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June 2011 "Blood Thinning Drugs"



THIS MONTH *"Blood Thinning Drugs"*

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Two medications make up the practitioner's primary armamentarium as options for patients who require blood thinning drugs. Our goal in this lesson is to discuss these two drugs. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. **The program ID # for this lesson is 707-000-11-006-H01-P. Pharmacists completing this lesson by June 30, 2014 may receive full credit.**

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 the participant will be able to:

1. Define the term 'platelets,' & describe their role in clot formation.
 2. Describe hemostasis, thrombosis, embolus, thrombolysis, thrombogenicity, ischemia, MI & cerebral infarction.
 3. Relate the mechanisms of action of coumadin & clopidogrel.
 4. Define 'anticoagulant.'
 5. List the side effects associated with coumadin & clopidogrel.
 6. State the mechanisms of action of other anticoagulants.
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Bill Feinberg (bill@wfprofessional.com)

INTRODUCTION

Coumadin and clopidogrel are two drugs that belong to a group of medications known as anticoagulants. In the scope of this lesson we will discuss: platelets, hemostasis, coagulation, thrombosis, myocardial infarction, and indications for use of coumadin and clopidogrel, along with their mechanisms of action, and adverse effects.

PLATELETS

Platelets, or thrombocytes, are small, regularly shaped, colorless fragments of cells found in the bone marrow and derived from megakaryocytes. Formed as a result of stimulation of thrombopoietin, which is produced by the liver and kidneys, they enter the blood and remain there for about 10 days. Thereafter, they move into the spleen where they are destroyed by phagocytosis. Platelets play an essential role in blood coagulation by providing the necessary hormones and proteins that lead to clotting. Thrombocytosis is a condition that occurs when the number of platelets is greater than normal and may result in the formation of blood clots (thrombosis) that can block arteries and result in strokes, heart attacks, pulmonary embolism or blockage of blood vessels in any part of the body, especially the legs. Low platelet count (thrombocytopenia) can lead to bleeding.

HEMOSTASIS

This is a complex process that leads to stoppage of bleeding following damage to the endothelium layer of the blood vessel walls. There are three types of blood vessels: the **arteries**, **capillaries** and **veins**. The arteries transport blood from the heart to the body. The aorta is the largest artery, and it carries blood away from the heart. It branches to form arteries such as the carotid, subclavian, celiac, trunk, mesenteric and renal. The capillaries are small blood vessels that allow exchange of water, nutrients, oxygen and other chemicals between blood and body tissues. The function of veins, such as the subclavian, jugular, renal, iliac and vena cava, is to carry blood from the capillaries back to the heart. The term arterial

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indicates flow of blood away from the heart. The opposite is true for the term venous. Oxygen attached to hemoglobin is carried by blood for distribution to all body parts. Arterial blood pressure is normally around 120 mm Hg systolic (contraction of the heart) and 80 mm Hg diastolic (heart at rest). Venous pressure does not normally change, and is about 10 mm Hg.

The endothelial cells of intact blood vessels do not allow blood clot formation due to the release of tissue plasminogen activator and to inactivating thrombin and adenosine diphosphate (ADP). Moreover, they prevent platelet aggregation by secreting nitric oxide and prostacycline. When injury occurs to blood vessels, the body will react to prevent blood loss. In a healthy individual, hemostasis (or coagulation) begins immediately after an injury to the blood vessel and its endothelium. There are three basic mechanisms that work together to cause stoppage of bleeding:

1. Vasoconstriction at the site of injury: This process occurs as a result of the release of vasoconstrictors such as thromboxane.
2. Platelet plug formation: This step follows vasoconstriction. Injury causes the exposure of blood to collagen fiber in the blood vessels. This results in gathering of platelets at the wound to block blood flow by forming a plug at the site of injury. The platelets become active and release ADP and thromboxane causing the aggregation of more platelets around the wound.
3. Blood clotting: Blood clotting, or coagulation cascade, is a series of processes by the exposed collagen and clotting factors. The blood contains clotting factors that consist of a protein-phospholipid mixture, present in the inactive form, but are activated when blood vessels are injured. The activation process occurs in a step-wise manner. The completion of each step will activate another clotting factor until the conversion of fibrinogen to fibrin is complete. The first factor activates the second and the second activates the third until the process is complete. This sequence of reactions is known as clotting, or coagulation cascade. It ultimately transforms blood from liquid to a semisolid state (clot).

When blood is exposed to the air, platelets react with fibrinogen, an inactive precursor of fibrin, to form fibrin, a gristly protein that polymerizes to form a mesh which along with platelets forms a hemostatic plug or clot at the wound site. This process requires the presence of the enzyme thrombin, calcium, vitamin K and clotting factors. The function of calcium is to assist fibrin to form the web-like mesh that is stabilized by factor XII. The resultant fibrin net traps blood cells within it forming the clot that inhibits the flow of blood. The clot becomes hard and ultimately dries up to form a scab. In the presence of vitamin K and calcium deficiencies, clotting time becomes prolonged. Internal blood clots may occur as in bruises. A blood clot that forms inside a blood vessel is considered dangerous and can lead to death.

THROMBOSIS

Thrombosis is the presence or formation of a blood clot (thrombus, Greek for clumper or curd) inside a vein, artery or in the heart. Thrombus formation is normal in case of injury to a blood vessel, but pathologic if formed inside the blood vessel where it remains. A thrombus that breaks up and becomes a free-floating clot is known as an embolus. A thrombus can be **mural, obturating, occluding, and parietal**.

Mural (muris, Latin for wall) thrombus is one that forms within the wall of a cavity, especially in a diseased area of the endocardium (heart muscle) or the aortic wall where it becomes attached.

An **obturating** thrombus is one that enlarges distally to its attachment site and points in the direction of the blood flow.

An **occluding** thrombus is one that clogs the entire blood vessel lumen and blocks blood flow.

A **parietal** thrombus is usually found either attached to a blood vessel or in the heart due to the presence of endocarditis or other cardiac diseases that affect large veins—for example, atherosclerosis and thrombophlebitis. When a parietal thrombus enlarges, it may become obstructive, especially if it occurs in small veins or arteries.

Following its formation, a thrombus may undergo **propagation, embolization, dissolution, or organization with recanalization**.

Propagation is enlargement of a thrombus that occurs in the direction of the heart, i.e forward flow in veins and backward flow in arteries.

Embolization takes place when a thrombus or part of it is detached from the wall of a blood vessel and moves with circulation. Such intravascular mass may block an artery located at a different site.

Dissolution occurs when a fibrinolytic drug is administered causing the dissemination of the thrombus and restoration of blood flow in a blocked artery.

Organization and recanalization is the process that results in growth of smooth muscle cells as well as fibroblasts and endothelium in a thrombus.

Recanalization involves the formation of channels within the thrombus—enough to allow blood flow.

EMBOLUS

An embolus (Greek embolus, wedge-shaped object or a stopper) is a blood clot that is dislodged from the formation site and travels to another narrower blood vessel in another part of the body where it blocks circulation. Emboli may be classified in accordance with their constituents.

Thromboembolism is a blood clot that partially or completely breaks away from its formation site, travels in the blood stream and eventually blocks a blood vessel, causing occlusion and obstruction of blood flow leading to blood stasis and ischemia.

Fat embolisms result from the release of endogenous fatty tissue into the blood stream. Fracture of tubular bone may result in the formation of fat embolisms. Intravenous injection of an emulsion may trigger fat embolisms.

Air embolisms may occur as a result of introduction of air into the vein during intravenous administration, alveoli rupture causing inhaled air to enter blood vessels, and accidental puncture of the subclavian vein. **Gas embolism** may be encountered during scuba diving.

THROMBOLYSIS

Thrombolysis is a process produced by fibrolytic drugs or physiologically resulting in the dissolution or breakdown of a blood clot. Plasmin is a serine protease that is found in the blood and acts by degrading many blood plasma constituents (proteins), in particular fibrin. The process that leads to the dissolution of fibrin is known as fibrinolysis. Additionally, plasma stimulates collagenase, antibodies and phagocytes to get rid of pathogens from the body, and to assist ovulation by softening of the Graafian follicles. Plasmin is released into the blood stream by the liver in the form of plasminogen which is converted to plasmin by a number of enzymes including tissue plasminogen activator, urokinase plasminogen activator, a protein found in the endothelial cells, and involved in clot breakdown, Kellikrein, a peptidase that cleaves peptide bonds, and Factor XII. Plasminogen deficiency results in thrombosis. Fibrinolysis is the natural reorganization and desorption of blood clots, a process where a fibrin clot is broken down at various structural places and leads to fragments in the blood stream where they are digested and solubilized by other pretease or by the liver and the kidney.

THROMBOGENICITY

Thrombogenicity is the tendency of a material (i.e. certain stents or coatings) to form a clot or embolus when in contact with blood.

ISCHEMIA

This is a term derived from Greek, (**isch** meaning restricting, **emia** denoting blood), and refers to a condition when blood supply is restricted in an affected area of the body. Such restriction prevents oxygen, and other nutrients, from reaching a particular organ or part of the body, resulting in the build-up of metabolic substance and damage to the tissue. Lack of blood flow may be triggered by various factors which include thromboembolism, embolism, tachycardia hypoglycemia, severe frost bite, hypotension, and atherosclerosis. Partial blockage of blood supply may cause hypoxia, whereas lack of oxygen in an area of the body may cause anoxia. Irreversible damage may occur in tissues such as those of the heart and brain, if oxygenated blood did not reach those areas within a few minutes. Ischemia of the heart muscle may be asymptomatic (silent ischemia) or may result in chest pain known as angina pectoris. The presence of narrowed cardiac arteries that restrict blood flow into the heart is known as coronary heart disease. If left untreated, heart attacks may occur, without previous warnings.

INFARCTION

An **infarct** is an area of dead tissue (necrosis) caused by obstruction of blood vessels that supply oxygenated blood and nutrients to that area. Infarction is the formation of an infarct. Obstruction of an artery may be caused by an arterial embolus, thrombus, atherosclerotic plaque, tumor or hernia that places pressure on an artery. Infarctions can be classified in accordance with the anatomical location in which they occur: **myocardial**, **cerebral**, **splenic** and **limb** are the most common ones.

Myocardial Infarction (MI), commonly known as a heart attack, is defined as an infarction that occurs as a result of blockage of a coronary artery that supplies oxygen and nutrients to a part in the heart muscle (myocardium). If left untreated, the deprivation of these substances can cause cells of the heart muscle to die and become permanently damaged. The damaged tissue is normally replaced by scar tissue within a few weeks. Blockage of the coronary artery is usually due to the formation of a blood clot that may form due to plaque buildup along the walls of the atherosclerotic artery. Blood clots usually do not form in normal arteries. Most cases of myocardial infarcts occur when a crack develops inside an atherosclerotic plaque. The process exposes the inner portion of the plaque to the blood thus triggering coagulation cascade. Blood clots can be formed elsewhere in the body (embolus) and can travel to a coronary artery. Spasms of a coronary artery caused by the intake of cocaine may contribute to an MI. Atherosclerosis is a condition which occurs as a result of thickening and hardening of the wall of an artery where multiple plaques are formed. An atherosclerotic plaque is made up of three layers:

1. Atheroma, located nearest the lumen of the artery, is a lump-like structure made of a soft yellow substance located in the center of the plaque. It consists mainly of macrophages.
2. A middle layer which consists of fatty substances such as cholesterol.
3. A calcification material that forms at the base of the atherosclerotic plaque.

Atherosclerotic plaque can be classified into **stable** and **unstable**. A **stable** plaque is usually asymptomatic and consists of an extracellular matrix and smooth muscle cells. The **unstable** one is made up of macrophages and is loose and susceptible to detachment and rupture. Soft unstable plaque may rupture causing a thrombus. Most infarcts occur at a location with less than 50% narrowing in a blood vessel. Sclerosis begins to form in early adolescence and usually is asymptomatic. Cardiac stress tests usually detect narrowing of about 75% while nuclear stress procedure can detect as low as 50%. Approximately one million persons in the US suffer from myocardial infarcts every year, and 400,000 die as a result of this condition. Risk factors for myocardial infarction include: previous cardiovascular diseases, age (over 65), smoking, family history of coronary artery diseases, elevated blood pressure, increased levels of triglycerides and low-density lipoprotein (LDL), decreased level of high density lipoprotein (HDL), diabetes, obesity, chronic kidney diseases, congestive heart failure, excessive consumption of alcohol, male gender, even though after the age of 75 risk of heart attacks to women equals that of men, sedentary life style, and intake of unhealthy diet. The following are recommendations to reduce the risks of infarctions:

1. Tobacco smoke cessation.
2. Maintenance of healthy diet. A dietician may need to be consulted. Foods high in saturated fat and sodium should be avoided.
3. Control of blood sugar in case of diabetes.
4. Maintenance of an exercise schedule that increases the heart rate. Jogging, swimming, fast walking, aerobic exercise, and cycling are examples.
5. Weight loss is essential, if the patient is overweight.
6. Avoidance of stress.
7. Having adequate sleep.
8. Avoidance of excessive intake of alcoholic beverages.

Symptoms of myocardial infarct seldom begin abruptly. They appear gradually over several minutes and are characterized by chest pain and a feeling of tightness, dyspnea and pressure. The pain may radiate to the jaw, neck and arms (in particular the left side), heart burn-like symptoms at the epigastrium, nausea, vomiting, excessive sweating, cough, anxiety, fatigue, and sudden death due to ventricular fibrillation. In some cases people may experience only mild discomfort in the chest and pain similar to indigestion. Occasionally MIs occur asymptotically (silent MI) and the occurrence of such an event is recognized later on during a routine electrocardiograph (ECG) examination. It should be kept in mind that not every chest pain and other stated symptoms are due to MIs. Peptic ulcers, gallbladder disorders and chest wall muscle strain may exhibit similar symptoms.

Diagnosis of MIs can be made after assessing the patient's complaints, observing ECG changes, and blood tests to measure troponin, a chemical found in the myocardium. Damage to the heart muscle cells results in the production of

troponin which appears in circulation. Increased blood level of troponin within 3-12 hours from the onset of chest pain or other symptoms indicates the presence of an MI. Recovery from MI depends on the patient's general health, age, the magnitude of the damage to the myocardium, the method and speed at which treatment was provided. It has been found that the mortality rate of individuals with low risk factors was 0.4% after 90 days of the attack, whereas the rate in high risk patients was 21.1%. Most complications occur immediately following the occurrence of the attack (acute stage), but may develop later on (chronic stage). Such complications include heart failure, especially if the damage to the myocardium is extensive, a tear in the heart muscle, mitral regurgitation, arrhythmias, especially ventricular fibrillation, ventricular tachycardia, atrial fibrillation, and the occurrence of another attack.

Cerebral Infarctions (Ischemic stroke): This event occurs as a result of irregularities in blood supply (ischemia) to the brain. Formation of a blood clot results in ischemic stroke which is different than a stroke due to cerebral hemorrhage. It has been estimated that one third of cerebral infarctions are fatal. Symptoms of cerebral infarction depend for the most part on location of infarction and the resultant ischemia. If an infarction takes place in the motor cortex, a contralateral hemiparesis (weakness in muscles and loss or reduced sensation of one side of the body), and not hemiplegia, which is total paralysis of a limb or trunk, may result. Risk factors for cerebral infarction are similar to those of the cardiac one.

Splenic Infarction: Interruption of oxygenated blood flow into the spleen is termed splenic infarction. This occurs as a result of occlusion of the splenic artery or one or more of its branches by a blood clot. Even though splenic infarction may be asymptomatic, it usually triggers severe pain in the upper quadrant of the abdomen and may radiate to the left shoulder.

Limb Infarction: Limb infarction is the formation of necrosis (tissue death) of nerves and muscles of an arm or a leg. The necrosis may become irreversible if blood supply is interrupted for 4 to 6 hours. Symptoms include absence of pulse and pain in the affected area, coldness in the limbs, muscle spasm, numbness and tingling, muscle weakness and skin paleness of the affected limb. These may be due to a thrombus, arterial embolus and an arterosclerotic fragment.

ANTICOAGULANTS

Anticoagulants, commonly known as blood-thinning drugs, are medications employed to prevent or reduce blood clotting. These medications are used by patients who suffer from life-threatening thrombotic disorders. In some of these disorders clotting substances are deficient or not functioning adequately. The outcome may be a risk of a hemorrhage. Certain blood clots readily form due to variations in blood clotting factors, the health status of blood vessels, and the presence of cardiac arrhythmias. Candidates for the intake of anticoagulants are those who:

1. Have mechanical heart valves and are at risk of clot formation. Individuals with valves made of animal tissue have reduced risk.
2. Have had myocardial and cerebral infarctions.
3. Have experienced or are at risk of deep vein thrombosis or pulmonary embolism.
4. Complain of arterial fibrillation.
5. Have undergone surgery, especially orthopedic. Following surgery the blood becomes more prone to clotting.
6. Suffer from angina pectoris, a condition caused by clogging of coronary arteries.
7. Have stents inserted in coronary arteries.

The most commonly employed anticoagulants are: **coumadin and clopidogrel.**

COUMADIN

This is a widely used oral anticoagulant. It is generally prepared and administered as the sodium salt and is given to patients who require long-term anticoagulant therapy. The drug has a narrow therapeutic index, and, as a result, it requires constant monitoring in order to achieve optimal results and to reduce the risk of overdose.

Coumadin is a vitamin K antagonist that exerts its action by blocking the activity of the enzymes that facilitate the cyclic interconversion of vitamin K, which is required for the carboxylation of several glutamate residues in prothrombin and factors VII, IX and X, as well as the endogenous anticoagulant proteins C and S. The blockade causes the formation of incomplete molecules of factors that have no coagulation activity. Depletion of vitamin K, which may occur as result of the use of coumadin, can enhance the formation of arterial and heart valve calcification.

Inhibition of vitamin K, which serves as a cofactor in the production of proteins C and S, results in the reduction of the rate of synthesis of these proteins. The anticoagulant activity of coumadin takes from two to three days for its effect to develop. Optimal activity may take up to two weeks after the initial therapy. In case of an immediate need for anticoagulant therapy, heparin is often administered concomitantly. Moreover, the slow effect of the initial administration of warfarin requires that patients be anticoagulated with heparin for about 5 days

Coumadin used clinically is a mixture of equal amounts of enantiomers R and S isomers. The levorotatory S-coumadin is four to five times more potent than dextrorotatory R-coumadin. Coumadin is quickly absorbed from the GI tract, reaching peak blood concentration in 90 minutes, has bioavailability of about 100% following oral administration, has a plasma half-life of approximately 36 hours and about 99% of the dose is bound to plasma albumin. Coumadin is metabolized in the liver to produce inactive metabolites that are conjugated to glucuronic acid, which is ultimately secreted in the liver and stool. Liver impairment results in potentiation of the anticoagulant activity of coumadin. Renal impairment has no effect on increasing responsiveness to coumadin.

Coumadin therapy should be carefully monitored to achieve optimal therapeutic efficacy and minimize hemorrhagic complications in patients. This led to the use of smaller doses and the development of the International Normalized Ratio to determine the therapeutic range for anticoagulant therapy

$$\text{INR} = \left(\frac{\text{PT}_{\text{Patient}}}{\text{PT}_{\text{Control}}} \right)^{\text{ISI}}$$

where, PT is prothrombin time and ISI is a measure of the thromboplastin's responsiveness compared to the World Health Organization reference standard. In the past a large loading dose was used. At the present time the dosing of coumadin is dependent on a patient's responsiveness. It is important that clinical signs and laboratory tests be monitored continuously to determine the dose. It may take a week to determine the initial adjustment of prothrombin time.

The dose depends on factors such as age (65 years and older), elevated baseline INR, poor general health, hepatic impairment, and the concurrent intake of medications that cause potentiation of the anticoagulant activity of coumadin. Additionally, risk factors for bleeding must be taken into consideration. For the most part the maintenance dose of coumadin ranges from 5 to 7 mg/day. Adequately anticoagulated patients should have a plasma concentration of approximately 2mg/mL of coumadin. Duration of therapy is determined by the disappearance or continuation of the risk factors of thrombosis. In the absence of such factors, therapy may be discontinued after 3 months.

As stated earlier, concurrent administration of coumadin with certain drugs must be avoided as serious drug interactions may occur. Drugs that may interact with coumadin and may cause increased anticoagulant effect include: binge alcohol, especially in the presence of hepatic disease, amiodarone, cimetidine, ciprofloxacin, disulfiram, erythromycin, metronidazole, fluconazole, miconazole, and tamoxifen. Drugs that may decrease anticoagulation with coumadin include: barbiturates, cholestyramine, griseofulvin, rifampin, and vitamin K and fresh vegetables containing vitamin K. Those that may increase bleeding risk include: aspirin, NSAIDs, and heparin. The presence of hepatic disease may potentiate the effect of coumadin.

Clinical indications for the use of anticoagulants include venous thromboembolism, myocardial infarction, cerebral infarction, arterial fibrillation, mechanical heart-valve replacement, pulmonary embolism, and valvular heart disease. Coumadin is contraindicated in pregnancy. The drug is capable of crossing the placental barriers enough to cause fatal bleeding, spontaneous abortion and stillbirth. Furthermore, it has been shown that it can cause birth defects in at least 5% of infants. Taking coumadin during the first trimester of pregnancy can cause skeletal abnormalities. Administration of coumadin in the second and third trimesters is much safer than in the first trimester. The most encountered birth defects at that period involve the central nervous system and include spasticity (hypertonia or tightness of the muscle), seizures and eye defects. The main adverse effects of coumadin are hemorrhage, cutaneous necrosis and osteoporosis. Even though the occurrence and severity is not high, hemoptysis (coughing of blood), bruising, bleeding from the nose, gums, urinary tract (bloody urine), and intestine (dark stool) may be encountered. Cutaneous necrosis usually emerges after the initiation of the therapy and is characterized by damage to the skin, especially that of the limbs, and increased risk of gangrene. This adverse effect usually occurs in patients who are deficient in protein C. Studies have shown that the intake of coumadin by women has increased the risk of vertebral and rib fractures due to reduction in the bone mineral density. The mechanism

of this adverse effect is not fully known, but it has been postulated that coumadin inhibits vitamin K-mediated carboxylation of bone protein.

CLOPIDOGREL

Clopidogrel, which is a derivative of thienopyridine, was approved by the FDA in 1997 as a platelet antiaggregatory agent for the prevention of vascular ischemic events in patients with coronary artery disease, peripheral vascular disease, cerebrovascular disease, and thrombosis after placement of coronary stent. It may be used concurrently with aspirin for the aforementioned diseases and as a replacement in cases where aspirin is contraindicated. It exerts its anticoagulant effect by irreversibly inhibiting the binding of ADP on its receptor, known as P2Y₁₂, on platelets. The P2Y₁₂ is a protein found mainly on the surface of blood platelet cells and plays an important role in blood coagulation. The onset of the antiplatelet activity of clopidogrel is slow, and as result, a loading dose of 300-600 mg is normally given. In a clinical study comparing the effect of clopidogrel with that of aspirin in the prevention of ischemic events, it was found that a dose of 75 mg clopidogrel resulted in an 8.7% reduction of ischemic events compared to a dose of 325 mg of aspirin. Safety-wise, it was found that clopidogrel is as safe as aspirin regarding causing bleeding and neutrophil reduction. As a result it was concluded that the use of clopidogrel in atherosclerosis disease is therapeutically more effective than and as safe as aspirin. The use of clopidogrel in patients who need antiplatelet therapy and suffer from gastric ulcers is recommended. The parent compound of clopidogrel has no antiplatelet activity. When taken, clopidogrel is activated by cytochrome P450 enzymes, in particular the drug-metabolizing enzyme CYP2C19. This liver enzyme is responsible for metabolizing clopidogrel to an active metabolite. The resultant active metabolite acts by forming a disulfide bridge with the platelet ADP receptor. Clopidogrel may be ineffective in persons whose body is incapable of converting the drug to its active metabolite. In 2010 the FDA issued a warning that patients who are poor CYP2C19 metabolizers may not obtain the anticoagulant activity of clopidogrel due to lack of active metabolite of the drug in the blood. Genetic testing for the presence of the enzyme should be conducted in patients who do not respond adequately to treatment with clopidogrel. Patients with such genetic defect need to be evaluated as they may be at risk for heart attacks and strokes. Clopidogrel is administered orally and is available in 75 mg as the bisulfate salt. It is quickly absorbed from the GI tract producing a peak plasma level of the active metabolite in about one hour following the intake of the medication. The blood concentration is relative to the dose taken and antiplatelet effect of clopidogrel is dose-dependent. The maintenance dose is 75 mg daily with or without food. When employed for acute coronary symptoms a loading dose of 300 mg is usually prescribed. It may be given with 82 mg of aspirin. The adverse effects of clopidogrel include: fatigue, headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, nosebleed, tarry stool, bruising and allergic reactions such as urticaria, difficulty in breathing, and hoarseness. Clopidogrel is contraindicated in the presence of hypersensitivity to the drug, peptic ulcers, intracranial bleeding, and pregnancy. Recent reports indicate that concurrent intake of proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, or lansoprazole may reduce the anticoagulant activity of the drug, thereby increasing the risk of infarctions. Special precautions should be taken when dosing clopidogrel concurrently with aspirin, coumadin, NSAIDs, fluvastatin, Prilosec, phenytoin, cimetidine, ciprofloxacin, ticlopidine, fluconazole, and in the presence of hepatic and renal impairments. Patients should be advised to disclose to the pharmacist and the physician the names of all medications taken, including nonprescription drugs. Moreover, the patient should tell health providers if surgery or dental work are to be performed. The intake of alcohol may increase the risk of bleeding in the stomach. Clopidogrel should be avoided in case of a bleeding ulcer, ulcerative colitis, or blood clotting disorders such as thrombocytopenia purpura or hemophilia. The FDA has assigned category B to clopidogrel. Even though the drug is not fetotoxic, it is recommended that it should be used during pregnancy if the benefits outweigh the risks of using. The recommended dose must be taken regularly. In case of a missed dose it is not recommended to double the dose. The missed dose should be skipped, and the intake of the regular dose should be resumed. Patients should not discontinue the medications without consulting a physician.

SUMMARY

Cerebrovascular and myocardial diseases occur mainly as a result of atherothrombotic infarctions and ischemia. Such diseases may affect younger adults, but mostly are encountered among the elderly. Anticoagulant and antiplatelet drugs are widely used to prevent the formation of thrombosis which may block blood supplies to parts of the brain and the heart. In addition to pharmacological therapy, reduction or elimination of the risk factors of these diseases should be implemented.

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FUTURE TOPICS FOR THIS YEAR
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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?

Define 'platelets' & describe their role in clotting	Yes	No
Describe hemostasis, thrombosis, embolus, thrombolysis	Yes	No
Relate mechanisms of action of coumadin & clopidogrel	Yes	No
Define 'anticoagulant'	Yes	No
List side effects associated with coumadin & clopidogrel	Yes	No
State the mechanisms of action of other anticoagulants	Yes	No

2. Was the program independent & non-commercial Yes No

	Poor			Average		Excellent	
	1	2	3	4	5	6	7

3. Relevance of topic

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

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

Please Select the Most Correct Answer

1. Which is true concerning platelets?

- A. Formed via inactivation by the hormone thrombopoietin
- B. Thrombocytosis occurs as a result of decreased number of platelets
- C. Also termed thrombocytes
- D. High platelet count is termed thrombocytopenia

2. Which is false about hemostasis?

- A. Endothelial cells of intact blood vessels allow formation of blood clots
- B. Veins carry blood from capillaries to the heart
- C. Hemostasis begins immediately after injury to a blood vessel & its endothelium
- D. Fibrinogen is an active precursors of fibrin

3. A thrombus that breaks up & becomes a free-floating clot is called a(an):

- A. Infarct
- B. Ischemia
- C. Embolus
- D. Thrombolysis

4. Vitamin K deficiency:

- A. Speeds up clotting formation
- B. Has minimal effect on clotting mechanism
- C. Can be compensated by the presence of calcium in order to form blood clot
- D. Prolongs blood clotting time

5. Which is true about clopidogrel?

- A. Must be taken on empty stomach
- B. Maintenance dose is 500mg daily
- C. Can be taken safely by patients with active peptic ulcer
- D. Proton pump inhibitors may reduce anticoagulant activity

6. Which of these is not an adverse effect of coumadin?

- A. Cutaneous necrosis
- B. Sudden elevation of blood pressure
- C. Hemorrhage
- D. Osteoporosis

7. Which is incorrect about coumadin?

- A. Capable of crossing placental barrier
- B. Intake during the first trimester of pregnancy is safe & effective
- C. Anticoagulant patients should have a plasma concentration of about 2mg/ml
- D. The levorotary S-form is 4 to 5 times more potent than the dextrorotary R-form

8. Which is true about clopidogrel?

- A. Irreversibly inhibits the binding of ADP on the platelet receptor
- B. The onset of antiplatelet activity is instantaneous
- C. Aspirin is safer & more effective
- D. Active in persons incapable of converting the drug to its active metabolite

9. Optimal activity of coumadin:

- A. May take up to 2 weeks after initial therapy
- B. Is achieved by concomitant administration of aspirin
- C. Can never be achieved in persons with liver impairment
- D. Is achieved following parenteral administration

10. Purple patches under the skin are called:

- A. Cutaneous gangrene
- B. Deep vein thrombosis
- C. Thrombotic thrombocytopenic purpura
- D. Thrombocytopenia

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