

Management of Hemorrhage Related to Direct Action Oral Anticoagulant Medication

Manejo das Hemorragias Relacionadas aos Anticoagulantes Orais de Ação Direta

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ABSTRACT

Introduction: Direct Oral Anticoagulant – DOACs are a new class of anticoagulant that directly inhibit the thrombin (dabigatran) or Xa factor (rivaroxabane, edoxabane and apixabane) in the coagulation cascade. These medications are being more frequently used for the treatment and prevention of thrombotic events, mainly in patients with atrial fibrillation, in substitute to warfarin or other vitamin K antagonists (VKAs). Although the incidence of hemorrhage is higher in AVKs than in DOACs, these events may also occur in this group, even in the form of intracranial hemorrhage (ICH), with risk of death. Nowadays, DOACs indications have progressively enhanced and the availability of their specific reverse agents certainly will enhance the safety of their usage. Idarucizumab, reverse agent of dabigatran, and alpha andexanet, reverse agent of Xa factor, have been approved by the Food and Drug Administration in the United States and ciraparantag may be approved in a near future. **Objective:** To review the literature on the manage of hemorrhage related to the use of DOACs. **Methods:** Review of literature that used articles from 1998 to 2017, from several platforms and journals. **Conclusion:** DOACs constitute a great advance in prophylaxis and treatment of thrombotic diseases, which presents elevated morbidity and mortality, and hemorrhages are the main adverse events related to their usage, being rarely necessary the immediate reverse of the anticoagulation. However, the existence of DOACs specific reverse agents enhance the safety of patients, whose anticoagulation may be rapidly reversed if necessary.

KEYWORDS: Atrial fibrillation; Blood coagulation; Pharmaceuticals effects.

RESUMO

Introdução: Os anticoagulantes orais diretos (direct oral anticoagulant – DOACs) são uma nova classe de anticoagulantes que inibem diretamente a trombina (dabigatran) ou o fator Xa (rivaroxabana, edoxabana e apixabana) na cascata da coagulação. Esses estão sendo cada vez mais utilizados para tratamento e prevenção de eventos tromboembólicos, principalmente em pacientes com fibrilação atrial, em substituição à varfarina ou outros antagonistas de vitamina K (AVKs). Embora a incidência de hemorragias seja maior nos AVKs do que nos DOACs, elas também podem ocorrer nesse grupo, até mesmo na forma de hemorragia intracraniana (HIC) com risco de morte. Atualmente as indicações dos DOACs vêm aumentando progressivamente, e a disponibilização de seus agentes reversores específicos certamente aumentará a segurança e, conseqüentemente, sua utilização. O idarucizumab, reversor da dabigatran, e o andexanet alfa, reversor dos inibidores do fator Xa, foram aprovados pelo Food and Drug Administration (FDA) dos Estados Unidos e o ciraparantag poderá ser aprovado em um futuro próximo. **Objetivo:** Revisar a literatura sobre o manejo da hemorragia relacionada ao uso dos DOACs. **Métodos:** Revisão da literatura que utilizou artigos de 1998 a 2017, de diversas plataformas e revistas. **Conclusão:** Os DOACs constituem um grande avanço na profilaxia e tratamento da doença tromboembólica, que cursa com elevada morbimortalidade, e as hemorragias são os principais eventos adversos relacionados ao seu uso, sendo raramente necessária a reversão imediata da anticoagulação. No entanto, a existência dos reversores específicos dos DOACs aumenta a segurança dos pacientes, que poderão ter sua anticoagulação revertida rapidamente, se necessário.

PALAVRAS-CHAVE: Fibrilação atrial; Coagulação sanguínea; Efeitos dos fármacos.

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INTRODUCTION

Oral anticoagulation is essential for the prevention and treatment of embolism and thrombosis. Only in the United States, over six million people use oral anticoagulant medication (OACs), which could be related to higher risk of bleeding and could also echo in morbidity and mortality of this group¹.

The incidence of diseases that require OACs have been progressively increasing and this is directly linked to the aging of the population. Atrial fibrillation (AF), the most prevalent arrhythmia in the world, presented an increase of 13% regarding incidence in the last two decades, and age is a risk factor not only for the development of AF but also for the risk of cardiovascular thrombotic events. Cerebral Vascular Accident (CVA) is the main complication of AF and it is related to this arrhythmia in 20% of the cases².

Direct Oral Anticoagulants (DOACs), represented by the direct inhibitors of Xa factor (rivaroxaban, edoxaban and apixaban), and thrombin direct inhibitor (dabigatran) are alternatives to the vitamin K antagonists (VKAs) for the prophylaxis and treatment of thrombotic events, greatly in part related to AF and present a series of clinical advantages when compared to VKAs, such as higher anticoagulant stability and less risk not only for intracranial hemorrhage but also bleeding³.

Regarding hemorrhage complications, due to the short half-life of these medications, in most cases only the suspension, associated to clinical support actions, may be enough to stop the bleeding. The usage of prothrombotic complex⁴, haemodialysis and the use of activated carbon (AC) may be useful in reducing the action of DOACs; however, in cases of overdose, massive bleeding, hemodynamic compromise or need of urgent surgical intervention, the reversion of the anticoagulant activity may be needed. To act in these more serious cases, DOACs specific reverse agents were developed, and the three main drugs are: idarucizumab, andexanet and ciraparantag.

OBJECTIVE

To review the literature regarding hemorrhage management related to DOACs.

METHODS

This review of literature study used articles from 1998 to 2017, researched in the platforms PubMed, Medline, Cochrane Library, SciELO and UpToDate and in the scientific journals Journal of the American Medical Association, New England Journal of Medicine and Blood, using the following keywords: atrial fibrillation, anticoagulation, DOAC, alpha andexanet, idarucizumab, ciraparantag.

DEVELOPMENT

Homeostasis is a normal physiological answer from the body that prevents significant blood loss after vascular damage. Coagulation cascade is a complex series of reactions that guarantees the occurrence of homeostasis (Fig. 1).

Anticoagulant system, which works in parallel to the fibrinolytic system, guarantees that the formation of the thrombus is a controlled and balanced procedure, allowing the degradation of already formed thrombus. DOACs are divided into direct inhibitors of thrombin or direct inhibitors of Xa factor, and their characteristics are presented in Table 1.

Exelate dabigatran is an oral pro-pharmaceutical that is converted in the liver into dabigatran, a direct, reversible, competitive inhibitor of thrombin⁵. There are tests of anticoagulant activity, such as the ecarin clotting time (ECT), thrombin time (TT) and partially activated thromboplastin (PATP) to detect the excessive activity of the dabigatran. TT is the most sensible in detecting low levels of dabigatran^{6,7}.

The direct inhibitors of Xa factor (rivaroxaban, apixaban and edoxaban) directly linked themselves to the active sites of X factor in the circulation and, linked to the clot, block the interaction with its substrate. They are metabolized by the kidneys (25-35%) and liver (up to 75%) and patients with hepatic insufficiency may present this drug accumulation, but in spite of that, these medications do not seem to be toxic to the liver⁸.

Rivaroxaban is a direct inhibitor, reversible and competitive of the Xa factor, orally administered. It should not be used in patients with clearance <15 mL/min, as well as in patients with important

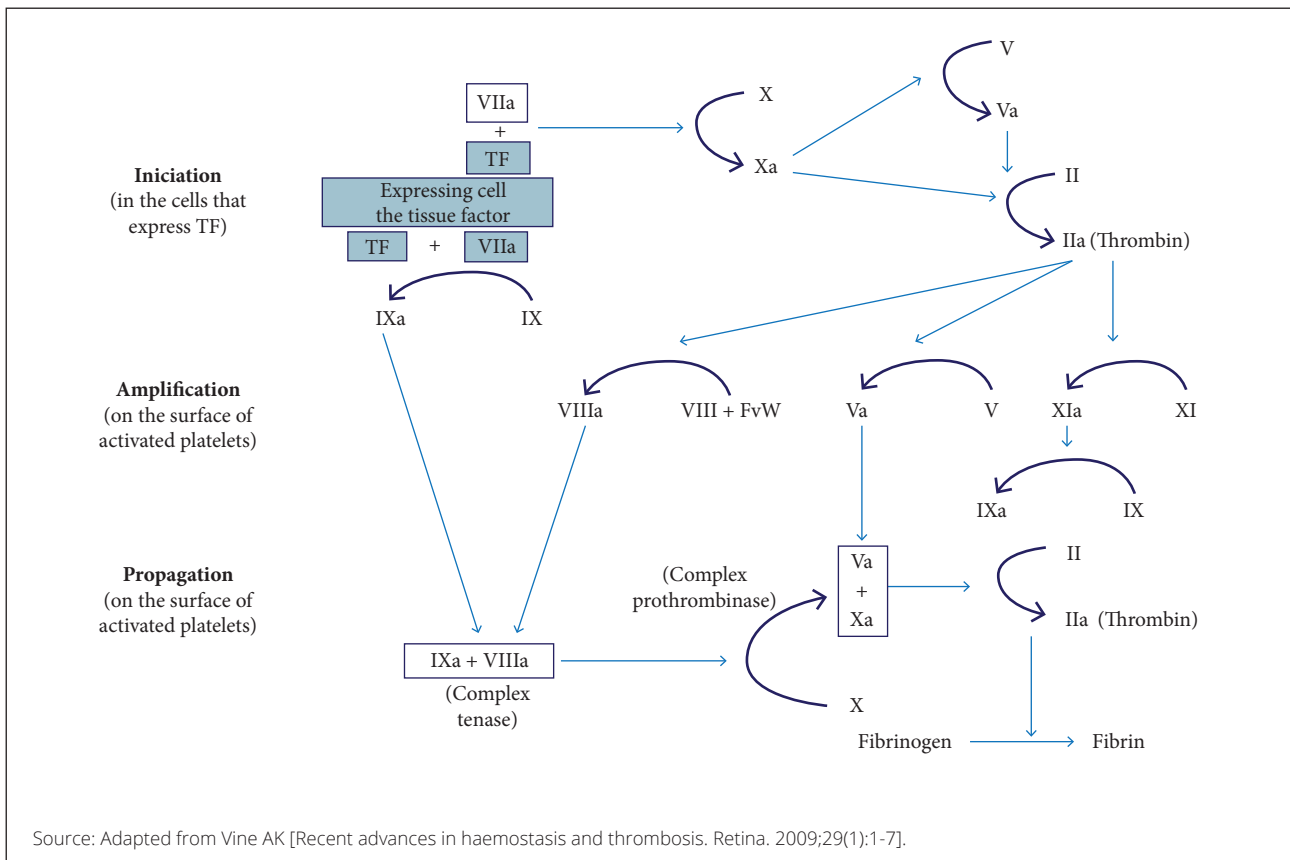


Figure 1. Coagulation cascade [tissue factor (TF) activated].

liver illness (Child-Pugh B and C with coagulopathy)⁹. This medication has not been tested in people under 18 years of age¹⁰.

Rivaroxaban interacts with CYP-3A4 and protein P suppressant drugs (such as ketoconazol, itraconazol, voriconazol, posaconazol and ritonavir) and its concomitant use with these drugs is not recommended¹¹. It is not necessary to perform tests to monitor the coagulation during the treatment with rivaroxaban, except in patients that present bleeding, suspect of medication intoxication or need of emergency surgery¹³.

Apixaban is a direct inhibitor, reversible and competitive of Xa factor, orally administrated, needing adjust of the dose according to the creatinine clearance. It is also recommended to reduce its dose in patients that use CYP-3A4 and protein P inhibitors¹⁴.

Edoxaban is a direct inhibitor of Xa factor, selective and reversible^{15,16}. Around 73% of the drug of the dose is eliminated unaltered in urine and faeces^{17,18}. The recommended dose for the prevention of Cerebral Vascular Accident in patients with AF is of 60 mg once a day, reducing to 30 mg once a day in patients with

creatinine clearance between 15-50 mL/min, weight <60kg or concomitant use of any protein P inhibitor (for ex., verapamil, quinidin, eritromicin and ketoconazol)¹⁹. This medication is not recommended for patients with terminal kidney failure, creatinine clearance, 15 mL/min or under hemodialysis.

The incidence of bleeding is 2-3% a year higher in patients using DOACs, being the incidence of CVA 1-0.5%²¹.

DISCUSSION

Hemorrhage management related to the use of DOACs varies according to the gravity of the case. Light hemorrhages may be resolved only with the temporary suspension of the drug and, in the most severe cases, fluid reposition may be needed, as well as hemodynamic support, mechanical compression, surgical hemostasis, and the use of blood derivatives. If all those measurements were not enough, one must use pro-coagulants, such as the prothrombic complex²¹.

Table 1. Properties of DOACs.

	Dabigatran	Rivaroxaban	Apixaban	Endoxaban
Action mechanism	Thrombin direct inhibitor	Xa factor direct inhibitor	Xa factor direct inhibitor	Xa factor direct inhibitor
Time to achieve seriec level	1 to 2 h if swallowed with food	2 to 4 h	3 to 4 h	1 to 2 h
Half-life	12 to 17 h (young people); 14 to 17 h (elderly)	5 to 9 h (young people); 11 to 13 h (elderly)	12 h	10 to 14 h
Dose (fanv)	150 mg twice a day	20 mg once a day	5 mg twice a day	60 mg once a day
Metabolism by cyp3a4	No	Yes	Yes	Minimum
Elimination	80% kidney	70% liver 30% kidney	30% kidney	50% kidneyl

Source: Crit Care Res Pract. 2018. ID:4907164.

Other therapies include hemodialysis, capable of removing up to 60% of the circulant dabigatran and AC, effective in reducing the absorption of anticoagulant in the first hours after the ingestion. In the cases of overdose, massive bleeding, need to restore hemostasis by hemodynamic compromise or need of urgent surgical intervention, the reserve of the anticoagulant activity may be needed, using DOACs reverse agents²¹. Their indications and characteristics are presented in Table 2 and Table 3.

Idarucizumabe, specific reserve agent of dabigatran, was approved for clinical use in October and November 2015, in the United States and Europe, respectively and in Brazil, its liberation occurred in April 2017. Alpha andexanet, reverse of Xa factor inhibitors, was approved by the Food and Drug Administration (FDA) in an accelerated scheme, however in Brazil its usage has not been cleared yet. The most recent DOACs reverse agent, ciraparantag, is in initial phase of studies and it proposes the reverse of all types of DOACs.

Clinical Measurements

In case of greater bleeding, which occurs in critical location in association with hemodynamic instability or fall of ± 2 g/dL of hemoglobine, DOACs must be suspended, being their specific reverse agents indicated, as well as volume replacement and local hemostasis²².

In case of external bleeding, local control measurements must be performed, preferentially with

criсталloides (0.9% saline, Ringer or Lactate), aiming the volemic restauration and hemodynamic stability. Hypothermia as well as acidosis must be corrected and, in case of symptomatic anemia and/or active bleeding, red blood cells must be transfused, in order to maintain hemoglobin at ± 7 g/dL in general patients and at ± 8 g/dL in coronary patients²³.

Plaquets transfusion must be performed if there is less than 50.000²⁴ and if fibronogenius crioprecipitate is less than 100 mg/dL. Care must be taken when indication DOACs in patients with morbidity that enhances the risks of bleeding, mainly dabigatran, since liver dysfunction may lead to coagulopathy and reduce the metabolism of the anticoagulant, enhancing the risk of hemorrhages. When DOACs specific reserve actions or agents are unavailable, non-specific reverse measurements should be performed.

Prothrombic complex is a complex of factors derived from human plasma capable of reversing the anticoagulating action of VKA. In animal studies, prothrombic complex was also efficient in reversing the effects of dabigatran²⁵, with recommended dose of 50 U/kg (maximum of 4.000 U)²⁶. There are no randomized studies evaluating the use of prothrombic complex in patients with higher bleeding due to the use of Xa factor inhibitors, therefore the dose is based on cases, series of cases and studies in pre-clinical phase, being the initial suggested dose of 50 U/kg²⁷. AC may be used to remove the non-absorbed drug by the gastrointestinal

Table 2. Indications of the DOACs reserve agents.

Bleeding with risk of death: intracranial hemorrhage, symptomatic extradural hemorrhage or in expansion or uncontrollable hemorrhage

“Closed” bleeding or in critical organs: intraspinal, intraeye, pericardium, pulmonary, retroperitoneal or intramuscular or compartmental syndrome

More persistent bleeding in spite of all the measurement for local hemostasis or risk of recurrent bleeding

Surgery or emergency intervention in patients with risk risk of bleeding during the procedure: neurosurgery, lumbar puncture, cardiac surgery, vascular or hepatic surgery

Source: J Thromb Haemost. 2015;14:623-7.

Table 3. Properties of the specific reverse of DOACs.

	Idarucizumabe	Alpha Andexanete	Ciraparantag
Target	Dabigatran	Direct inhibitor do fator Xa, LMWH, fondaparinux	Direct inhibitor of Xa factor, low molecular weight heparin, fondaparinux, heparin, dabigatran
Compound	Human monoclonal antibody fragment	Recombinant molecule derived from human Xa factor	Bonding through the non-covalent hydrogen actions, diminishing the bonding to endogenous targets
Action mechanisms	Afinity of bonding to dabigatran 350 times higher than the affinity of dabigatran-trombin bonding	Alteration of the receptor of the Xa inhibitors with greater afinity of the bonding than “natural” Xa factor	100-400 mg intravenous administration
Dose	5 g (divided into two doses of 2.5 g intravenously adminstrated)	400-800 mg in bolus, followed by 4-8 mg/min in continuous infusion in 2h	Within 10 min
Start of the action	Immediate	Within de 5 min	Yes
Reservsion duration	12 h	1 to 2 h	24 h
Elimination	Renal	Indefinite	Indefinite
Clinical Study	Reverse-AD	Annexa-A and AnnexA-R	Ansell et al ³⁷ .
Development phase	III/approved	III	II
Adverse effects	Cutaneous reaction, bruises at the site of application and epistaxis	Urticaria, disgeusia, headaches and flushing	Disgeusia, headaches and flushing

LMWH: Low Molecular Weight Heparin

Source: Critical Care Research and Practice. 2018. ID: 4907164.

tract and should be performed in up to 2 to 4 hours after the ingestion²⁸.

Hemodialysis is useful for bleeding related to dabigatran, due to low affinity to this molecule by

plasmatic proteins, due to the excretion mostly by the kidneys²⁹. On the other hand, Xa inhibitors cannot be dialysed, since present strong bonding to plasmatic proteins²¹.

Antifibrinolytic agents may be indicated to patients with greater bleeding caused by either Xa inhibitors or dabigatran. Activated VII factor, fresh frozen plasma or cryoprecipitate must be avoided due to the lack of studies showing benefits and the associated high risks (for ex., transfusional reaction, volume overload)²¹.

DOACs reverse agents are indicated in case of urgent reversion of the anticoagulant effect, such as in massive bleeding, in the presence of hemodynamic instability or when patient needs urgent/emergency surgery in the presence of the usage of such pharmaceuticals.

Idarucizumab may be used to reverse the action of dabigatran. A fragment of the human monoclonal antibody produced in ovarium cells of hamsters from China connects to dabigatran with high affinity and specificity. The recognition and the bonding to dabigatran are due to the structural similarity to thrombin mediated by hydrophobic and hydrogen interactions and saline bridges. The dose adjustment is not necessary according to kidney and liver function, weight or age. The peak of idarucizumab concentration is reached in a few minutes, followed by quick elimination³⁰.

When 5 g of idarucizumab is administered, 32.1% will be recovered in urine in the period of 6 hours and less than 1% in the next 18 hours. The remaining will be eliminated through protein catabolism, mainly through the kidneys. Transitory proteinuria has been observed, which normally reaches its peak after 4 hours of administration and disappears between 12 to 24 hours. In the absence of dabigatran in the organism, idarucizumab has no effect in the formation of thrombin or in the coagulation parameters (dTT, ECT, TT, PATP). In phase 1 studies, no statistically significant differences were demonstrated between the side effects found in patients that received placebo or idarucizumab, neither relevant clinical findings or altered laboratory parameters, vital signs, electrocardiogram or physical exams alterations were found³. Idarucizumab dose selection for the use in clinical tests was based on targets to neutralize the dose of dabigatran used in patients with AF on RE-LY study (150 mg of dabigatran twice a day). The 5 mg dose was chosen to reverse the dose of the anticoagulant in patients with moderate kidney function. In the studies that involved patients of masculine and feminine gender of different ages and kidney functions, the administration of idarucizumab, in the dose of 2.5 g every 12 hours,

resulted in the satisfactory reversion of anticoagulation by dabigatran, being this dose selected for further studies. Idarucizumab has shown to be effective and safe in the reversion of the anticoagulant effect of the dabigatran, in bleeding situations. The safety observed in the study gives support to the use in emergency situations, and the medication has already indications for the treatment of severe hemorrhages³¹.

Alpha andexanet is a specific reverse agent of the Xa inhibitors created by bioengineering. It is a recombinant molecule with structure similar to the endogenous Xa factor, with high affinity to the Xa factor inhibitors, as well as the direct and indirect ones (rivaroxaban, edoxaban, apixaban, low molecular weight heparin and fondaparinux), but it does not have catalytic effect, so it does not perform the cleavage of the prothrombin to thrombin. The bonding site of Xa factor was substituted by alanine, which allows the bonding and removal of Xa factor inhibitors in the intravascular, restoring the activity of the endogenous Xa factor, with consequently reduction of the anticoagulant activity³².

Andexanet alpha has intravenous administration, being the first dose in bolus, followed by a maintenance dose in the next 2 hours³³. The start of the action is in 2 to 5 minutes after the drug infusion and its half-life is in 30 to 60 minutes. The Xa inhibitors anticoagulant levels rise after a few hours of andexanet administration, and the drug is not removed with the reverse agent, as it happens with dabigatran, when the antibody idarucizumab is used^{34,35}. Dose adjustment is not necessary. In 2 minutes after the administration, alpha andexanet showed reversion of the anticoagulant effects of all Xa factor inhibitors, including the reduction of its activity and the restoration of thrombin generation and coagulation time. Endovenous administration in bolus, followed by continuous infusion of andexanet resulted in sustained reduction of the anti-Xa factor, which returned to the levels of the placebo group 2 hours after the stop of the infusion³⁴.

Ciraparantag (PER977) is a small cationic synthetic molecule, which bonds to the Xa inhibitor factor, thrombin direct inhibitors, non-fractionated heparin and low molecular weight heparin through non-covalent hydrogen bridges. Phase 2 studies investigating reversion of edoxaban and evaluating the doses of ciraparantag are in progress and plans for phase 3 studies have already been announced³⁶.

CONCLUSION

DOACs constitute a great advance in prophylaxis and treatment of thrombotic disease, which presents elevated morbidity/mortality. These drugs are of easy use, present high efficiency and safety and do not need of therapeutic dose adjustment by the coagulogram, which have been elevating their use. An important obstacle regarding DOACs use was the impossibility of reversion of their action in case of severe bleeding or emergency surgeries.

Although rarely necessary, in case of immediate reversion, the existence of reverse agents enhances the security of patients, which may lead to the enhancement of their usage. For this reason, it is very important the availability of DOACs specific reverse agents, even knowing that most

cases regarding bleeding related to their use do not need any drastic intervention.

AUTHORS' CONTRIBUTION

Conceptualization, Ganem IRA; Martins LCB and Tomé CEM; Methodology, Ganem IRA and Tomé CEM; Investigation, Ganem IRA; Martins LCB and Tomé CEM; Writing – first version, Ganem IRA; Martins LCB and Tomé CEM; Writing – revision & editing, Ganem IRA; Martins LCB and Tomé CEM; Grant acquisition, Ganem IRA; Martins LCB and Tomé CEM; Resources, Ganem IRA; Martins LCB and Tomé CEM; Supervision, Martins LCB and Tomé CEM.

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