Gestão de Anticoagulantes Orais Diretos num Serviço de Urgência

Emergency Department Management of Direct Oral Anticoagulants Agents

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Resumo:

Introdução: Os anticoagulantes orais diretos tornaram-se comummente utilizados em várias patologias, em detrimento dos antagonistas da vitamina K ou da heparina de baixo peso molecular, sendo crucial a resposta do Serviço de Urgência na gestão dos seus potenciais efeitos adversos e na sua reversão para realização de procedimentos invasivos urgentes. Os testes de coagulação habitualmente realizados correlacionam-se pouco com a concentração plasmática dos anticoagulantes orais diretos, sendo necessário o doseamento de anti-Xa ou anti-IIa.

Métodos: Este estudo analisa os processos clínicos de doentes admitidos no Serviço de Urgência sob anticoagulantes orais diretos e submetidos a doseamento de anti-Xa ou anti-IIa, durante um período de 6 meses.

Resultados: Dos 88 doentes nessas condições, a principal indicação para hipocoagulação era a presença de fibrilhação ou flutter auricular e eventos trombóticos prévios. O doseamento de anti-Xa ou anti-IIa foi essencialmente realizado por eventos hemorrágicos ou necessidade urgente de procedimentos técnicos invasivos.

À admissão, a maioria dos doentes tinha níveis de anticoagulantes orais diretos superiores a 50 ng/mL e mais de metade dos doentes teve necessidade de suspensão do fármaco à data de alta (até nova reavaliação). Realizaram complexo protrombínico, 26% e 5% fizeram idarucizumab para reversão da sua acção, face à gravidade clínica, não tendo sido possível a administração de andexanet alfa dado a sua indisponibilidade no hospital.

Quanto às readmissões aos 6 meses, apenas 5 doentes foram novamente ao Serviço de Urgência, todos por hemorragia recorrente ou anemia, sem registos de eventos tromboembólicos nesse mesmo período.

Conclusão: O doseamento de anti-Xa ou anti-IIa minimizou complicações desnecessárias associadas a procedimentos técnicos invasivos ou cirúrgicos urgentes. A criação de protocolos no Serviço de Urgência, acessíveis a todas as especialidades que aí trabalham, quanto à utilização da quantificação de anticoagulantes orais diretos e principais indicações, deverá ser uma prioridade na gestão da anticoagulação, guiando decisões clínicas e reduzindo a duração de internamento hospitalar, comorbilidades e mortalidade.

Palavras-chave: Administração Oral; Anticoagulantes; Inibidores do Fator Xa; Serviço de Urgência Hospitalar.

Abstract:

Introduction: Nowadays, direct oral anticoagulants are commonly used and Emergency Department response regarding its adverse effects and its reversion when invasive procedures are needed is crucial. Regular coagulation tests correlate poorly with plasma concentrations of direct oral anticoagulants, so specialized anti-Xa and anti-IIa assays are necessary.

Methods: In this study, we analyzed all the Emergency Department electronic medical records corresponding to patients that had direct oral anticoagulants quantification assays performed during a six-month period.

Results: Of the 88 admissions evaluated, the main indications for anticoagulation were atrial fibrillation or flutter and previous thrombotic events. Direct oral anticoagulants quantification was performed mainly due to hemorrhagic events and need for urgent invasive technical procedures.

At admission, most patients had direct oral anticoagulants concentrations > 50 ng/mL and more than half had their anticoagulation suspended at discharge (pending further evaluation in an outpatient setting). 26% did prothrombin complex and 5% did Idarucizumab, due to clinical severity. None of the patients did Andexanet alfa due to its unavailability.

Regarding readmissions within 6 months, only 5 patients were readmitted, with recurrent bleeding or anemia and no thromboembolic events were registered.

Conclusion: Direct oral anticoagulants quantification minimized unnecessary complications associated with urgent surgical and invasive technical procedures. Creating Emergency Department protocols, accessible to all specialties, regarding direct oral anticoagulants quantification and its main indications, should be a priority in anticoagulation management, guiding clinical decisions and reducing duration of hospital stay, comorbidities and mortality.

Keywords: Administration, Oral; Anticoagulants; Emergency Service, Hospital; Factor Xa Inhibitors.

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Introduction

Direct oral anticoagulants (DOACs) are essentially used in the prevention and treatment of most thromboembolic disorders and atrial fibrillation. Regarding patient experience and comparing with vitamin K antagonists or low molecular weight heparin, DOACs are easier to use and have no requirements for routine monitoring.[1] Its widespread use comes with some downsides, including bleeding events that may need management in the Emergency Department (ED), making it mandatory for healthcare professionals to know how to approach these patients and improve the standard protocols in that setting.

When dealing with thrombotic or hemorrhagic events presenting in patients taking DOACs, in emergency settings, besides time of last dose taken, hepatic or renal impairment and potential pharmacological interactions, we need to be able to laboratorially monitor DOACs' effects. Even in elective invasive procedures associated with minor or major bleeding risks, such as gastrointestinal endoscopy, cardiac or dental procedures, when the patient has an extreme body weight or when therapeutic failure is suspected, it is important to know if the drug is still present and if it is associated with any bleeding risk. In urgent settings associated with uncontrolled or high bleeding risk, DOACs reversal agents are recommend when its concentration is above 50 ng/mL. Its concentration should be lower than 30 ng/mL to avoid any risk.[2]

Prolongation of the activated partial thromboplastin time (APTT) and prothrombin time/international normalized ratio (PT/INR) correlate poorly with plasma concentrations of DOACs. A normal APTT or PT/INR does not guarantee normal haemostasis[3] and, if prolonged (APTT for dabigatran and PT /INR for anti-Xa anticoagulants), it may help to identify that the patient has recently taken the drug but cannot assess the clinical degree of anticoagulation.[4]

Specialized anti-Xa and anti-IIa assays have been developed and are recommended for quantitative measurements of anticoagulants, requiring individual calibration to each specific drug (rivaroxaban, apixaban, edoxaban and dabigatran, respectively).[5,6] Unfortunately, these are not widely available in ED laboratories.

This study was designed to evaluate different aspects of ED management of oral direct anticoagulants and assess potential use of anti-Xa and anti-IIa assays at the ED.

Material and Methods

The authors present a retrospective and observational data analysis performed at the ED of Centro Hospitalar Vila Nova de Gaia/Espinho, a tertiary referral hospital in the North Region of Portugal that directly serves 340 000 people, with a medium influx of 400-450 patients daily at the ED.

Using the data base from the Coagulation Laboratory from Immunohematology Department, we retrieved the results from all the agent's quantification (anti-Xa or anti-IIa specific) performed during a six-month period, from January 1st to June 30th of 2022, including only ED admissions. Afterward, we screened and analyzed all the ED electronic medical records corresponding to those results. We gathered information about patients' characteristics (sex, age and provenience/referral), the clinical events that led to the ED admission, DOACs used, its dosage and quantification, the outcomes after the anti-Xa and anti-IIa assay results were available, the impact of renal impairment and the recommendations regarding anticoagulation at discharge.

Results

After a first analysis, we obtained a total of 124 results of DOACs quantification. Only 88 of them concerned ED admissions and were included in this study.

Of the 88 patients, 48% (n = 42) were women, with a mean age of 79,8 years. Most of the patients were admitted directly from home (69%, n = 61), with 14% (n = 12) referred from a long-term care facility and 11% (n = 10) from other medical institutions. Only two people were referred from primary care centers.

DOACs most used in this population were apixaban (52%, n = 46), and rivaroxaban (22%, n = 19), with edoxaban and dabigatran representing only 15% (n = 13) and 11% (n = 10), respectively. With respect to anti-Xa DOACs, the majority of patients were under standard dose, while patients taking anti-IIa DOAC (dabigatran) were mostly under adjusted dose (Table 1).

Regarding the main indications for anticoagulation in our sample, 88% (n = 77) had a heart arrhythmia [atrial fibrillation (n = 73) and atrial flutter (n = 4)] and 13% had previous thrombotic events, such as pulmonary thromboembolism (n=4), deep venous thrombosis (n = 4), arterial thrombosis (n = 2) and intracardiac thrombosis post-myocardial infarction (n = 1).

Table 1: Distribution of direct oral anticoagulants dosing.

		Standard Dose*	Adjusted Dose**
Anti-Xa	Apixaban (n = 46, 52%)	28 (61%)	18 (39%)
	Rivaroxaban (n = 19, 22%)	11 (58%)	8 (42%)
	Edoxaban (n = 13, 15%)	12 (92%)	1 (8%)
Anti-IIa	Dabigatran (n = 10, 11%)	2 (20%)	8 (80%)

*standard dose for each DOAC: apixaban 5 mg twice daily; rivaroxaban 20 mg once daily; edoxaban 60 mg once daily; dabigatran 150 mg twice daily.
** adjusted dose for each DOAC: apixaban 2.5 mg twice daily; rivaroxaban 15 mg once daily; edoxaban 30 mg once daily; dabigatran 110 mg twice daily.

Of the 88 ED admissions that required DOACs quantification (Fig. 1), 59% were due to hemorrhagic events (n = 52), 23% (n = 20) needed urgent invasive technical procedures,

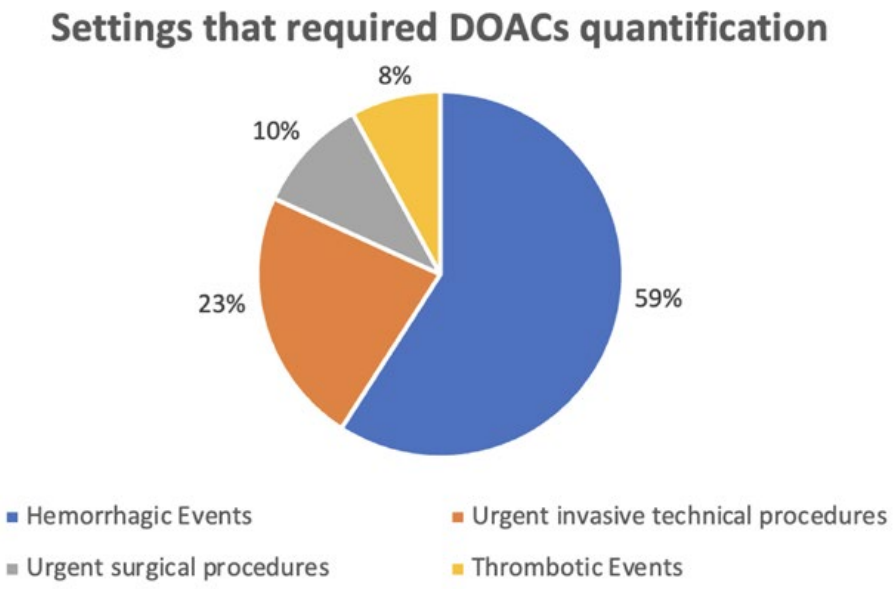

Figura 1: Reason for DOACs quantification at the ED.

10% (n = 9) were proposed for urgent surgical procedures and only 8% (n = 7) had clinical suspicion of acute thrombotic events.

The main events related to each setting are described at Table 2.

Table 2: Events that required DOACs quantification.

Hemorrhagic Events (n = 52, 59%)	Intracranial hemorrhage	20 (38%)
	Gastrointestinal hemorrhage	15 (29%)
	Genitourinary tract hemorrhage	13 (25%)
	Respiratory tract hemorrhage	3 (6%)
	Deep subcutaneous hematoma	1 (2%)
Urgent invasive technical procedures (n = 20, 23%)	Percutaneous drainage	9 (45%)
	Placement of dialysis catheter	4 (20%)
	Placement of cardiac implantable devices	3 (15%)
	Bronchofibroscopy	1 (5%)
	Thoracocentesis	1 (5%)
	Lumbar puncture	1 (5%)
	Pericardiocentesis	1 (5%)
Urgent surgical procedures (n = 9, 10%)	Gastrointestinal surgery	3 (33%)
	Hepatobiliary surgery	2 (22%)
	Limb amputation	2 (22%)
	Orthopedic surgery	1 (11%)
	Urologic surgery	1 (11%)
Thrombotic events (n = 7, 8%)	Acute ischemic stroke	4 (57%)
	Acute coronary syndrome	3 (43%)

Intracranial (n = 20), gastrointestinal (n = 15) and genitourinary (n = 13) hemorrhage were the most frequent events where DOACs quantification was required at ED. Among urgent invasive technical procedures, percutaneous drainage (n = 9) (nephrostomy and cholecystostomy) and placement of dialysis catheter (n = 4) were often proposed and in need of DOACs quantification. Regarding urgent surgical procedures, major surgeries as gastrointestinal (n = 3) and hepatobiliary (n = 2) procedures due to acute cholecystitis and appendicitis, bowel perforation and hernia incarceration, were the main reasons for its request. Although less frequent, DOACs concentration was also measured in clinical suspicion of acute thrombotic events such as ischemic stroke or coronary syndrome.

Analyzing DOACs quantification results (Table 3), 75% of patients (n = 66) had concentrations >50 ng/mL, representing a higher hemorrhagic risk. Concerning each DOAC, dabigatran users were the most affected (10 out

Table 3: DOACs quantification.

		DOACs concentration <50 ng/mL	DOACs concentration >50 ng/mL
Anti-Xa	Apixaban (n = 46, 52%)	28 (61%)	18 (39%)
	Rivaroxaban (n = 19, 22%)	11 (58%)	8 (42%)
	Edoxaban (n = 13, 15%)	12 (92%)	1 (8%)
Anti-IIa	Dabigatran (n = 10, 11%)	0 (0%)	10 (100%)
	TOTAL (n = 88, 100%)	22 (25%)	66 (75%)

of 10), even though already under adjusted dose, as noted before. Apixaban and edoxaban users were mostly above 50 ng/mL (n = 37, 80% and n = 10, 77%, respectively), and rivaroxaban was the anti-Xa agent with more patients under the cutoff for the need of reversal (only 47% of patients had concentrations above 50 ng/mL).

From the total of 52 patients with hemorrhagic events, 85% (n = 44) had concentrations > 50 ng/mL, with only 15% (n = 8) with DOACs concentration < 50 ng/mL.

Relatively to associated renal impairment, 20 patients (23%) had creatinine clearance below 30 mL/min/m2, using modification of diet in renal disease (MDRD) equation. Of these, 14 (70%) had DOACs concentration >50 ng/mL, 9 (64%) using apixaban.

Regarding patient's management after DOACs quantification results, 69% (n = 61) had their DOACs suspended until being submitted to invasive technical/surgical procedures or their bleeding stopped, 26% (n = 23) did prothrombin complex and 5% (n = 4) did idarucizumab (Praxbind®) – Table 4. None of the patients did andexanet alfa.

Discussion

DOACs Era began with its widespread use for prevention and treatment of thromboembolic disorders and atrial fibrillation, detrimental to vitamin K antagonists and low molecular weight heparin that have more complex administration, restrictions and monitoring. DOACs are taken either once or twice-daily, in fixed-dose regimens, with dosage determined mainly by indication, age and/or creatinine clearance, body weight and without any monitoring usually required.[7]

The choice between DOACs is usually guided by clinician's experience, considering their possible disadvantages such as increased likelihood of bleeding, lack of specific antidotes for reversing their action and universal consensus on the laboratory approach for monitoring in urgent conditions.[8]

Using APTT and PT/INR, when prolonged, only measures anti-IIa and anti-Xa presence, respectively, not to what degree. For dabigatran, the dilute thrombin time (dTT), the ecarin clotting time (ECT) and ecarin chromogenic assay (ECA) may be used to quantify dabigatran concentration. An anti-Xa assay, calibrated with drug-specific standards, can be used for rivaroxaban, apixaban and edoxaban.[3,4,9] However, these are not routinely performed and not widely available, yet.

Table 4: Management of DOACs on ED.

		Suspension only	Prothrombin complex	Idarucizumab
Anti-Xa	Apixaban (n = 46, 52%)	31 (67%)	15 (33%)	0 (0%)
	Rivaroxaban (n = 19, 22%)	14 (74%)	5 (26%)	0 (0%)
	Edoxaban (n = 13, 15%)	10 (77%)	3 (23%)	0 (0%)
Anti-IIa	Dabigatran (n = 10, 11%)	6 (60%)	0 (0%)	4 (40%)
	TOTAL (n = 88, 100%)	61 (69%)	23 (26%)	4 (5%)

Most of the patients were admitted in hospital wards (n = 28, 32%), intermediate/intensive care units (n = 18, 20%) or directly to the operation room (n = 6, 7%).

Seven patients (8%) died within 24-48 hours of ED admission, 4 of them of intracranial hemorrhage complications, the other 3 nonrelated to hemorrhagic causes; all of them had DOACs concentration > 50 ng/mL.

In our sample, 29 patients (33%) were directly discharged home from the ED. Most of them (n = 22, 76%) had indication of suspension of DOACs until further reevaluation, 4 were discharged with dose adjustment and only 3 patients had their DOACs maintained at discharge as their diagnosis at ED was not related to DOACs adverse effects nor had implications on its posterior use.

Assessing patients' readmission within 6 months, only 5 patients were readmitted, with recurrent bleeding or referred laboratorial evidence of anemia. There were no thrombotic events registered at the ED within this period, even in patients where DOACs were suspended.

The measurement of residual DOACs' concentrations in emergency settings can help clinical decision making and optimal patient management.[2] In this setting, DOACs quantification should be easily accessible (ideally with results within less than 30 minutes) and not delay life-saving procedures or treatments.

In this study, most patients were anticoagulated with apixaban and the main indication for DOACs was a heart arrhythmia, with a mean age of subjects of 79.8 years old. Most patients in this study were under the standard dose, except for patients taking dabigatran who were mostly under adjusted dose, probably due to clinician's awareness of its creatinine clearance's sensitivity, in contrast to anti-Xa DOACs.

In our setting, DOACs quantification was available and routinely used in the ED. It was mainly requested due to hemorrhagic events (59%, n = 52), essentially intracranial,

gastrointestinal and genitourinary hemorrhages. The need for urgent invasive technical procedures was also a frequent indication (23%, n = 20), with only 8% (n = 7) for suspicion of acute thrombotic events such as ischemic stroke and coronary syndromes.

Depending on DOACs levels, each patient was evaluated for the need of drugs' reversal and DOACs quantification allowed an earlier surgical or invasive procedure, minimizing unnecessary complications, delayed patients' discharge or prolonged hospital stays. ED physicians should also be familiar with hemostasis and anticoagulant reversal, particularly to manage life-threatening or uncontrolled bleedings, urgent surgeries/invasive procedures or in candidates to thrombolysis. Additionally, they should provide hemodynamic support and restore blood volume by transfusion of blood products, as needed.[1,9] In such situations, the timing of the last DOACs dose allows estimation of the time left for elimination, depending on the agent, clinical status and plasma concentrations, generally within 5 half-lives.[6]

In this study, 75% of patients had concentrations > 50 ng/mL, with apixaban users being most frequently in this range. From all hemorrhagic events admitted at the ED (n = 52), 84.6% had concentration > 50 ng/mL. These results allowed a faster identification of those who may need anticoagulation reversal. Additionally, the likelihood of renal impairment increases with age and in acute settings, making the probability of it influencing DOACs concentration higher. In every case, it is important to adjust its dosage and monitor creatinine clearance to prevent further unnecessary complications associated with anticoagulation agents.

The severity of the cases admitted to the ED required mostly only suspension of DOACs (n = 61), with 26% (n = 23) needing prothrombin complex and 5% (n = 4) had a clinical severity that justified idarucizumab for its reversal. Despite DOACs' known potential bleeding risks, its degree is relatively benign and without further complications, when managed promptly. Accordingly, after discharge from ED, most patients had indication of suspension of DOACs until further reevaluation, to maintain surveillance of possible recurrent adverse events. Only 5 patients returned to the ED within 6 months, with recurrent bleeding or referred laboratorial evidence of anemia, without any registry for thrombotic events within that period.

Anticoagulant management was very diverse between physicians and within different pathologies. Protocols to manage anticoagulants' adverse effects and define patients' follow up are a key element, guiding clinical decisions and making it consistent, diminishing the chance of medical error. The main objective is to balance bleeding vs thrombosis risk, reduce ED readmissions and major complications that may lead to increased comorbidities and mortality.

This study has some limitations that can impact on its research value, such as being a retrospective and observational data analysis with a low number of DOACs quantification requests, limited in time and relatively short follow up. It also relies on electronic medical records that may be not properly detailed about patients' management, due to time constraints associated with urgent/emergent settings.

Conclusion

This study shows the importance of management of DOACs by ED physicians, since nowadays these are the mainstay treatment and prevention of thromboembolic events, following patients' higher average life expectancy. Additionally, it shows the importance of routine use of anti-Xa and anti-IIa at the ED, allowing DOACs management within the needs of each patient and event's severity.

Besides that, it is also important to alert patients on how to proceed if any adverse effects exist and when to search for medical assistance. The priority should be on implementing ED protocols to define when DOACs quantification is essential, regardless of which specialty is involved, to simplify its management in situations such as acute hemorrhagic or trauma events, suspicion of thrombotic events in need for thrombolysis, emergent surgeries or urgent invasive procedures. When specific antidotes are available, if clinical severity requires, they should be used due to their high efficacy on reversal. Its application should never delay life-saving procedures or treatments. If not available, prothrombin complex should be given as an alternative, along with hemodynamic support and transfusion of blood products. ■

Declaração de Contribuição

AIB – Elaboração, colheita de dados, revisão e escrita do artigo.
DF – Revisão do artigo
Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

AIB - Elaboration, data collection, revision and writing of the article.
DF - Revising the article
All authors approved the final draft.

Responsabilidades Éticas

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
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