

Noval Oral Anticoagulants - Review of Articles

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Abstract: Anticoagulants are pharmacological agents that inhibit the coagulation cascade. Utilising these agents in various situations of medical practice is pivotal. In the past options were limited to heparin and warfarin in which the monitoring and safety profile was cumbersome. In recent times there is paradigm shift to novel oral anticoagulants (NOACs) which are Direct Thrombin Inhibitors and prevent thrombin by cleaving fibrinogen to form fibrin. the major advantages are absence of food interactions; few strong drug interactions; predictable pharmacokinetic and pharmacodynamic profiles; rapid onset and offset of action; short half-life; and absence of the need for laboratory monitoring. Routine monitoring is not required, regardless of body weight, age, sex, race, and demographic variations. Disadvantages of NOACs, such as their higher cost, absence of specific antidotes, and limited experience and dosing, however, should be taken into consideration.

1. Introduction

Anticoagulants are pharmacological agents that inhibit the coagulation cascade. Utilising these agents in various situations of medical practice is pivotal. In past years, search for newer anticoagulants has discovered novel agents for preventing and managing thromboembolic disorders. Notable are , agents that directly works over the enzymatic activity of thrombin and factor Xa. Usage of these new agents requires detailed knowledge of their individual properties, dosing, risks, and benefits. These direct thrombin inhibitors and direct factor Xa inhibitors block major procoagulant activities involved in the generation of a fibrin clot.^[1]

Thrombin is the final enzyme in the clotting reaction that produces fibrin; formed by the proteolytic break of prothrombin by factor Xa. The latter acts immediately in the preceding step of thrombin in the clotting cascade, and direct factor Xa inhibitors bind to its active site. and inhibit activity without requiring cofactors. Both thrombin and factor Xa are active in circulating and clot-bound forms.^[2]

Unlike warfarin therapy, the predictable pharmacologic profile of these new agents let physicians to use these drugs without routine monitoring. In addition, these agents have less food interactions and exhibit much limited drug-drug interactions owing to their minimal metabolism via the CYP450 enzyme system.^[3]

In recent times with paradigm shift, these novel oral anticoagulants (NOACs), are being frequently applications in total hip and knee replacement and other major surgery, the treatment and prevention of venous thromboembolic disorders, stroke prevention in atrial fibrillation (AF), cancer chemotherapy and many more.

2. Mechanism of Action

Direct Thrombin Inhibitors prevent thrombin by cleaving fibrinogen to form fibrin. They bind to thrombin directly,

instead of enhancing the activity of antithrombins, as with conventional agent, heparin. The only oral drug in this group is dabigatran.^[4]

Direct Factor Xa inhibitors works on Factor Xa which is a trypsin-like serine protease that plays a pivotal role in blood coagulation. It holds a central position that links the intrinsic and extrinsic pathways to the final common coagulation pathway. Factor Xa catalyses conversion of prothrombin to active form, thrombin. These inhibitors prevent cleaving prothrombin to form thrombin and bind directly. There is no parenteral direct factor Xa inhibitor in clinical usage yet. The drugs include rivaroxaban, apixaban, edoxaban, and betrixaban.^[5]

Recommendations for each agent are based largely on the efficacy and safety in specific patient populations and clinical indications. However still not very frequently used by clinicians, due to lack of knowledge, dosing and cost effectiveness. Pharmacokinetic differences make one agent a better choice compared to another for a given patient.^[2,4]

It has been studied and observed that Premature discontinuation of rivaroxaban and other direct factor Xa inhibitors increase the risk of thrombotic events in the lack of adequate alternative anticoagulants. Also, epidural, spinal hematomas have occurred in patients treated with rivaroxaban who were receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. These patients, therefore, must be monitored for signs and symptoms of neurologic impairment.^[2,5]

Direct thrombin inhibitors

Dabigatran etexilate is a prodrug which is converted by liver to dabigatran, an active direct thrombin inhibitor that inhibits both free and bound thrombin. This was the first such novel oral anticoagulant to be available in market since 2010. The half-life is long being about 12 to 17 hours in patients with normal renal function.^[6]

Dabigatran etexilate is unaffected by food, has potential of getting denatured by moisture so should be kept and stored in original blister pack or container. Once the bottle is opened, this must be used within 4 months. It has been observed that there is dramatic increases in oral bioavailability after removal of the capsule shell.

This is commonly used in the prevention and management of venous thromboembolism (VTE) and in stroke prevention in patients with atrial fibrillation (AF) being contraindicated with prosthetic heart valves and in pregnancy.^[6] The dosing varies and is available as 75-mg, 110-mg, and 150-mg capsules. Given as a fixed dose without monitoring, the maximal effect is achieved within 3 hours of ingestion. Renal excretion is the predominant pathway of elimination with 80% excreting in the urine, thus dose adjustment is advised with reduced GFR.^[6]

Dosing for VTE prophylaxis in surgical patients is 110 mg one to four hours after surgery, followed by 220 mg once daily for 28 to 35 days after major surgery.^[2,6]

For stroke prevention in AF, 110 mg is given twice daily or 150 mg twice daily if creatinine clearance (CrCl) >30 mL/min whereas for secondary prevention and treatment of VTE, 150 mg is administered twice daily with CrCl >30 mL/min.

Prior to the start of therapy with dabigatran one should measure platelet count, prothrombin time, and activated partial thromboplastin time to assess and document coagulation status before anticoagulation therapy.

Dyspepsia is a commonly felt side effect with an incidence of 12% to 33% in some studies. In addition, as with all anticoagulants, dabigatran does increase bleeding risk. The antidote idarucizumab was approved by the FDA in 2015.^[2,6]

Idarucizumab (Praxbind) is a humanized anti dabigatran monoclonal antibody fragment that may be used in emergency reversal of the anticoagulant effect. This agent should be administered following failure of all conservative bleeding management measures. It should be administered only to patients having convincing evidence of significant dabigatran levels based on clinical history of ingestion or laboratory testing. Idarucizumab should not be administered to patients with a normal thrombin time. The dose is 5 g (two 2.5-g vials), which can be administered either as two consecutive infusions or as a bolus.^[2]

Direct factor xa inhibitors

These drugs inactivate the free and bound factor Xa. Most of them are oral agents and no parenteral drugs available in this group. Otamixaban was developed as an intravenous drug but discontinued owing to excessive bleeding. All of these drugs are metabolized in the kidney and liver.^[7,8] Rivaroxaban is the first direct factor Xa inhibitor introduced and has a half-life of 7 to 17 hours. It is used for prevention and treatment of VTE and in stroke prevention in patients with AF. Rivaroxaban is generally given at a fixed dose without monitoring. The 15- and 20-mg tablets are taken with food. Dosing is based on clinical condition and renal

status. For VTE, 15 mg is given twice daily for 21 days, followed by 20 mg once daily. The AF dose is 20 mg once daily with the evening meal (CrCl >50 mL/min) or 15 mg once daily with CrCl <50 mL/min.^[2,9,10]

This drug should not be used in patients with CrCl <15 mL/min or with CYP3A4 and P-glycoprotein inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir. Routine monitoring of coagulation time is not necessary because drug levels are relatively predictable for a given dose. Like all anticoagulants, this drug increases bleeding risk, but its antidote is still under study.^[2,9,10]

Because of high plasma protein binding, this drug is not dialyzable. Concomitant use of any other agent that impair hemostatic pathway including, aspirin, platelet inhibitors, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors markedly increases the risk of bleeding. They, being renally eliminated must be used cautiously in patients with CrCl <30 mL/min. This drug should be used during pregnancy only if the potential benefits justify the potential risk to mother and fetus. There is no antidote available for rivaroxaban overdose, and the use of activated charcoal to reduce absorption is tried. Apixaban is a newer oral factor Xa inhibitor with a half-life of 5 to 9 hours. It can also be used for the prevention and treatment of VTE and stroke prevention in patients with AF. This drug is used for VTE prophylaxis and for initial and extended treatment but contraindicated during pregnancy. The dosing of apixaban differs according to clinical indication, age, weight, and renal function. Dosing for VTE prophylaxis is 2.5 mg twice daily for 35 days (hip replacement) or 12 days (knee replacement). For secondary prevention and treatment of VTE, 10 mg is administered twice daily for 7 days, followed by 5 mg twice daily. For stroke prevention in AF, 5 mg is given twice daily (CrCl >50 mL/min) or 2.5 mg twice daily.

This drug is safest in renal derangement patients among all direct factor Xa inhibitors. Laboratory testing prior to initiating apixaban and monitoring is the same as for rivaroxaban. In cases of emergency as surgery or Road traffic accident monitoring can be accomplished through the measurement of antifactor Xa activity.^[11,12]

Edoxaban is an oral direct, specific inhibitor of factor Xa with an approximate 10,000-fold selectivity for factor Xa over thrombin. Edoxaban was approved by the FDA in January 2015 for the prevention of stroke and noncentral nervous system systemic embolisms. This has half-life of 10 to 14 hours, and it has the same indications as rivaroxaban and apixaban. It is given at a fixed rate with no monitoring. The typical dosage is 30 or 60 mg once daily. Edoxaban is renally eliminated and is a substrate for P-glycoprotein. The dose adjustment is advised in patients with CrCl of 15 to 50 mL/min. As with other anticoagulants, edoxaban increases bleeding risk and is administered in the setting of increased thrombotic risk. Edoxaban is rapidly absorbed, and it was estimated that its absolute bioavailability is 58.3%. This drug has dual mechanisms of elimination: Approximately one-third is eliminated via the kidney and the remainder via feces.^[2,13]

Betrixaban is a long-acting inhibitor with a half-life of 19 to 27 hours. It is used in the prevention of VTE in hospitalized adult patients. It is also given in a fixed rate with no monitoring. The typical dosage is 160 mg on the first day followed by 80 mg once daily. Doses are given at the same time with food. For individuals with CrCl <30 mL/min, 80 mg is given on the first day, followed by 40 mg daily. For VTE prophylaxis, the duration of therapy is 35 to 42 days.^[2,14]

Imminent Risk of Death: For patients who are at imminent risk of death from bleeding associated with direct factor Xa inhibitor anticoagulation, administering an unactivated 4-factor prothrombin complex concentrate (PCC) at a dosage of 25 to 50 units/kg is suggested. If a 4-factor PCC is unavailable, a 3-factor PCC may be used; supplementation of 3-factor PCC with fresh frozen plasma has been used to supply factor VII, which is present at minimal levels in 3-factor PCCs.^[2]

Major Bleeding: For patients with major bleeding (including life-threatening bleeding), administering an antifibrinolytic agent (e.g., tranexamic acid) is suggested. The use of this agent may also be appropriate in individuals with less serious bleeding if the patient has ongoing bleeding or other comorbidities that increase bleeding risk.^[2]

3. Advantages of NOACs over VKAs

NOACs have various advantages in the prevention and treatment of patients with a predisposition toward AF, deep venous thrombosis, pulmonary embolism, stroke, and other conditions that are related to inherited or acquired thrombophilia.^[2]

The following are the main advantages of NOACs compared with VKAs in preventing various factors that are responsible for thromboembolic disorders and in the treatment of thromboembolic diseases: absence of food interactions; few strong drug interactions; predictable pharmacokinetic and pharmacodynamic profiles; rapid onset and offset of action; short half-life; and absence of the need for laboratory monitoring. Routine monitoring is not required, regardless of body weight, age, sex, race, and demographic variations.^[2,15]

Additional advantages of NOACs over VKAs include wide therapeutic windows, greater efficacy in AF, and lower risk of intracranial hemorrhage, except for dabigatran, which has an intracranial hemorrhage rate equal to that of warfarin at doses of 150 mg.^[2]

4. Conclusion

Long-term use of oral anticoagulant therapy with VKAs presents several problems related to major drug and food interactions, individual variability in the effect, and the need for continuous monitoring. This caused a search for new ways to discover additional anticoagulant medications. The advantages of NOACs over VKAs are their high efficacy in preventing stroke in AF and nonvalvular AF, lower incidence of major bleeding, convenience of use,

minor drug and food interactions, rapid onset and offset of action, short half-life, and lack of the need for laboratory monitoring.

Disadvantages of NOACs, such as their higher cost, absence of specific antidotes, and limited experience and dosing, however, should be taken into consideration. In addition, NOACs should not be used in patients with severe renal and hepatic disease, patients with mechanical heart valves, patients younger than age 18 years, and the elderly.

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