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Dabigatran, a New Oral Anticoagulant & Its Role in Clinical Practice

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INTRODUCTION

Warfarin, a vitamin K antagonist, has been the mainstay of oral anticoagulant therapy for more than 60 years. Warfarin acts to antagonize the effect of vitamin K required for the synthesis of active clotting factors II, VII, IX, and X and anticoagulant proteins C and S. Antagonism of vitamin K reduces the amount of these clotting factors, thereby producing anticoagulation. Although warfarin is effective in prevention and treatment of most thrombotic disease, it has limitations in relation to titrating a safe and therapeutic anticoagulation level. It requires adjusted and variable doses dependent upon INR. It also has a narrow therapeutic range. To achieve the desired therapeutic level, warfarin requires frequent monitoring and takes about 5 days for a stable antithrombotic effect to be achieved. Warfarin is influenced by several factors such as age, genetic status, medications, diet, and some medical conditions that contribute to variability of patient response. Although the safe use of warfarin is a challenge, there has not been a market competitor for oral long-term anticoagulation until recently.

Three new oral anticoagulants, dabigatran, apixaban and rivaroxaban are in the late stages of development and are being studied for prevention and treatment of venous thrombosis, acute coronary artery syndrome and prevention of stroke in patients with atrial fibrillation. In the United States, to date, only dabigatran has been approved for treatment and stroke prevention in patients with atrial fibrillation.

Dabigatran (Pradaxa) is a new oral direct thrombin inhibitor approved by the FDA in October 2010.

INDICATIONS

Dabigatran is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

DOSAGE & ADMINISTRATION

- 150 mg PO BID in patients with creatinine clearance >30 ml/min.
- 75 mg PO BID in patients with creatinine clearance 15-30 ml/min.
- If creatinine clearance < 15 - not indicated

Instruct the patient to swallow the capsule whole with or without food. The missed dose should be skipped if it cannot be taken at least 6 hours before the next dose.

CLINICAL PHARMACOLOGY

Dabigatran inhibits free and clot-bound thrombin, and thrombin induced platelet aggregation. Elimination of dabigatran occurs predominantly via the kidneys. Peak concentration after oral administration is in 1-2 hours. Half life is 12-17 hours in healthy subjects, but may be longer depending on renal function. Dabigatran has little interaction with other drugs or food.

ADVERSE REACTIONS

- Bleeding.
- GI side effects: epigastric discomfort, abdominal pain, dyspepsia, burning or nausea.

Bleeding and GI side effects are the most frequent reasons for discontinuing dabigatran.

MONITORING

Monitoring is not required for most patients; however, in certain clinical circumstances monitoring may be needed.
Dabigatran is eliminated by the kidneys, so in patients with renal insufficiency, dabigatran monitoring may be

needed. In addition, monitoring may be needed in patients who have recurrent TIA/CVA symptoms despite a therapeutic dose of dabigatran and to evaluate compliance. Monitoring may also be needed in patients with bleeding and to provide guidance in management of overdose. There is no antidote to dabigatran. In the event of hemorrhagic complications medication should be discontinued and supportive treatment should be initiated. Appropriate monitoring may help guide therapy.
It is recommended to discontinue dabigatran 1-5 days prior to surgery or invasive procedure depending on creatinine clearance; however monitoring of dabigatran effect prior to surgery may also be needed. Additionally, dose adjustment is not recommended based on the patient's weight; however monitoring may be reasonable in obese or malnourished patients.

EFFECT ON COAGULATION TESTS

- The aPTT and Thrombin Time are prolonged in patients on dabigatran; however, their correlation with thrombosis and bleeding has not yet been clearly established.
- Changes in aPTT or TT in monitoring treatment should be interpreted with great caution.
- INR is also prolonged in patients on dabigatran.
- Ecarin clotting time (ECT) shows a close linear correlation with the plasma concentrations of direct thrombin inhibitors, including dabigatran. However, this test is not generally available in hospital laboratories. ECT has been used largely as a research tool.

ASSAYS FOR MONITORING

Monitoring is performed using a thrombin time coagulation assay that provides a **quantitative assessment of dabigatran concentrations** in human citrated plasma. The assay is calibrated with the direct thrombin inhibitor, dabigatran. Briefly the diluted test plasma is mixed with normal pooled human plasma and clotting is initiated by the addition of human thrombin. The clotting time measured is directly proportional to the concentration of dabigatran in the tested plasma. This assay covers a stable, linear working range for Dabigatran of 0.05 to 0.5 ug/ml. It is important to note that the presence of heparin or of other anti-thrombin substances, different from dabigatran, may interfere with the assay.

OVERDOSE

- There is no antidote to dabigatran.
- Dabigatran primarily excreted from the urine, therefore in case of bleeding, there is a need to maintain adequate diuresis.
- Dabigatran can be dialyzed with removal of about 60% of drug, but data are limited.
- Treatment is supportive, with replacement of blood products in case of bleeding and correcting other coagulopathies.
- Measurement of dabigatran concentration, aPTT or ECT may guide therapy.

SUMMARY

Dabigatran is a new oral anticoagulant drug that has been approved in the US for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation. Studies for use of this drug in treatment and prevention of DVT/PE show good effectiveness and safety profile. Other oral direct thrombin inhibitors are also in their final stages of development. These new agents may soon provide an alternative choice of anticoagulation. Advantages of these drugs may include: 1. A wider therapeutic index than warfarin, thus reducing the risk of hemorrhage, 2. A rapid onset of action, which may eliminate the need for overlap with parenteral anticoagulants, 3. Little interaction with other medications and food, and 4. No need for monitoring or dose adjustment. Limitations for use of these agents, however, include: high cost, renal elimination, which prevents their use in patients with severe renal impairment or on dialysis, and finally, lack of an available antidote, which makes it difficult to support patients with bleeding.

REFERENCES

1. Connolly SJ, Ezenkowitz MD at all; RE-LY Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. NEJM. 2009; 361(12):1139-1151
2. Pradaxa. [Full prescribing information], 10/2010.
3. Lindahl TL, Baghaei F at all; Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost. 2011 Feb 1; 105(2):371-8.

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