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 0.85 \text{ if female}}{72 \times \text{serum creatinine [mg/dl]}}
\]

There was a group of cases consisting of subjects that consulted for epistaxis while lacking OAT antecedents. Statistically significant relationships were sought between patients anticoagulated with dabigatran and acenocoumarol and others not anticoagulated, by obtaining \( P \) probability values given by Student’s t-test for quantitative variables between 2 populations that admitted normal distribution; ANOVA test when 3 groups were involved; and from the correlation coefficient \( R \) obtained from \( \varphi^2 \) to compare ratios. Given that the sample sizes of the groups admitted to hospital were smaller, the degrees of liberty were limited to \( n-1 \), with \( n \) being the total volume of patients involved in the statistical correlation.

Results

The data gathered in this 29-month follow-up are presented in Tables 3 and 4. The total consultations for acenocoumarol-anticoagulated patients were much higher, based on their introduction much earlier and with greater experience. In emergency services, the volume of visits from those treated with dabigatran was greater, which was explained by the fact that this was a new agent introduced in the NHS therapeutic arsenal, about which epistaxis as a secondary effect needed to have intensity and frequency established because there was no existing documentation. The higher percent of subjects with high blood pressure (HBP) among the VKA-anticoagulated cases would promote an increase in their consultations for epistaxis; however, the ratio of poorly controlled illness was very similar in those treated with dabigatran and acenocoumarol. The dabigatran group tended to bleed less, with or without OAT, with statistical significance. The OAT therapy was continued in all patients attended in the specialist centre. In contrast, OAT was withdrawn from all patients admitted to hospital and substituted with low molecular weight heparin treatment.

Although the hospital admissions for dabigatran-related epistaxis were fewer than those due to acenocoumarol, the relative volume was greater. In addition, among the dabigatran cases 80% required administration of packed red cells and the volume needed was higher, as the mean haemoglobin loss reached 4.8 g/dl. In these 5 patients, no medication interactions or concomitant liver disease was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>HAS-BLED Score for Evaluating Thromboembolic and Haemorrhagic Risk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Points</td>
</tr>
<tr>
<td>H (hypertension)</td>
<td>Uncontrolled hypertension with systolic BP≥160 mmHg</td>
</tr>
<tr>
<td>A (abnormal kidney and/or liver function)</td>
<td>Kidney disease (chronic dialysis, kidney transplant or plasma creatinine≥2.3 mg/dl) or liver disease (cirrhosis or biochemical data indicative of liver deterioration, total bilirubin×twice the normal upper limit, AST−ALT×3 times the normal upper limit, etc.)</td>
</tr>
<tr>
<td>S (stroke)</td>
<td>Prior history of ictus</td>
</tr>
<tr>
<td>B (bleeding)</td>
<td>History of bleeding, anaemia or predisposition towards any haemorrhagic occurrence</td>
</tr>
<tr>
<td>L (labile INR)</td>
<td>Unstable INR, whether excess or low (&lt;60% of the time within therapeutic range)</td>
</tr>
<tr>
<td>E (elderly)</td>
<td>Age≥65 years</td>
</tr>
<tr>
<td>D (drugs and/or alcohol)</td>
<td>Medications that affect haemostasis (antiaggregants, heparins, thrombolytics) and/or ingestion of ≥8 alcoholic drinks a week</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: Adapted from Pisters et al.²
found to justify the excess anticoagulant function. However, urea was increased 3 times above the reference range in these patients from the time they were admitted. This elevation was initially justifiable because of dehydration and/or blood absorption, and creatinine values ranging from 1.3 to 3.1 mg/dl. In addition to the posterior packing performed in emergency services, 2 patients underwent endoscopic cauterisation, while another 2 received arterial embolisation. The reason for avoiding the endoscopic option was the impression of oozing haemorrhage continuously given by the anterior rhinoscopy in these patients.

### Table 2 Conditions for Authorisation and Exclusion for Anticoagulation With Dabigatran in Preventing Ictus and Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation.

**Clinical situations**
- Patients with known hypersensitivity or with specific contraindication to the use of acenocoumarol or warfarin
- Patients with antecedents of intracranial haemorrhage
- Patients with ischaemic ictus that present clinical and neuroimaging criteria for high risk of intracranial haemorrhage
- Patients in treatment with VKA that have severe arterial thromboembolic episodes in spite of good INR control
- Patients in treatment with VKA that have presented serious haemorrhagic episodes in spite of good INR control

**Situations related with INR control**
- Patients that have initiated VKA treatment in which it is impossible to keep INR control within the range (2–3) in spite of good therapeutic control
- Impossibility of access to conventional INR control

**Contraindications or inconveniences**
- Patients that are not collaborators or that are not under supervision
- Patients with frequent falls
- Pregnancy
- Acute haemorrhage at least during the first 2 weeks following the episode
- Recent or scheduled surgical interventions in the central nervous system
- Severe and/or uncontrolled hypertension
- Severe renal or hepatic diseases
- Haemostasis alterations (vasospasm, coagulation, fibrinolysis, platelet function) that is hereditary or acquired with clinically relevant risk of haemorrhage

INR: international normalised ratio; VKA: vitamin K antagonists.

### Table 3 Epidemiological Features of Epistaxis in the Patient With Dabigatran and Acenocoumarol.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n=163)</th>
<th>Acenocoumarol (n=912)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care in specialist centre</td>
<td>7 (4.29%)</td>
<td>37 (4.05%)</td>
<td>15</td>
</tr>
<tr>
<td>Volume of attention in emergency care</td>
<td>40 (2.10 attentions/patient)</td>
<td>106 (1.79 attentions/patient)</td>
<td>152 (1.50 attentions/patient)</td>
</tr>
<tr>
<td>Patients attended in emergency services</td>
<td>19 (7.69%)</td>
<td>59 (6.46%)</td>
<td>101</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.1±8.4 years</td>
<td>64.2±7.5 years*</td>
<td>68.2±10.8</td>
</tr>
<tr>
<td>Sex</td>
<td>68.4% males (13M/6F)</td>
<td>71.1% males (42M/17F)</td>
<td>–</td>
</tr>
<tr>
<td>Mean prior duration of OAC (months)</td>
<td>7.4±3.2 months</td>
<td>28.5±17.1 months*</td>
<td>–</td>
</tr>
<tr>
<td>High blood pressure (mmHg)</td>
<td>13 (7.9%)</td>
<td>183 (20.0%)*</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (8.5%)</td>
<td>93 (10.1%)</td>
<td>9</td>
</tr>
<tr>
<td>Liver disease</td>
<td>9 (5.5%)</td>
<td>47 (5.1%)</td>
<td>6</td>
</tr>
<tr>
<td>Documented kidney failure</td>
<td>2 (1.2%)</td>
<td>14 (1.5%)</td>
<td>3</td>
</tr>
<tr>
<td>Comorbidity (no. of diagnoses/patient)</td>
<td>6.2±4.1 (range, 1–11)</td>
<td>5.1±3.3 (range, 2–8)</td>
<td>6.1±3.0 (range, 1–9)</td>
</tr>
<tr>
<td>Associated medications</td>
<td>3.4±1.1 (range, 0–5)</td>
<td>4.1±1.2 (range, 0–7)*</td>
<td>3.1±2.8 (range, 0–6)</td>
</tr>
<tr>
<td>Previous history of bleeding without OAC</td>
<td>24 (14.7%)</td>
<td>196 (21.4%)*</td>
<td>17</td>
</tr>
<tr>
<td>Prior epistaxis with OAC</td>
<td>29 (17.7%)</td>
<td>240 (26.3%)*</td>
<td>–</td>
</tr>
</tbody>
</table>

OAC: oral anticoagulation.
* With either dabigatran or with acenocoumarol.
* *P*<.001.
Table 4  Epidemiological Features of Epistaxis in the Emergency-Care Patient With Dabigatran and Acenocoumarol.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (n=19)</th>
<th>Acenocoumarol (n=59)</th>
<th>Controls (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital admission</strong></td>
<td>5 (26.3%)</td>
<td>17 (28.8%)</td>
<td>18 (17.3%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>74.2±5.6 years</td>
<td>65.3±7.8 years†</td>
<td>60.1±12.8 years‡</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>84.2% males (16M/3F)</td>
<td>76.4% males (44M/15F)</td>
<td>61.8% males (62M/39F)</td>
</tr>
<tr>
<td><strong>Prior epistaxis with this OAC</strong></td>
<td>1 (5.2%)</td>
<td>41 (69.4%)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Prior mean duration of the OAC</strong></td>
<td>6.6±3.4 months</td>
<td>32.5±18.7 months†</td>
<td>–</td>
</tr>
<tr>
<td><strong>Previous stoppages</strong></td>
<td>13 in 11 patients (57.8%)</td>
<td>28 in 21 patients (35.5%)</td>
<td>66 in 60 patients (59.8%)</td>
</tr>
<tr>
<td><strong>Posterior stoppages</strong></td>
<td>5 (26.3% patients)</td>
<td>17 (28.8% patients)</td>
<td>18 (17.3%)‡</td>
</tr>
<tr>
<td><strong>Admitted</strong></td>
<td>n=5</td>
<td>n=17</td>
<td>n=18</td>
</tr>
<tr>
<td><strong>Patients with need of PRC</strong></td>
<td>4 (80% admitted)</td>
<td>10 (58.8% admitted)†</td>
<td>7 (38.3% admitted)‡</td>
</tr>
<tr>
<td><strong>Reduction in haemoglobin</strong></td>
<td>720±402 cc PRC per patient</td>
<td>352±304 cc PRC per patient†</td>
<td>–</td>
</tr>
<tr>
<td><strong>Other intervention needs</strong></td>
<td>4 patients (80%): 2 endoscopic cauterisations and 2 highly selective embolisations</td>
<td>6 patients (35.2%): 4 endoscopic cauterisations and 3 highly selective embolisations</td>
<td>–</td>
</tr>
<tr>
<td><strong>Documented kidney failure</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Creatinine on admission</strong></td>
<td>1.58±0.35 mg/dl</td>
<td>0.89±0.28 mg/dl†</td>
<td>0.77±0.30 mg/dl†</td>
</tr>
<tr>
<td><strong>Creatinine clearance at 24h</strong></td>
<td>42.5±10.6 ml/min</td>
<td>77.4±18.8 ml/min†</td>
<td>85.2±12.6 ml/min†</td>
</tr>
<tr>
<td><strong>Urea on admission</strong></td>
<td>74.8±31.4 mg/dl</td>
<td>46.1±22.1 mg/dl†</td>
<td>39.0±12.7 mg/dl†</td>
</tr>
<tr>
<td><strong>Comorbidity (no. diagnoses/patient)</strong></td>
<td>3.8±2.1 (range, 1–6)</td>
<td>5.4±3.3 (range, 2–8)†</td>
<td>3.0±1.8 (range, 1–5)†</td>
</tr>
<tr>
<td><strong>Associated medicines</strong></td>
<td>4.1±1.1 (range, 0–5)</td>
<td>6.2±0.4 (range, 0–7)†</td>
<td>2.1±1.1 (range, 0–4)†</td>
</tr>
<tr>
<td><strong>Prior history of bleeding without OAC</strong></td>
<td>0 (0%)</td>
<td>2 (11.7%)†</td>
<td>5 (27.1%)†</td>
</tr>
<tr>
<td><strong>Previous epistaxis with OAC</strong></td>
<td>1 (20%)</td>
<td>5 (29.4%)</td>
<td>–</td>
</tr>
<tr>
<td><strong>HAS-BLED score for haemorrhagic risk</strong></td>
<td>4.9±1.8</td>
<td>5.2±1.6</td>
<td>2.1±1.8†</td>
</tr>
<tr>
<td><strong>Hospital stay</strong></td>
<td>5.9±1.9 days (4–7)</td>
<td>4.3±1.1 days (3–10)</td>
<td>3.6±2.4 days (2–6)</td>
</tr>
</tbody>
</table>

APT: activated partial thromboplastin time; HBP: high blood pressure; OAC: oral anticoagulation; PRC: packed red cells; PT: prothrombin time; TT: thrombin time.

*With either dabigatran or with acenocoumarol.

\[ P<0.001. \]

Among the cases of epistaxis from acenocoumarol, the mean haemoglobin loss was less: 3.1 g/dl. The need for transfusing blood products, for surgical or embolisation interventions, was also significantly less. One of the 5 patients admitted to hospital anticoagulated with dabigatran received a complex of vitamin-K-dependent factors (Octaplex®, Octapharma, San Fernando de Henares, Madrid, Spain), without clinical response. In 7 of the acenocoumarol group, hypocoagulability climbed with the complex in hours.

The classic clotting times showed an INR elevation for thrombin time (TT) higher than 3 times the unit in 60% of
the subjects admitted for dabigatran, and in only 17% of those treated with acenocoumarol. The PT never changed with dabigatran and was at levels of therapeutic hypocoagulability in all those cared for with VKA.

The scores on the haemorrhagic risk scale HAS-BLED for the patients under OAT with dabigatran and acenocoumarol were higher for the second drug, without statistically significant differences. However, the mean hospital stay was a day and a half longer among the dabigatran patients, due to both the persistence of slight bleeding after removing the packing, which made it necessary to keep them under observation, and from the fact that there were no easily accessible clotting tests available to monitor the process.

Renal creatinine clearing deteriorating between 50 and 86 ml/min in these 5 cases. Consequently, the choice was made to associate treatment through dialysis with a dialysate flow rate 700 ml/min for 3 h and a blood flow of 200 ml/min. This led to an elimination of 45%–68% of the dabigatran concentrations. Other actions such as administering activated prothrombin or platelet concentrate were avoided, in spite of the impression of oozing bleeding in 2 of the patients because there was no thrombectomy or on the haemogram or systemic petechial haemorrhaging.

Within the seriousness of the blood losses and concomitant cardiovascular disease, any hypovolemic decompensation was quickly resolved, and all subjects were discharged in the end. One of the 5 patients with dabigatran cared for was re-anticoagulated with acenocoumarol.

The control group of subjects with epistaxis not anticoagulated over these 2 years reached 152 instances of medical care in 101 individuals, with a mean of 1.52 medical care instances in emergency services per patient. Mean age was 60.1±12.8 years, with 61.8% of them being males. In 66 individuals (65.3%), anterior packing was applied; posterior packing and hospital admission was necessary in only 18 (17.3%) of these individuals. Of these, 7 (38.3%) required transfusion of packed red cells, while in 5 (27.1%), endoscopic surgery was needed for cautery or selective embolisation; the HAS-BLED bleeding risk score was 2.1±1.8 and the hospital stay was 3.6±2.4 days.

Discussion

New agents in OAT have been developed in the last few years. The direct inhibitor of thrombin, dabigatran etexilate (Pradaxa®), and those of activated factor X, rivaroxaban (Xarelto®) and apixaban (Eliquis®), have been demonstrating favourable risk–benefit under various clinical conditions in which hypocoagulability is indicated, optimising the effect and minimising secondary ones. Its continual use is compared with that of VKA, a matter of wide discussion in the respective evaluations by the European regulatory agencies for its authorisation.

Dabigatran etexilate is used as an antithrombin initially approved for preventing venous thromboembolism in patients undergoing elective surgery for hip or knee replacement, at a dosage of 220 mg a day. It was later approved in subjects with AF and acute coronary syndrome. Dabigatran is predicted to be the treatment of choice for treating deep vein thrombosis in the coming years. It is inactive in the form administered, but it is quickly hydrolysed by esterase in plasma and liver because the prodrug presents rapid intestinal absorption.

It inhibits the action of free thrombin and united with fibrin and of the platelet aggregability that they induce. In its plasma transit, dabigatran shows low protein binding, favouring almost exclusively renal elimination, while it also offers the possibility of removing the molecule from the blood stream by dialysis. The result of this is that there has to be careful management of patients with renal failure who undergo this anticoagulation, as well as the fact that its use in individuals with clearing lower than 30 ml/min is contraindicated.

Epistaxis is seen as a frequent adverse reaction according to the summary of product characteristics of the product sold in our country, in agreement with the adverse reaction intensity scale classified by organs and systems. That is, its incidence is greater than or equal to 1 out of every 100 subjects treated, but less than 1 out of 10. However, the first national guidelines primer neglected to even mention it in the section on secondary manifestations. The Food and Drug Administration (FDA) database on secondary effects for dabigatran since 2004 shows an incidence of 0.87%; this is lower than gastrointestinal haemorrhage—the one most often documented (3.48%)-but more normal than haematuria (0.64%), cerebral intraparenchymal haemorrhage (0.57%), haemoptysis (0.35%), subdural haematomata (0.29%), and gingival haemorrhage (0.27%).

However, according to the same database, up to 1000 patients treated with dabigatran have died since 2004, 14.8% of them with epistaxis involvement, and, in 15%, a grave life-threatening risk is recognised. The recommended dosage among patients with AF brings the greatest incidence of haemorrhage, 84% of the current indications for dabigatran, with a progressive decrease in this data that coincides with the fact that this OAT was included in other prothrombotic disorders.

The concomitance of illnesses or treatments that significantly increase the risk of greater bleeding makes a careful risk–benefit assessment necessary. Evidently, dabigatran should only be administered if the benefit outweighs the risks of bleeding. The anticoagulant does not generally require routine monitoring of its hypocoagulability level except when there is a suspicion of excessive exposure to the agent or the presence of additional factors of risk. In relation to this, establishing the INR for PT and activated partial thromboplastin time (APTT) yields a high index of false positives, explains the intensity of the antithrombotic effect poorly and is not in keeping with the seriousness of a dabigatran-related haemorrhage or the risk of suffering one. There is only 1 article by Kim, in 2013, that presents a case of coagulopathy during its use with elevations of INR for PT and APTT in the context of renal failure.

In fact, there is no specific, standard determination that gives orientation on the level of anticoagulation by this agent. The sensitivity and specificity of INR for TT—even being the most physiopathologically acceptable test because it evaluates the common pathway in the coagulation cascade—goes no higher than 75%. Ecarin clotting time (ECT), among the numerous haemostatic circumstances that prolong it, seems to correlate well with the anticoagulant effect of dabigatran.
Drugs that can increase the risk of haemorrhage should not be administered concomitantly with dabigatran or should be administered with precaution. Fibrinolytic agents should undergo monitoring using ECT and TT, not exceeding the value of the ranges of reference or INR by 1.5, respectively.

In this context, anamnesis for the patient with epistaxis needs to place special emphasis on medicinal interactions. The P-glycoprotein (P-gp) inducing agents, such as rifampicin, carbamazepine, phenytoin, or St John's wort (Hypericum perforatum), cause a reduction of plasma concentrations of dabigatran, minimising and cancelling its effect. Conversely, dabigatran etexilate is a substrate of the P-gp efflux transporter. It is thus expected that using strong P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole, dornedaron, and clarithromycin) will lead to an increase in the plasma concentrations of the anticoagulant. Ketoconazole by systemic administration, cyclosporine, itraconazole, tacrolimus, and dornedaron are likewise contraindicated. This information is fully included in the website of the European Medicines Agency.14 Dietary alterations, on the other hand, barely influence hypocoagulation from non-VKA agents.10

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and therefore have no in vitro effects on human cytochrome P450 enzymes. Consequently, no medicinal interactions related with it are foreseen.

It is known that patients treated with dabigatran etexilate are at greater risk of haemorrhage during surgical interventions. Consequently, the treatment should be discontinued temporarily in the face of such procedures, without an anticoagulant monitoring being justified.

In addition, clearing with dabigatran in patients with kidney disease can be drawn out. Acute failure makes it obligatory to suspend the treatment.

To this end, in subjects with creatinine clearing higher than 80 ml/min, dabigatran has a half-life of 13 h, so withdrawal of this OAT is recommended 24 h before a surgical procedure.12 When such clearing ranges between 50 and 80 ml/min, the half-life lengthens to 15 h and dabigatran suspension is recommended 48 h before the intervention. For clearing less than 50 ml/min, half-life ranges from 18 to 24 h; consequently, the treatment should be stopped more than 72 h of the surgery.16 The amount of drug eliminated by dialysis is proportional to blood flow, up to a maximum of 300 ml/min. The anticoagulant activity of dabigatran lowers as plasma concentrations reduce. Some authors now propose maintenance with LMWH for 4 days postoperatively17; however, OAT should be introduced the day after the procedure, which does not justify the concomitance of both anticoagulant therapies in the opinion of other publications.15–17

The incidence of major bleeding with dabigatran at 220 mg a day is 1.8%, but it is 13.8% for any haemorrhagic occurrence. The RE-NOVATE and RE-MODEL studies consider the adverse reaction of major bleeding as that which fulfills any of the following 7 characteristics: bleeding that is mortal, or clinically symptomatic beyond what is expected and associated with a haemoglobin drop above 2 g/dl, or that requires transfusion of 2 or more units of packed red cells more than the expected, or retroperitoneal (with confirmation via echography or CT), intracranial (with CT or MR confirmation), or symptomatic intracranial or intraspinal; or that requires cessation of the treatment and/or surgical plans. The 5 cases that needed to be admitted for epistaxis with dabigatran etexilate complied with 4 of the 7 criteria of the definition of major bleeding. In 10 cases in our study, 4 of these requisites were fulfilled among those anticoagulated with dabigatran–6.1%–as compared to the 39 that verified these requisites with acenocoumarol–4.27% of the total of this group.

With a confidence interval (CI) of 95%, the risk quotient for major bleeding for dabigatran at 110 mg and 150 mg twice a day compared with VKA, in any controllable kidney function, was lower for antithrombotic OAT, without statistical significance. For normal creatinine clearance (above 80 ml/min), it was 0.59% for 110 mg twice a day and 0.84% for 150 mg twice a day. For clearances between 50 and 80 ml/min, it was 0.76% and 0.89%, respectively. For clearances between 30 and 50 ml/min (high risk although not absolutely contraindicated), it was 1.00% and 0.94%, respectively, without differences with acenocoumarol. In fact, it is generally accepted that the haemorrhagic risk of the new VKA is much lower than that of the coumarins.18,19

The deterioration of subtle kidney diseases, especially in elderly subjects where a moderate haemassic loss leads to redistributing blood volume and consequent renal hypoperfusion, is subsidiary to a prerenal failure with rapid clearance reduction. This should be rapidly monitored by the physician that is in charge of a poorly controlled epistaxis from dabigatran.

However, in the population of patients studied in the RE-MODEL and RE-NOVATE trials (5539 patients treated), the patients concomitantly suffered from hypertension (51%), diabetes (9%), and coronary artery disease (9%); 20% had antecedents of venous insufficiency, but none of these diseases influenced the effects of dabigatran on preventing venous thromboembolism or on bleeding rates.

Given that there is no specific antidote for dabigatran, in refractory epistaxis using the following can be considered: activated prothrombin complex concentrates (factor 8 inhibitor bypassing activity, FEIBA), recombinant coagulation factor VIII, frozen fresh plasma or even concentrates of coagulation factors II, IX, and X. There is certain experimental evidence that backs these roles of these medications in reversing the anticoagulant effect.20,21 However, the data on their use in clinical or physiopathological terms, and also on the possible clinical risk of rebound thromboembolic disease, are very limited and not very optimistic.22 In them, the coagulation tests are unreliable after the reversal techniques suggested, as occurred with our patients, although we used Octaplex and not FEIBA.

In cases of thrombocytopenia or suspicion of platelet aggregability disorders, administering platelet concentrates should be considered.

That is why aggressive episodes of haemorrhage from dabigatran are commonly documented, bearing in mind the supposed optimisation of the risk–benefit balance over the VKA. The majority of them adopt physical attitudes of packing in the face of external haemagic losses or surgical compression in internal forms.21

Using posterior packing in cases of epistaxis in subjects anticoagulated with dabigatran once it has been
retired for over 24 h is not a measure that resolves the situation. This makes it necessary to combine therapeutic medical-surgical attitudes than differ from others more known with acenocoumarol. Renal function deterioration as a physiopathological mechanism that raises the time active dabigatran is present in serum and affects the plausibility of dialysis treatment of the agent in unremitting episodes of epistaxis.24

The fact that there is so little documentation available on actions in dabigatran-anticoagulated patients and epistaxis is certainly noteworthy. Our experience with 19 patients seen in emergency services and 5 of them admitted from their inclusion in NHS improves awareness of the potential secondary effects generated for the specialist. Consequently, no specific action guidelines for management are offered, which is a reason for preoccupation among other groups that provide health care for haemorrhagic complications.25-27

This is an agent recently introduced into Spain, with an anticoagulant mechanism that prevents rapid and correct monitoring, and for which no effective antidote is known. As a result of all this, we find epidemiological data that make it necessary to be prudent. Our cases attended in hospital admission had guidelines for recently started OAT and the medical-surgical procedures surpass the environment to which the physician is accustomed. In epistaxis the thorinolaryngologist is not in conditions to guarantee the effect of the drug nor to maintain its effective therapeutic interval. Blood pressure is not an eliminating factor in the results found, bearing in mind the same percent of cases admitted for either of the 2 anticoagulants; however, there are more, with statistical significance, anticoagulated subjects with high blood pressure admitted to hospital than control group subjects not exposed to OAT. We agree with some authors in emphasizing the need for a system of analytic monitoring of the product.28,29

However, we have found only 3 publications that specifically mention epistaxis as a serious haemorrhagic condition.12,30,31 The evolution was terrible in both cases, and although strict kidney function control is recommended, its stabilisation is slow. Above and beyond any comorbidity, it is notable that only 1 of the 8 patients documented was younger than 70 years old. This generates a reasonable suspicion, yet to be proved, that subclinical kidney failures become obvious when there is a sudden haematric loss in an elderly individual. Blood products and administering coagulation factors does not affect the base of treatment following nasal stoppages, and ligatures or endoscopic treatment and embolisations did not yield the expected benefit. Optimisation in treatment was obtained based on quick contact with the dialysis unit because, in the absence of normal packing efficacy and invasive procedures, the physiopathological aspect of the mechanism of action of the anticoagulant took on a key role in reversing the epistaxis, an attitude that probably prevented fatal outcomes.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References


