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“New Oral Anticoagulants”

April 2016

For many years warfarin was the primary choice for anticoagulant therapy. Now there are a number of newer oral anticoagulants (NOACs) that have been approved by the FDA. In this lesson we review these. Our goal is to discuss therapeutic options. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 707-000-16-004-H01-P for pharmacists & 707-000-16-004-H01-T for technicians. Participants completing this lesson by March 31, 2019 may receive full credit. Release date April 1, 2016.**



To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

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The objectives of this lesson are such that upon completion participants will be able to:

Pharmacists:

1. Describe the candidates for use of oral anticoagulants.
2. Explain the mechanism of action for the common oral anticoagulants.
3. List risk factors that lead to cardiovascular disease.
4. Discuss adverse reactions & contraindications associated with oral anticoagulants.
5. Compare the action of warfarin to that of the new oral anticoagulants.
6. Describe methods to reverse the action of warfarin and dabigatran.

7. List advantages of new oral anticoagulants over warfarin.

Technicians:

1. List risk factors that lead to cardiovascular disease.
2. Discuss adverse reactions & contraindications associated with oral anticoagulants.
3. Describe methods to reverse the action of warfarin and dabigatran.
4. List advantages of new oral anticoagulants over warfarin.

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OVERVIEW

Blood consists mainly of red cells that transport oxygen to the body, white blood cells, that protect the body from infection, and platelets that play an important role in the clotting process. Platelets are the smallest of these. They are colorless, have no nuclei, but have a sticky surface and are found in the bone marrow as a result of fragmentation of large nucleus cells. Once in the blood, they remain in the body for about 5-10 days after which they enter the spleen where they are destroyed by phagocytes. The main function of the platelets is to contribute to blood clotting by sticking to the lining of damaged blood vessels. When a blood vessel is injured, a signal is transmitted to the platelets which respond by transforming to the active form and rushing to the site of injury. Once there, the platelets develop elongated hair-like structures.

Candidates for the intake of anticoagulants include those who:

1. Have had myocardial or cerebral infarctions.
2. Have experienced or are at risk of deep vein thrombosis (DVT) or pulmonary embolism (PE).
3. Experience atrial fibrillation (AFib).
4. Have undergone surgery, especially orthopedic (hip or knee replacements)--- the blood becomes more prone to clotting.
5. Suffer from angina pectoris, a condition that causes clotting of blood in coronary arteries.
6. Have stents inserted into coronary arteries.

STATISTICS

According to statistics compiled by the American Heart Association, the Center for Disease Control (CDC), the National Institutes of Health (NIH) and other governmental sources, it is stated that cardiovascular disease is the leading cause of death worldwide—accounting for 17.3 million deaths annually. The number is expected to reach 23.6 million by 2030. In 2011, about 787,000 Americans died from heart disease, stroke, and other cardiovascular diseases. Approximately 375,000 die every year in the U.S. from all heart diseases alone. Cardiovascular diseases are responsible for more deaths than all forms of cancer combined. About 85.6 million people in the U.S. suffer from some form of cardiovascular disease, or they are living with the after-effects of heart attacks or strokes. From an economic perspective, cardiovascular disease and stroke are costing Americans over \$320.1 billion every year. That includes health expenditures and lost productivity. Of the heart attacks suffered in the U.S. each year, about 120,000 die patients die.

In 2010 stroke occurred in 33 million persons worldwide. It is the second leading cause of death worldwide after heart disease. In the U.S. stroke kills approximately 127,000 people each year. Every 4 minutes an American will die of stroke. African Americans have nearly twice the risk of stroke than others, and a much higher death rate. About 795,000 patients have a stroke in the U.S. each year, and this is in spite of the fact that over the past 10 years the death rate from stroke has fallen about 35%.

RISK FACTORS

The following are the risk factors of heart, stroke and cardiovascular disease:

1. Tobacco, including second hand smoke: about 20% of men, 16% of women, and 16% of students in grades 9 - 12 in the U.S. are smokers.
2. Physical activity: about 31% of adults in the U.S. do not participate in physical activity.
3. Healthy diet: less than 1% of adults in the U.S. meet the American Heart Association definition for ideal, healthy diet.
4. Overweight/obesity: it has been estimated that over 159 million American adults are overweight or obese.
5. Cholesterol blood level: about 34% of Americans have total cholesterol higher than 200 mg/dL.
6. High blood pressure: about 33% of American adults (80 million) have high blood pressure and half of these do not have it under control.
7. Diabetes: about 21 million adult Americans (9%) have been diagnosed with diabetes and about 33% have pre-diabetes.

ANTICOAGULANTS

Clopidogrel (Plavix®)

Clopidogrel is an antiplatelet medication intended to reduce the risk of clot formation in patients who suffer from coronary artery disease (CAD), peripheral artery disease (PAD) and cerebrovascular disease. Additionally, it is used in patients who have had myocardial infarction (heart attack) or stroke. CAD involves narrowing of the coronary arteries that deliver oxygen and nutrients to the heart, and also vessels that remove deoxygenated blood from the heart muscle—which are known as cardiac veins. Blocking the arteries results in myocardial

infarction. PAD involves narrowing of the arteries in the body, other than those located in the heart, and most commonly in the legs and arms. Cerebrovascular disease, or stroke, occurs following the narrowing of the arteries that supply the brain with oxygen. Anticoagulants are used to treat chest pain caused by new heart attacks, unstable angina, as well as prevention of clot formation after certain procedures such as insertion of cardiac stents. These drugs are also employed in the prevention of heart attacks and strokes in patients who suffer from atrial fibrillation (AFib). Patients should be informed that such medications can increase the vulnerability to bleeding from both minor and major injuries. Internal bleeding from the stomach or intestines may occur. Drinking alcohol should be avoided due to gastric irritation that may trigger bleeding.

Clopidogrel is an orally administered anticoagulant that prevents blood from clotting in diseased blood vessels that are narrowed and hardened as a result of accumulation of fibrous tissue, fatty deposits (plaques) made of cholesterol and other cellular products. It is a thienopyridine derivative that acts as a selective and irreversible inhibitor of chemoreceptor P2Y₁₂ which is an adenosine diphosphate (ADP) found on the surface of blood platelets. P2Y₁₂ plays an important role in platelet aggregation (sticking together) and coagulation. The active metabolite of clopidogrel binds to P2Y₁₂. Since clopidogrel is a prodrug, it is converted or metabolized within the body to a therapeutically active metabolite that inhibits platelet aggregation. The enzymes CYP450 including CYP2C19 are responsible for the metabolism process in the liver which results in the production of active metabolites. The active metabolites will inhibit the binding of ADP to the P2Y₁₂ receptor leading to inhibition of platelet aggregation. The inhibition is irreversible and as a result platelets that interact with clopidogrel metabolites will be influenced for 7 to 10 days. This is the life expectancy of platelets. Clopidogrel may be therapeutically ineffective in individuals who are incapable of converting the drug into its active metabolites. In 2012 the FDA issued a warning that patients whose system is deficient in CYP2C19 metabolite may not obtain the anticoagulant activity of clopidogrel. By blocking platelet aggregation, clopidogrel can prevent formation of blood clots and keep blood flowing normally within the arteries.

There seems to be no change in the effect of clopidogrel on platelet aggregation when given to patients 75 years of age and over as well as to those with hepatic impairment. The therapeutic activity is reduced by 25% when given to patients with renal impairment. The drug is well absorbed following oral intake. Its metabolism is achieved by a pathway mediated by esterase resulting in the formation of inactive carboxylic acid derivatives. The other pathway is mediated through the action of cytochrome P450 enzymes (CYP2C19, CYP2C9, CYP2C10, CYP2C8 and CYP1A2). Clopidogrel is excreted mainly through the urine and feces. Its half-life is about 6 hours; the active metabolite's is approximately 30 minutes. Clopidogrel can be taken with or without food and preferably around the same time each day.

Adverse effects include: an increase in GI bleeding risk (especially when administered with aspirin), nosebleed, bruising, hematuria, rash, difficulty in breathing, itching, abdominal pain, headache, dizziness, tarry stool, bloody vomit and changes in vision. The drug is contraindicated in individuals with conditions that have bleeding tendencies such as peptic ulcer, hypersensitivity, concurrent use with proton pump inhibitors such as omeprazole or esomeprazole as both drugs can diminish the antiplatelet activity of clopidogrel. Clopidogrel, as well as the thienopyridines, can increase the risk of bleeding during surgery. As a result,

the drug should be discontinued five days prior to surgery. Grapefruit (or the juice) should be avoided. The drug may interact with the Furanocoumarins in the grapefruit. These block the enzyme that normally metabolizes clopidogrel, thereby causing unwanted elevation of the drug level in the blood.

Pregnancy category of the drug is B, indicating that animal studies have shown no evidence of harm to the fetus; however, there are no adequate studies in pregnant women indicating an adverse effect. Clopidogrel can interact with a large number of prescription, OTC, and herbal products. Some of these interactions are not clinically significant. Certain antifungals and NSAIDs should not be taken with clopidogrel. Stent patients should routinely avoid aspirin plus clopidogrel.

The dose varies from one patient to another. The number of daily doses, the interval between doses, and duration of the therapy is determined by the health care provider. The adult dose for the prevention of clots is usually 75 mg once daily. In certain cases a loading dose of 300 mg may be given followed by a daily dose of 75 mg. In certain situations, aspirin in 75-325 mgs once daily may be given in combination with clopidogrel. A missed dose of the anticoagulant should be taken immediately, but if it is less than 12 hours before the next dose, the missed dose should not be taken and normal dosing should be resumed. Like other antiplatelet drugs, the use of clopidogrel should not be discontinued without the advice of the health care provider as this may increase the risk of heart attacks and blood clot formation.

Dabigatran (Pradaxa®)

Dabigatran is a member of new oral anticoagulant (NOACs) that have become available as an alternate to warfarin. It acts through direct competitive inhibition of thrombin during the final step of the coagulation cascade. Thrombin plays an important role during coagulation cascade which consists of a series of steps in a particular order following the exposure of blood to collagen fiber and clotting factors in the injured blood vessel. The cascade ultimately transforms blood from liquid to a semisolid state (clot). Thrombin is a serine protease enzyme that causes cleavage needed to convert the protein fibrinogen to fibrin that catalyzes coagulation-related reactions and promotes normal blood clotting.

As a direct thrombin inhibitor, dabigatran blocks the action of the enzyme thrombin and inhibits cleavage of fibrinogen to fibrin, thus preventing clot formation. The drug is used to reduce the risk of strokes and systemic embolism in patients with atrial fibrillation (AFib) not caused by heart valve problems (nonvalvular). It is also used in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of parenteral anticoagulants. DVT is a blood clot that usually occurs in the legs, but it could be encountered in any part of the body. If the clot breaks off, fragments may travel with the bloodstream and lodge in the lungs, causing potentially fatal PE. It is estimated that more than 350,000 people develop DVT and PE annually. AFib is an irregular and usually rapid heartbeat that causes poor blood flow and may result in an increase in the risk of clot formation leading to heart attacks, strokes, heart failure and other cardiac complications. AFib affects over 3 million Americans annually.

Dabigatran was approved by the FDA as the first anticoagulant alternative to warfarin to reduce the risk of strokes and nonvalvular AFib. Later on it was employed for treating DVT and PE. The drug is available in 2 dosing strengths for nonvalvular AFib. The dose depends on the patient's kidney function. Therefore, some blood testing may need to be performed periodically.

The main adverse effect of dabigatran is an increase in the risk of bleeding tendencies. In case of appearance of symptoms such as bleeding from the gums, nosebleed, internal bleeding, pink or brown urine, red or tarry stool, abdominal distress, bruising, coughing or vomiting of blood, severe headache and dizziness, a health provider should be consulted. Sudden discontinuation or missing a dose may increase the risk of thrombotic event. In case of missed dose the information procedure as with clopidogrel should be followed. Like with all anticoagulant users, it is recommended that a medical identification card or bracelet be carried or worn indicating that the patient is on anticoagulants. Patients who are physically active in indoor or outdoor sports should take special care not to cause any injuries. Pregnant women or women who plan to become pregnant within three months or who are breast feeding need to consult with a physician or a pharmacist. Patients who are allergic to the drug should indicate this to the physician. Contraindications include: active pathological bleeding, allergic reactions such as anaphylaxis, and presence of an artificial heart valve which can facilitate an increased risk of thromboembolism.

Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that acts by inhibiting Factor Xa (FXa) which plays a vital role in the coagulation cascade. It does not require a cofactor such as anti-thrombin III to exert its action. It has no direct antiplatelet activity but indirectly inhibits platelet aggregation caused by thrombin. Rivaroxaban's direct inhibitory effect results in preventing blood coagulation and clot formation. It has a rapid onset of action. Its anticoagulation effect begins 2 to 4 hours after its intake and lasts for 8 to 12 hours. The normal activity of FXa returns after 24 hours, and, as such, a once daily dose is safe and effective. Rivaroxaban is used to reduce the risk of strokes and systemic embolism in patients with nonvalvular AFib. It is also used in reducing the risk and treatment of DVT and PE, especially in preventing DVT which could lead to PE in patients undergoing knee or hip replacement surgery. Like with other anticoagulants the use of NSAIDs, aspirin, antiplatelet medication and other anticoagulants should be avoided. Premature discontinuation or frequently missing doses may increase the risk of clot formation and subsequent heart attacks and strokes. It can be used during pregnancy, if benefits outweigh the risk to mother and fetus. Rivaroxaban is considered pregnancy category C. Excretion in human milk has not been determined. The drug is available in 10 and 20 mg tablets. The average dose for nonvalvular AFib is 20 mg daily preferably in the evening. For the treatment of PE and DVT the dose is 15 mg every 12 hours for 24 days, then 20 mg daily for 6 months taken with or without food. It should be taken at the same time each day. Patients who plan to undergo spinal or epidural procedures while on rivaroxaban should relay this to the physician as such procedures may increase the risk of bleeding on or near the spine. Side effects include allergic reactions such as rash, hives, itching, difficulty in breathing, swelling of the lips or tongue, bloody or tarry feces, dark urine, coughing of blood, slurred speech, confusion, bleeding gums and bowel or bladder dysfunction. The drug was approved by the FDA to prevent DVT, for patients undergoing knee or hip replacement surgery, on July 1, 2011. In November of the same year the FDA approved its use in the prevention of strokes in patients who suffer from nonvalvular AFib.

Apixaban (Eliquis®)

Apixaban is an orally administered anticoagulant intended to reduce the risk of strokes and systemic embolism in patients with nonvalvular AFib. It acts as a direct Factor Xa inhibitor. It reduces the risk of recurring DVT and PE after initial therapy. The recommended dose for the prevention of DVT following hip and knee replacements is 2.5 mg twice daily for 7 days followed

by 5 mg taken twice daily. It is available in 2.5 and 5 mg tablets. The main contraindications are active pathological bleeding and severe hypersensitivity. It can cause serious and potentially fatal bleeding. It is not recommended for use in the presence of prosthetic heart valves. Pregnant and nursing mothers should consult with a health care provider before use. Discontinuation of apixaban during therapy without adequate continuous anticoagulation may place the patient at increased risk of stroke, heart attack and systemic embolism in those with nonvalvular AFib. However, the drug should be discontinued at least 48 hours prior to surgery or invasive procedures with high or moderate risk of bleeding, and 24 hours before surgery or invasive procedures with low risk. Dosage should be adjusted for patients with liver or kidney impairment. Side effects include increased risk of bleeding. This possibility increases when used with other medications such as other anticoagulants, heparin, aspirin and NSAIDs. On August 21, 2014, apixaban was approved by the FDA for treating recurring DVT and PE. Furthermore, in December 2014 it was approved for the prevention of DVT and PE in patients who had recently undergone knee or hip replacements.

Edoxaban (Savaysa®)

Edoxaban was approved by the FDA in January 2015 for treating DVT and PE in patients who had been treated with parenteral anticoagulants for 5 to 10 days and to reduce the risk of strokes and systemic embolism in individuals with nonvalvular AFib. The drug acts by inhibiting factor Xa in coagulation cascade, prothrombinase and thrombin-induced platelet aggregation. The drug should not be used in patients with nonvalvular AFib whose creatine clearance is more than 95 mL/minute. Warning about discontinuation of intake of edoxaban is similar to other anticoagulants. Side effects include nosebleed, reduction of menstrual bleeding, difficulty breathing, weakness, bloody or tarry feces, rash and vomiting of blood. It is available in 15 mg, 30 mg and 60 mg tablets.

REVERSAL (ANTIDOTE) FOR ANTICOAGULANTS ACTION

Prior to the discovery of new oral anticoagulants (NOACs) the only oral coagulant that was available for treatment and prevention of thromboembolism was warfarin. This drug acts by antagonizing recycling vitamin K and thus depleting active vitamin K. The vitamin is essential and needed in the coagulation process. Depletion of vitamin K caused by warfarin can be reversed (antidote) in cases of life-threatening or uncontrolled bleeding that occurs as a result of overdose. Furthermore, patients on chronic warfarin therapy may require urgent reversal of anticoagulation. Thus, vitamin K is injected when there is a need for a rapid reversal of anticoagulation caused by warfarin (antidote). The drawback of vitamin K is its slow onset of action. The process can take 4 - 6 hours.

Unlike warfarin, the main disadvantage of the use of other oral anticoagulants is the absence of a drug that reverses the anticoagulation activity (antidote) in case of an emergency. The only exception is dabigatran. On October 16, 2015 the FDA granted an accelerated approval for the use of idarucizumab (Praxbind®) to reverse the anticoagulation action (antidote) of dabigatran.

Idarucizumab (Praxbind®)

Idarucizumab is a humanized monoclonal antibody used as an antidote to reverse the action of dabigatran in emergency cases such as excessive or uncontrolled bleeding. It is effective within minutes. Idarucizumab exerts its action by binding to dabigatran and its acylglucuronide metabolites. The binding effect of idarucizumab to dabigatran is much stronger than its binding

activity to thrombin, thereby, nullifying the anticoagulant effect. Idarucizumab is available in a 2-5 g/ml solution in a single dose vial for injection.

COMPARISON BETWEEN WARFARIN AND OTHER ORAL ANTICOAGULANTS

- Clopidogrel was approved by the FDA in 1997, dabigatran in 2010, rivaroxaban in 2011, apixaban in 2012, edoxaban in 2015 and warfarin in 1954.
- Clopidogrel is used for reducing the risk of clot formation in patients who suffer from CAD, PAD and cardiovascular disease as well as in patients who have had heart attacks or stroke.
- Dabigatran, rivaroxaban and apixaban are used for the prevention of stroke, heart attack or a systemic embolism in patients with nonvalvular AFib. They are approved for treating acute venous thromboembolism (VTE) and prevention of recurrent events.
- Rivaroxaban and apixaban are approved for prophylaxis of VTE in patients undergoing knee or hip replacement surgery.
- Edoxaban is approved for treating DVT and PE in patients who have been treated with parenteral anticoagulants for 5 to 10 days and to reduce the risk of stroke and systemic embolism in patients with nonvalvular AFib. However, the drug should not be used in patients with nonvalvular AFib whose creatinine clearance is more than 95 mL/minute.
- Warfarin has been used for stroke prevention in nonvalvular AFib, VTE prophylaxis, thromboembolism prevention in heart valve replacement and myocardial infarction.
- Only warfarin and dabigatran have antidotes.
- Bioavailability of dabigatran is 3-7%; 80-100% for a 10 mg/dose of rivaroxaban; 50% for apixaban; 2% for edoxaban; 50% for clopidogrel and 100% for warfarin.
- T_{max} for dabigatran is from 1-2 hours; for rivaroxaban from 2-4 hours; for apixaban from 3-4 hours; for edoxaban from 1-2 hours; for clopidogrel 7-8 hours, and for warfarin 4 hours but peak anticoagulant effect is delayed 72-96 hours.
- Protein binding of dabigatran is 35%; rivaroxaban 92-95%; apixaban 87%; edoxaban 10-14%, clopidogrel 98%; and warfarin 99%.
- Half-life of dabigatran is 12-17 hours; rivaroxaban 5-9 hours, but increases to 11-19 hours in the elderly; apixaban 12 hours; clopidogrel 6 hours and warfarin 40 hours.
- Mechanism of action of oral anticoagulants is as follows: dabigatran is a direct competitive inhibitor of thrombin; clopidogrel is a blocker of antiplatelet aggregation; apixaban, rivaroxaban and edoxaban are direct factor Xa inhibitors and warfarin is a vitamin K antagonist.
- Effect of food: clopidogrel, dabigatran, apixaban and edoxaban may be taken with or without food. Rivaroxaban in dose of 15-20 mg used to treat VTE and AFib should be taken in the evening with food. Warfarin should not be taken with vitamin K rich foods such as green leafy vegetables.
- Unlike warfarin, clopidogrel and NOACs need no routine PT/INR monitoring of anticoagulation blood levels. Prothrombin time (PT) is a test employed to determine the proper time it takes for blood to clot. It is utilized to check for bleeding problems as well as to determine whether an anticoagulant is functioning properly. PT is also referred to as INR test (International

Normalized Ratio).

It does not appear that one of the NOACs is superior over the other. However, all have advantages over warfarin.

SUMMARY

Blood clot formation in the arteries can lead to stroke, heart attacks and DVT. Cardiovascular disease is the leading cause of death worldwide. Warfarin has been in use as an anticoagulant since the 1950s and the only orally available therapy against blood clot formation until the 1990s. Even though it is inexpensive and effective in the prevention and treatment of thromboembolism, it has many drawbacks. It has been practically replaced by the new oral anticoagulants which are safer and more effective.

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Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?
- | | |
|--|--------|
| Describe candidates for use of NOACs | YES NO |
| Discuss adverse reactions associated with NOACs | YES NO |
| Compare warfarin to NOACs | YES NO |
| List advantages of NOACs over warfarin | YES NO |
| Describe methods to reverse action of dabigatran | YES NO |

Low Relevance 1 2 3 4 5 6 7 Very Relevant

3. Relevance of topic _____

4. What did you like most about this lesson? _____

5. What did you like least about this lesson? _____

Please Mark the Correct Answer(s)

- | | |
|--|--|
| <p>1. The anticoagulant activity of clopidogrel is due to:
 A. Inhibition of Vitamin K
 B. Inhibition of platelet aggregation
 C. Suppression of white blood cells
 D. Speeding of blood flow in arteries</p> <p>2. To become therapeutically active clopidogrel must be converted to its metabolite:
 A. True
 B. False</p> <p>3. The only NOAC whose activity can be reversed is:
 A. Rivaroxaban B. Apixaban
 C. Edoxaban D. Dabigatran</p> <p>4. Patients on NOACs are required to have routine PT blood tests.
 A. True
 B. False</p> <p>5. Thrombin is a serine protease enzyme that cleaves fibrinogen to fibrin.
 A. True
 B. False</p> | <p>6. Which of these acts by inhibition of Xa factor?
 A. Warfarin B. Dabigatran
 C. Rivaroxaban D. Idarucizumab</p> <p>7. Annually, approximately 125,000 Americans die of heart disease & the same number from strokes.
 A. True
 B. False</p> <p>8. Regular physical activity is NOT a risk factor for cardiovascular disease.
 A. True
 B. False</p> <p>9. Idarucizumab is a thrombin inhibitor.
 A. True
 B. False</p> <p>10. Which of the following drugs is a Vitamin K antagonist?
 A. Edoxaban B. Warfarin
 C. Rivaroxaban D. Idarucizumab</p> |
|--|--|

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