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Management of the gastrointestinal system bleeding caused by direct-acting oral anticoagulants

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Abstract

Arterial and venous thromboembolism is a common and serious clinical condition where anticoagulation is administered for its treatment and prophylaxis. Anticoagulants prevent the formation of new thrombi and thus the extension of the existing thrombus. Direct-acting oral anticoagulants (DOAC) include dabigatran, which is a thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are anti-Xa agents. These are administered in the secondary prophylaxis and treatment of various diseases of thrombus. Although it is specified that they reduce the risk of bleeding due to all causes, many important studies have also reported that they increase the risk of gastrointestinal system (GIS) bleeding. Therefore, similar to Vitamin K antagonists (VKA), their use is contraindicated in active bleeding, active ulcers, hemorrhagic angiodysplasia, and recurrent bleeding requiring recurrent transfusion. However, these contraindications are mostly transient. We aimed to analyse the risk, prophylaxis and management of the active GIS bleeding in patients taking DOAC in this article

Keywords: direct-acting oral anticoagulants, gastrointestinal system bleeding, venous thromboembolism

1. Introduction

Arterial and venous thromboembolism is a common and serious clinical condition where anticoagulation is administered for its treatment and prophylaxis. Anticoagulants prevent the formation of new thrombi and thus the extension of the existing thrombus. Anticoagulant drugs can be broadly classified as standard (unfractionated) heparin (SH), low molecular weight heparin (LMWH), parenteral direct thrombin inhibitors, fondaparinux, danaparoid, Vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOACs). Although new generation direct-acting oral anticoagulant agents are not proven to be significantly superior to Vitamin K Antagonists (VKA) in terms of efficacy, they have recently become more preferred, especially because they do not require regular laboratory monitoring.

Direct-acting oral anticoagulants include dabigatran, which is a thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are anti-Xa agents. These are administered in the secondary prophylaxis and treatment of venous thromboembolism (VTE) and pulmonary embolism (PE), in the prophylaxis of VTE that may develop after major elective orthopedic surgery, in reducing stroke and systemic embolism that may occur in non-valvular atrial fibrillation, whereas its use in acute coronary syndrome is still controversial.

Although it is specified that direct-acting oral anticoagulants are as effective as heparin therapy and reduce the risk of bleeding due to all causes, many important studies have also reported that they increase the risk of gastrointestinal system (GIS) bleeding (Cohen et al.,2015; Deutsch et al., 2017)

2. General characteristics of direct-acting oral anticoagulants

Drugs in this group act rapidly and their effectiveness starts between 30 minutes and four hours (Tmax 1.5-4 hours). Their oral bioavailability is variable. Dabigatran is a substrate of P-gp in the cell membrane. After oral intake, it causes P-gp re-secretion in the intestines and may interfere with drugs that inhibit or stimulate the P-gp transporter. FXa inhibitors, on the other hand, can interfere with drugs that affect this mechanism as they are metabolized by the CYP 3A4 system. They are known to interact most commonly with azole agents, rifampicin, and some antiviral agents, whereas it is not known whether they are pharmacologically related to proton pump inhibitors (PPIs).

Although it is advantageous due to its rapid onset of action, oral administration, minimal interference with foods and drugs, not requiring laboratory follow-up, being safer in terms of

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intracranial bleeding, it has such disadvantages as loss of effectiveness when the dose is skipped, limited effectiveness in renal dysfunction, failure to discern patient-compliance to drug and its high-price. The most fundamental difference between thrombin inhibitors and factor Xa inhibitors is the renal excretion of the drug. Dabigatran elimination is predominantly from the kidneys, while the kidneys are less involved in the elimination of Factor Xa inhibitors.

When evaluated in terms of the gastrointestinal system, similar to VKA, its use is contraindicated in active bleeding, active ulcers, hemorrhagic angiodysplasia, and recurrent bleeding requiring recurrent transfusion. However, these contraindications are mostly transient. Other contraindications include potential bleeding GIS lesions that cannot be reached by endoscopic or surgical treatment and Child-C cirrhosis. It is known that the risk of bleeding increases in those with a history of GIS bleeding, but this is not an absolute contraindication (Deutsch et al., 2017).

2.1. Dabigatran

It prevents fibrin formation from fibrinogen by directly inhibiting free and bound thrombin (FIIa). It is a pro-drug with a bioavailability of 6.5%. It has no interaction with food. Tmax is 0.5-2 hours and $t_{1/2\ is}$ 12-14 hours (longer in the presence of renal failure). Its metabolization is very low and the excretion is from the kidney with a rate of 85%. Dialysis can be applied in case of overdose. The average dose is administered as 150 mg or 110 mg b.i.d. When glomerular filtration rate (GFR) is 30-50 ml/min, it is administered as a low dose of 110 mg b.i.d.

2.2. Rivaroxaban

Its bioavailability is 80-100% below 15 mg, while it is 66% when fasted and 100% when fed with 15 mg and above. Tmax is 2-4 hours, and $t_{1/2\ is}$ 5-9 hours in young patients, whereas 11-13 hours in elderly patients. It has high metabolism and excretion is 1/3 fecal and 66% renal. The average dose is administered as 20 mg qd in AF patients, 15 mg b.i.d (21 days) in DVT-PE patients, and 20 mg qd afterward. If GFR is 15-30 ml/min, 15 mg qd should be administered.

2.3. Apixaban

Its bioavailability is 50% and it has no interaction with food. Tmax is 3-4 hours, and $t_{1/2}$ is 12 hours. Its metabolism is high and its excretion is 50% fecal and 27% renal. Dialysis can very rarely be useful in overdose or intoxication. The average dose is 5 mg b.i.d or 2.5 mg b.i.d, and 2.5 mg b.i.d should be preferred for those with a GFR of 15-30 ml/min.

2.4. Edoxaban

Its bioavailability is 62% and it has no interaction with food. Tmax is 1.5 hours and $t_{1/2}$ is 10-14 hours. It has low metabolism with 60% fecal and 35% renal excretion. Dialysis can very rarely be useful in overdose or intoxication also. The average dose is 60 mg q.d, and 30 mg q.d should be preferred for those with GFR 15-50 ml/min.

Drug dose should be reduced taking into consideration the bleeding risk of patients (old-age, low weight, or renal insufficiency). DOACs are contraindicated in hepatic insufficiency as it affects coagulation and significantly increases the risk of active bleeding. Based on their pharmacokinetics, DOACs should never be used in combination with other anticoagulants (unfractionated heparin, LMWH).

The effectiveness of DOACs that do not normally require follow-up should be evaluated in some specific situations such as life-threatening bleeding. Routine coagulation testing has no significant role in this. Only the presence of normal activated partial thromboplastin time can be considered as a finding that dabigatran affect is in desired therapeutic range. Also normality of Prothrombin time (PT) suggests that drug levels are normal in patients receiving anti-Xa treatment. Measuring thrombin time (TT) for dabigatran and anti-Xa activity for others is helpful. Normal TT indicates that dabigatran is not used at an effective dose. TT prolongation is detected in cases higher than the treatment dose. Diluted TT, Ecarin chromogenic test (ECA) and Ekarin coagulation time (ECT) can be performed in these cases (Deutsch et al., 2017).

3. Gastrointestinal system bleeding risk with direct-acting oral anticoagulants

Gastrointestinal system bleeding is an important adverse event associated with the use of anticoagulants, and discontinuation of anticoagulation during bleeding can lead to thromboembolic events. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA), anticoagulants are not ulcerogenic drugs. Little pathophysiological evidence is available for anticoagulants in the development of GIS bleeding. The annual risk of GIS bleeding in patients taking anticoagulant therapy is assumed to be 1.5-5%. This risk increases in the presence of comorbidities and multiple drug use, as well as the administration of antithrombotics and NSAIDs in the elderly **(**Sharma et al., 2015). When comparing DOACs with VKA, studies are reporting an increase of 25% in the risk of GIS bleeding, whereas some studies have not shown an elevated risk (Ruff et al., 2014; Miller et al., 2012; Chai-Adisalisopha et al., 2014; Sherwood et al., 2015; Tamayo et al. 2015; Camm et al., 2016; Abraham et al., 2015; Youn et al., 2018).

In comparative studies of all DOACs with VKA, although the risk of GIS bleeding was similar, dabigatran and rivaroxaban were reported to have a higher risk in terms of GIS bleeding compared to VKA (Burnett et al., 2016). However, Chan et al., in their study, stated that the low dose of dabigatran (2x110 mg) did not increase the risk of major GIS bleeding compared to VKA (Chan et al., 2016)**.** Besides, in another study, it was reported that rivaroxaban caused non-critical GIS bleeding at a higher rate (Chan et al., 2016).

4. Gastrointestinal System Bleeding Prophylaxis in Patients Taking Direct-Acting Oral Anticoagulants

Patients considered to have an elevated risk of bleeding should be consulted with cardiology or neurology for a temporary

reduction in their drug doses. Since there is an increased risk of bleeding in combination with NSAIDs, ASA, and other antithrombotic drugs, these drugs should be avoided whenever possible. PPI can be added to the treatment if there is a history of ulcer or GIS bleeding. During concomitant use of anticoagulants and acid suppressants, the treatment should be personalized and a decision should be made based on a risk-benefit assessment (Bang et al., 2020).

Although Helicobacter Pylori (HP) eradication is not yet recommended before DOAC treatment, it is still a controversial issue. Bleeding parameters, complete blood count, and serum creatinine values should be monitored annually and dose adjustment and follow-up should be done when necessary (Chan et al., 2015).

5. Active GIS bleeding management in patients taking direct-acting oral anticoagulants

In GIS bleeding occurring during the use of Direct-Acting Oral Anticoagulants, treatment must be interrupted, the last date of the drug use should be queried and renal function and basal coagulation testing should be performed. In case of minor bleeding, the next dose should be skipped or treatment should be interrupted.

In case of moderate to severe bleeding, it is required to perform supportive therapy, mechanical compression (where practical), fluid and blood infusions, and activated charcoal should be administered if dabigatran has just been taken. In the presence of major bleeding, hemodynamic stability must first be achieved. Transfusion of erythrocyte suspension is recommended in cases where Hb <7/dl or <9 g/dl in the presence of severe comorbidity. Fluid replacement should be applied, and if there is hypothermia or acidosis, it should be corrected as it may worsen the coagulopathy. If necessary, cryoprecipitate replacement can be applied so that the fibrinogen is above 100 mg/dL.

If hemodynamically stable and/or adequately responding to resuscitation, it is recommended to observe the patient closely and postpone the endoscopy for 12-24 hours. This ensures the maintenance of drug clearance and normal hemostatic functions. The theoretical advantage of this approach is that endoscopic treatment can be performed more easily and safely in a patient who has not been fully anticoagulated. Otherwise, emergency endoscopy may be appropriate for active bleeding in patients with permanent or intermittent hemodynamic instability. In this case, the use of nonspecific pro-hemostatic agents may be considered to accelerate the reversal of anticoagulation activity.

Initiation of activated recombinant factor VII or prothrombin concentrate, administration of activated charcoal and hemodialysis in those taking dabigatran, and the use of a monoclonal antibody called idarucizumab as an antidote in life-threatening bleeding are practiced. It binds to dabigatran and removes the anticoagulant effect within minutes. In case of bleeding in those who take DOACs, if the drug is taken within the last 2-4 hours, activated charcoal, Four-factor prothrombin complex concentrate (4F-PCC) or activated prothrombin complex concentrate (aPCC) 50 IU/kg iv can be applied. For those who take dabigatran, 5 g of idarucizumab can be administered and it should be kept in mind that hemodialysis can also be administered for these patients. Studies on PER977 (Ciraparantag), which binds direct and indirect inhibitors of water-soluble synthetic FXa and thrombin, are still ongoing.

Emergency endoscopy indications are not different from those taking non-DOAC anticoagulants. It is recommended that endoscopy be performed within the first 24 hours from the onset of bleeding. The short half-life of DOACs provides an important advantage for emergency endoscopy approaches. Since normal coagulation characteristics are achieved in the period of 4 half-lives after discontinuation of DOACs, the last DOAC administration should be questioned carefully and the period of possible bleeding risk should be calculated.

Alternative treatments may be considered in life-threatening bleeding, in cases that cannot be controlled by endoscopy with a recent history of DOAC intake. Nonspecific procoagulant drugs, aPCC, or PCC or tranexamic acid can be administered (Bennet et al., 2014). Factor Eight Inhibitor Bypassing Activity (FEIBA) is an aPCC and is the primary agent that should be selected. A total of 30-50 IU/kg should be administered intravenously, with a maximum flow rate of 2 IU/kg/min (Marlu et al., 2012; Dager et al., 2013).

Specific antibodies are being developed against DOACs. Idarucizumab is a human monoclonal antibody fragment (Fab) developed for dabigatran, while andexate alpha is a recombinant factor Xa molecule produced for rivaroxaban, apixaban and edoxaban, which does not affect hemostasis. Idarucizumab was approved by the FDA in 2015. It is used in situations such as the perioperative management of an emergency surgical procedure with life-threatening bleeding or a high risk of bleeding that cannot be delayed for up to 8 hours. The recommended dose of idarucizumab is two consecutive infusions of 2.5 g each administered at a maximum interval of 15 minutes (lasting for 5-10 minutes) or as a bolus. Dabigatran plasma concentration should be measured before administration of idarucizumab and, if re-bleeding occurs, 12-18 hours after this bleeding. In such cases, an additional 5 g of idarucizumab infusion can be administered if there is a concentration above 30 ng/ml. Hemostasis tests are normalized within minutes at a rate of 88-98% in patients (Pollack et al., 2015). Idarucizumab does not require dose adjustment in renal failure.

Andexanet alfa shows a rapid onset of action (within 2-5 minutes) by restoring thrombin formation and normal clotting in patients treated with rivaroxaban, apixaban, and edoxaban. The first bolus followed by a two-hour infusion and andexanet reduces anti-factor Xa activity by 79% with effective hemostasis. Andexanet (recombinant Factor Xa) was approved

by the FDA in 2018 and is effective on FXa inhibitors and does not require renal dosage adjustment (Siegal et al., 2015; Connoly et al., 2016). With the introduction of these antidotes, it is believed that the management of bleeding complications in patients treated with DOACs will be easier.

For non-life-threatening bleeding in the absence of kidney or liver failure, temporary discontinuation of DOAC is likely sufficient. There is no evidence for the use of vitamin K or fresh frozen plasma (FFP) to reverse the effects of DOACs. Hemodialysis can be used to rapidly and effectively reduce the plasma concentration of dabigatran (65% at 2-4 hours) and is considered the most effective strategy for in-patients with renal insufficiency with dabigatran-associated bleeding; however, it is not effective for other DOACs (i.e.; rivaroxaban, apixaban, and edoxaban) that bind to plasma proteins at higher rates than dabigatran. No direct data is available about when to continue DOACs following gastrointestinal bleeding. When DOACs are discontinued, the risk of thrombosis is stated to be 4.8% for 30 days and 6.8% for 90 days (Kyaw and Chan, 2018).

Data on the resumption of DOACs after gastrointestinal bleeding are lacking. The principles adopted for VKAs may be extrapolated to DOACs, but caution should be exercised because, unlike warfarin, DOACs cause anticoagulation within a few hours. In one study, it was shown that resumption of anticoagulation within seven days of the admission of an index GIS bleeding did not affect the 90-day hospital readmission rates for recurrent GIS bleeding, and it was stated that it may be reasonable to continue DOAC treatment within seven days (Valanejad et al., 2020).

The time of resumption of anticoagulant therapy is controversial in patients with clinically significant GIS bleeding and no source of bleeding detected on endoscopy. The decision should be made based on estimates of the risks of re-bleeding and thrombosis in these patients. Also, in patients in whom the endoscopist is not fully confident in achieving hemostasis, there cannot be a definitive recommendation to continue anticoagulant therapy. In such cases, it is recommended that another endoscopist evaluate the patient as a second opinion (Radaelli et al., 2015).

Patients taking DOACs and who have undergone endoscopic procedures should be followed-up for 6 hours due to the risk of bleeding. In some studies, it is stated that if hemostasis is achieved, the drug can be resumed at 12-24 hours after the procedure, even if there is high risk. Later initiation of the drug may be considered in procedures that may have delayed bleeding, such as endoscopic mucosal resection or endoscopic submucosal dissection. Based on the decision of the endoscopist, it is recommended to resume treatment 48-72 hours after endoscopic procedures, which are considered to have a high risk of bleeding (Tien et al., 2020). Also, it should be kept in mind that discontinuing the drug for more than 48 hours increases the risk of thrombosis.

6. Conclusion

Physicians gain more experience in the management of DOAC treatment where side effects of gastrointestinal bleeding are more frequently encountered, before, during, and after the endoscopy procedure. However, better information should be obtained about these clinical conditions, which can sometimes be life-threatening, to ensure minimization of morbidity and mortality

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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