Direct Oral Anticoagulants

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Introduction

The direct oral anticoagulants are drugs that represent a new class of anticoagulants working by directly blocking active coagulation enzymes either thrombin or factor Xa (Table 24.1). All have been shown to have a lesser rate of intracranial hemorrhage in atrial fibrillation patients and all the Xa inhibitors have less bleeding when used as therapy for venous thrombosis.

Table 24.1 Direct oral anticoagulants

Direct thrombin inhibitor
Dabigatran
Pharmacology
Time to maximum concentration: 1–2 hours
Half-life: 12–17 hours
Renal elimination: 80%
Dosing:
Prophylaxis 220 mg or 110 mg dDay
Venous thrombosis treatment: 150 mg bid (acute thrombosis after 5 days parenteral heparin)
Stroke prevention atrial fibrillation: 150 mg bid
Renal clearance: dose reduced to 75 mg bid if CrCl <30 and contraindicated CrCl <15
Affects aPTT – can use to see if patient still has drug effect – 1.5–2 × 0.5–2 hours after dose
Drug-drug interaction – P-gp inhibitors: Dronedarone, ketoconazole – dose reduced to 75 mg bid or contraindicated if renal impairment. P-gp inducers: rifampin. St. John's wort – contraindicated
Reversal agent: Idarucizumab 5 g IV
Factor Xa inhibitors
Apixaban
Pharmacology
Time to maximum concentration: 3–4 hours
Half-life: 12 hours
Renal elimination: 25%
Dosing
Prophylaxis 2.5 mg bid
Venous thrombosis treatment: Initial treatment for acute thrombosis of 10 mg bid × 7 days and then 5 mg bid, contraindicated if CrCl <25
Stroke prevention atrial fibrillation: 5 mg bid
2.5 mg bid if 2 out of the 3: age over 80, creatine >1.5, weight less than 60 kg – contraindicated with CrCl <15
Drug-drug interaction: CYP 3A4 agents (azole antifungals (except fluconazole) or HIV-protease inhibitors) – reduced dose to 2.5 mg bid
Does not effect INR – use anti-Xa or specific levels to monitor
Reversal agents: PCC 50 units/kg or andexanet 400 mg IV bolus and then 4 mg/min for 120 minutes (if 10 mg apixaban dose within 8 hours, then 800 mg IV bolus followed by 8 mg/min for 120 minutes)
Betrixaban
Pharmacology
Time to maximum concentration: 3–4 hours
Half-life: 19–27 hours
Renal elimination: 20%

(continued)

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T. G. DeLoughery (ed.), *Hemostasis and Thrombosis*,
https://doi.org/10.1007/978-3-030-19330-0_24

Table 24.1 (continued)

Dosing
Prophylaxis: First day 180 mg, then 80 mg daily for 35–42 days
Drug-drug interaction: P-gp inhibitors – cut dose by 50%
Does not affect INR/aPTT – use anti-Xa or specific levels to monitor
Reversal: PCC 50 units/kg
Edoxaban
Dosing
Prevention: 15 mg/day
Thrombosis therapy: 60 mg/day or 30 mg/day if weight <60 kg, CrCl 30–60, or on strong P-gp inhibitors
Stroke prevention in atrial fibrillation: 60 mg/day or 30 mg/day if weight <60 kg, CrCl 30–60, or on strong P-gp inhibitors
Drug-drug interactions: dose reduced 50% – verapamil, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole, or itraconazole. Contraindicated – protease inhibitors and cyclosporine
Affects INR – use anti-Xa or specific levels to monitor
No specific antidote: PCC 50 units/kg
Rivaroxaban
Pharmacology
Time to maximum concentration: 2–4 hours
Half-life: 5–9 hours
Renal elimination: 66%
Dosing
Prophylaxis 10 mg qD
Therapy venous thrombosis: DVT 15 mg BID × 3 wks and then 20 mg/day, contraindicated CrCl <30
Stroke prevention in atrial fibrillation 20 mg/day – dose reduced to 15 mg/day CrCl 50–15
Drug-drug interaction: CYP 3A4 agents (azole antifungals (except fluconazole) or HIV-protease inhibitors)
Affects INR – use anti-Xa or specific levels to monitor
Reversal Agents – PCC 50 units/kg or andexanet 800 mg IV bolus and then 8 mg/min for 120 minutes (if >8 hours since dose, then 400 mg IV bolus followed by 4 mg/min for 120 minutes)

General Considerations

The advantage of the DOACs are no food interactions, fewer drug interactions, and no need for monitoring in most patients. However, there are certain caveats to use. One is they are absolutely contraindicated in patients with mechanical cardiac valves. The other is being fixed-dose drugs, they need to be used with caution with extremes of weight (see Chap. 28). Finally, these drugs are more expensive than warfarin, and this can be an issue for many patients.

Thrombin Inhibitor: Dabigatran

Generation of thrombin is a pivotal step in hemostasis. Thrombin not only cleaves fibrinogen into fibrin to form a thrombosis; it also activates platelets and many procoagulant factors including V, VIII, XI, and XIII. Thus, it represents a potent target for antithrombotic agents. Clinical studies of the direct thrombin inhibitor ximelagatran provided proof that novel oral anticoagulants could replace warfarin in therapy of thrombosis, but a high incidence of liver toxicity kept this drug off the market. Dabigatran is a direct thrombin inhibitor that has been tested in phase III trials to be effective for stroke prevention in atrial fibrillation and for venous disease prophylaxis and therapy.

Dabigatran reaches a peak activity after 2–3 hours after ingestion with a half-life of 12–14 hours. Dabigatran is 80% renally excreted, so for patients with creatinine clearances less than 30 ml/min, a lower dose should be used. It does not require activation by cytochromes, but its metabolism is affected by P-glycoprotein (P-gp) interactions.

For stroke prevention, the dosing is 150 mg bid. In countries where the 110 mg dose is available, this dose bid is often used for patients felt to be at higher risk of bleeding such as the frail elderly. In the United States, a 75 mg dose is approved for patients with creatine clearances between 30 and 15 ml/min. For prevention of venous thrombosis after orthopedic surgery, the dose is 220 mg daily to 150 mg in patients with creatine clearances of 15–30 ml/min. Therapy of acute venous thrombosis is 150 mg bid after patients have received an initial 5 days of low-molecular-weight heparin.

Drug interactions are with agents that are strong inhibitors of P-gp such as dronedarone or ketoconazole, especially in the setting of renal disease.

Studies have shown the bleeding risks of dabigatran are the same as warfarin with two exceptions. In atrial fibrillation patients with risk of gastrointestinal bleeding is higher, but the risk

of intracranial hemorrhage is lower. It does appear that dabigatran – like other thrombin inhibitors – has a slight risk of myocardial infarctions (relative risk 1.3 – an absolute risk increase 0.2–0.3%). The other notable side effect is that 15% of patients will complain of dyspepsia.

The aPTT is sensitive to dabigatran – usually peak levels are twice normal controls and trough 1.2–1.5 times control. Animal studies suggest reversal of anticoagulant effect can be achieved with use of prothrombin complex concentrates 50 units/kg. A specific neutralizing antibody – idarucizumab – is approved for reversal. The dose is 5 g IV for life-threatening bleeding. In patients with renal disease, a thrombin time should be checked after the idarucizumab dose to ensure complete reversal. Dabigatran can also be dialyzed off, but this seems impractical for most acute bleeding issues.

For surgeries dabigatran is held for 48 hours before procedures and 3–4 days if there is renal impairment.

Factor Xa Inhibitors

Factor Xa is responsible for generating thrombin. Inhibition of coagulation at this step prevents thrombin generation and its powerful positive feedback for coagulation. Animal studies suggested that Xa inhibitors also can be inhibited by prothrombin complex concentrates dosed at 50 units/kg. A specific antidote – andexanet – for Xa inhibitors has been approved for use. Andexanet is a modified factor Xa that cannot support coagulation but has a higher affinity for Xa inhibitors and neutralizes the anticoagulant effect of these drugs. The dose is dependent on both the anticoagulant used and time from last dose (Table 24.1). There may be a prothrombotic effect, so feasible patients should resume anticoagulation once they are stable.

Apixaban

Apixaban is a factor Xa inhibitor that is 66% bioavailable and has a peak onset of action in 1–3 hours after ingestion with a half-life of 8–15 hours. It is only ~25% renally excreted but is metabolized by CYP 3A4 and P-gp. Apixaban has been shown to be effective for prevention and treatment of venous thromboembolic diseases as well as stroke prophylaxis in atrial fibrillation. Studies have shown that rates of bleeding – including intracranial hemorrhage – are decreased with apixaban with no other apparent side effects.

Dosing for venous thromboembolic prevention is 2.5 mg bid. For treatment of acute venous thrombosis, a higher initial dose is used – 10 mg bid times for 1 week and then 5 mg bid. Six to 12 months after the thrombosis, the dose can be cut to 2.5 mg bid. For stroke prevention in atrial fibrillation, the dose is 5 mg bid – 2.5 mg bid if the patient has two or more of these risk factors: age over 80, creatinine over 1.5 mg/mL, or weight less than 60 kg.

Only drugs that are strong inhibitors of both CYP 3A4 and P-gp interfere with apixaban metabolism. These would be azole antibiotics and HIV antiviral agents. For patients taking 5 mg bid, one would need to cut the dose in half to 2.5 mg bid.

Apixaban does not affect classic tests of hemostasis (INR and aPTT) but can be measured using anti-Xa assay. Given the wide availably of this test once standards are made, there should be widespread availability of specific assays.

For surgery apixaban is held for 48 hours and for patients with renal impairment 72 hours.

Betrixaban

This Factor Xa inhibitor is 47% bioavailable with a peak onset in 2–3 hours. Its two unique features are a long half-life of 19 hours and minimal renal excretion. Another potential advantage is the lack of metabolism by CYP3A4. Betrixaban has been the subject of few clinical studies and is currently approved for prevention of thrombosis in medical patients. Dosing is a 160 mg dose on the first day followed by 80 mg daily for 35–42 days. If patients are on P-gp inhibitors, the dose should be halved. The dose should be also halved if the creatinine clearance is less than 30 ml/min.

Edoxaban

Edoxaban is 45% bioavailable and has a peak onset of action in 1–1.5 hours with a half-life of 9–11 hours. It is 33% renally excreted. Clinical trials show effectiveness in the treatment and prevention of venous thromboembolism plus stroke prevention in atrial fibrillation.

30 mg daily of edoxaban is the dose for prevention of venous thrombosis. For therapy the dose is 60 mg daily with a dose reduction to 30 mg for patients with creatinine clearance between 30 and 60 min/ml, weight less than 60 kg, or on P-gp agents. Like dabigatran, in clinical trials edoxaban was started after 5 days of parenteral heparin in patients with acute venous thrombosis.

As noted above, drug interactions with edoxaban are with the P-gp inhibitors, and the dose should be reduced by 50% when taking verapamil, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole, or itraconazole. The use of the P-gp inhibitors protease inhibitors and cyclosporine is contraindicated.

Edoxaban dose affects the INR, and this can be used to determine if there is a significant drug effect. For surgery drug should be held for 24–48 hours depending on the bleeding risk of surgery.

Rivaroxaban

Rivaroxaban is readily absorbed, being 80–100% bioavailable, and has a half-life of 5–9 hours. It is metabolized by cytochrome CYP 3A4 and P-gp. It has been shown to be effective for prevention and treatment of venous thromboembolic diseases as well as stroke prophylaxis in atrial fibrillation and acute coronary syndromes. Besides bleeding there appears to be no unique side effects of rivaroxaban.

The dose for prevention of venous thrombosis is 10 mg daily. For treatment of venous disease, a higher initial dose is used for acute events 15 mg bid for 3 weeks and then 20 mg daily. Six to 12 months after the thrombosis, the dose can be cut to 10 mg daily. For stroke prevention in atrial fibrillation, the dose is 20 mg daily – 15 mg for patients with creatine clearances between 50 and 15 ml/min.

Like apixaban, drugs that are strong inhibitors of both CYP 3A4 and P-gp – azole antibiotic and HIV antiviral agents – interfere with rivaroxaban metabolism.

Rivaroxaban does affect the protime and INR so these can be used to detect drug effect. Like apixaban, soon specific monitoring should be available via anti-Xa levels.

For surgery rivaroxaban is held for 24–48 hours for patients with renal impairment.

Diseases Where the Direct Oral Anticoagulants Have Been Studied

Atrial Fibrillation

For stroke prevention in atrial fibrillation, apixaban and dabigatran have shown superiority over warfarin in stroke prevention, while edoxaban and rivaroxaban are non-inferior. All showed decreased rates of intracranial hemorrhage. Apixaban has also been shown to be superior to aspirin with no worsening of bleeding. The direct agents also have the advantage of no monitoring and much reduced drug interactions.

Prevention of Venous Thrombosis

For orthopedic thrombosis prevention in hip and knee replacement, apixaban and rivaroxaban have been shown to be superior to enoxaparin with dabigatran being non-inferior. Edoxaban has been tested in a Japanese orthopedic population and also shown effective. The direct agents have been widely accepted for this indication due to ease of use (oral and not injection) and cost.

Treatment of Venous Thrombosis

All agents have been shown to be effective in treatment of venous thrombosis with the three Xa inhibitors shown to have less bleeding. In clinical

trials apixaban and rivaroxaban were used as initial therapy of acute thrombosis – using higher doses at the initiation of therapy – while dabigatran and edoxaban used an initial course of heparin. Three agents – apixaban, dabigatran, and rivaroxaban – have also been studied for long-term therapy of venous thromboembolism with all being safe and effective.

Cancer Patients

Previous clinical trials have shown that warfarin was inferior to LMWH in cancer patients. Despite recommendations for LMWH, only a minority of cancer patients received this agent long term for treatment of venous thrombosis. There is increasing data that DOACs as just as – if not more – effective as LMWH in treatment of cancer related thrombosis and appear to be as safe. The only exception is that patients with upper gastrointestinal cancers appear to have an increased rate of bleeding with DOACs compared to LMWH.

Acute Coronary Syndrome and Coronary Arterty Disease

Three direct oral anticoagulants – apixaban, dabigatran, and rivaroxaban – have been tested in patients with acute coronary syndromes. All had shown increased rates of bleeding, but the low-dose rivaroxaban 2.5 mg bid did show improved cardiac outcomes but at the cost of increased bleeding including intracranial hemorrhage.

There are studies with apixaban, dabigatran, and rivaroxaban showing that when combined with a P2Y12 inhibitor such as clopidogrel in patients with both recent coronary stents and atrial fibrillation, the rates of bleeding were decreased with minimal loss of antithrombotic effectiveness compared to “triple therapy” with warfarin/aspirin/P2Y12 inhibitors. This may be a useful option for most patients except those at high risk of stent thrombosis such as those with recent myocardial infraction and complex coronary anatomy.

Monitoring

Although designed to be used without monitoring, there are occasions when it will be useful to know if patients have a measurable drug effect. One indication is with the patients with recurrent thrombo-embolic event to see if they have been compliant. Another is a bleeding patient or a patient needing to go to surgery to see if there is a persistent drug effect. Currently for dabigatran, the PTT is the best test. Some reference laboratories have used a modified thrombin time to quantitate levels. For rivaroxaban, the pro-time/INR is used, but for apixaban neither the PTT nor INR appears to be sensitive. As noted above, soon specific levels should be obtainable by using anti-Xa levels.

Suggested Reading

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