A STUDENT'S BASIC GUIDE TO ANTITHROMBOTIC DRUGS

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Have you ever looked at the long list of antithrombotic drugs and been completely overwhelmed? Have you ever wondered why your patient has been prescribed clopidogrel or ticagrelor, drugs that sounds more like gremlin names than any recognizable western medicine? I have good news, you are not alone! In this "Student's Basic Guide to Antithrombotic Drugs" we address the basics of blood coagulation and some of the drugs that are commonly used for blood ANTIcoagulation. Whether you are are a Pre-PA student, just starting your didactic training in PA school, or starting on your clinical rotations, understanding the antithrombotic drugs will be a huge asset as you learn to take care of your patients. By the end of this article, I hope you feel more confident and calm when studying these important drugs!

As with any complex topic, it is important to break everything down to simple concepts. Let's start with a very basic review of the clotting process! Even before starting PA school, most people know that BLOOD CLOTS can be both GOOD and BAD. Blood is a complex fluid tissue that has many functions in the human body. Blood thrombosis and coagulation, or "blood clotting", is the process that typically occurs to prevent blood loss from vessels that have been damaged.

Even though thrombosis is a normal process to prevent hemorrhage, there can be alterations resulting in thrombus (plural = thrombi) formation in unwanted places. If a thrombus occludes an important artery, it may cut off blood flow to the surrounding tissues resulting in what is called ischemia. Complete blockage of blood flow results in tissue death, or ischemic infarction. When this occurs, it is bad news! We are probably most familiar with two examples that have serious consequences; thrombi occurring in the brain resulting in a stroke, or thrombi occurring in the arteries of the heart causing a heart attack (myocardial infarction).

First, let's clarify some definitions:

- Thrombus: a "blood clot" composed of fibrin, platelets, and red blood cells
- Embolus: a mass (can be a fragment of thrombi, gas, fat, tumor, etc.) within a blood vessel that is carried from one location to another
- Thromboemboli: a piece of thrombus that has broken off and traveled by circulating blood to another location (for example, pulmonary emboli typically occur after a deep vein thrombus in the leg has traveled to the lung)
- Hemostasis: blood clotting and anticlotting factors are in balance

By the way, can thrombi form in both arteries and veins? The answer is yes! If you have not already done so in your studies, I recommend making a list comparing symptoms in which thrombi have formed in arteries and that which have occurred in veins.

Thrombus Formation

Now to understand how antithrombotic drugs work, we must start with "How do clots form?". While it's a basic question, the more that we understand this foundational question the more we will understand the many antithrombotic drugs. If you have ever turned the page to view the "clotting cascade" in a textbook, you find something similar to the New York subway system. It's intimidating and difficult to remember because of all the crazy pathways and terminology!

So let's try to simplify this process of coagulation and clot formation. First, we must understand that there are many "factors" involved in blood coagulation. These factors are often precursor proteins that become converted to active enzymes in a process that involves protein cofactors (non-enzyme components). In other words, there is a series of proteins and substances that you need to activate other proteins and substances when forming a thrombus. It's like a domino effect!

Blood coagulation occurs when there has been some disruption to normal hemostasis. Injured blood vessels that typically release substances to prevent blood coagulation, suddenly start to release inflammatory substances that promote thrombus formation. This injury to the interior (endothelium) of a blood vessel triggers platelets to stick to the exposed lining of the vessel wall. As a result, released substances cause the platelets to adhere and aggregate (stick to the vessel wall and clump together) to form a hemostatic plug. What are some of these released substances? Exposed collagen, glycoproteins, and von Willebrand Factor. Hint: remember these terms in bold! They are factors and substances affected by antithrombotic drugs.

Next, the sticky platelets release substances called ADP and thromboxane A2. In this process, something called cyclooxygenase-1 is also produced, which is an enzyme needed to synthesize thromboxane A2.

Are you with me so far? Congratulations, you now know the basic beginnings of clot formation!

The coagulation cascade occurs simultaneously and involves what is termed the intrinsic and extrinsic pathways. There are many components, clotting factors, that are named by roman numerals. Each of the factors become activated and are then labeled roman numeral + the letter "a". For example, factor X becomes factor Xa when activated.

Both the extrinsic and intrinsic pathways consist of a sequence of reactions leading ultimately to fibrin formation. The intrinsic pathway is initiated by factor XII, which when converted to factor XIIa interacts with factor XI, leading to factor XIa. This triggers factor IX to factor IXa which finally converts factor X to

factor Xa with the help of factor VIII. Factor Xa then causes prothrombin to convert to thrombin. Ahhhh! Why all the factors?! One tip is to remember that these are just numbers labeling the factors. The most important key here is the sequence of events all trying to accomplish the same goal . . . thrombus formation and coagulation.

What is referred to as the extrinsic pathway occurs also during this time. Another special substance called tissue factor is released from damaged tissue. Tissue factor continues to initiate the clotting process by binding to a clotting factor labeled VIIa. Together these two substances cause factor X to become activated. Therefore, the end result of this tissue factor activation is the production of thrombin. What does thrombin do? Thrombin causes the conversion of fibrinogen to fibrin, the precursor form of the substance to the active form. And what does fibrin do? It adds stickiness to the platelet clump that we talked about in the beginning.

Antithrombotic Drugs

Why are there so many drugs available for treating and preventing blood clots? Because of the way thrombi are formed, we can target different steps in process. Antithrombotic drugs are commonly used for a host of medical conditions in which thrombi have or are likely to form including atrial fibrillation, coronary artery disease, deep vein thrombosis, and pulmonary embolism. Let us look at some of the important categories of antithrombotic drugs that differ in their mechanism of action.

- Antiplatelet: inhibit platelet activation or aggregation
- Anticoagulants: affect fibrin formation
- Fibrinolytic: degrade fibrin

The rest of this article will look at two of these categories of drugs and give you key points about the most common drugs, how they work, and how they are used clinically. We will address fibrinolysis and fibrinolytic drugs in another article.

Disclaimer: Please note that all medications are to be taken as directed by a licensed healthcare provider. The following information is for educational purposes only and should always be used in conjunction with the most current recommendations and guidelines.

Antiplatelet Drugs

As the name indicates, antiplatelet drugs affect platelets! The following table lists the most common antiplatelet drugs and how they work. All of the terms that you learned earlier will be put to use!

Table 1. Common Antiplatelet Drugs and Mechanism of Action*

Drug (Trade Name)	Mechanism of Action	End Result

aspirin (Bayer, Ecotrin)	Inhibits thromboxane A2, by inhibiting cyclooxygenase-1 (COX-1)	Prevention of platelet activation and recruitment
clopidogrel (Plavix)	Irreversibly block ADP	
prasugrel (Effient)		
ticagrelor (Brilinta)	Reversibly block ADP	
dipyridamole (Persantine; with aspirin, Aggrenox)	Increases adenosine and cAMP concentrations, reducing platelet function	Prevention of platelet aggregation
abciximab (Reopro)	Block glycoprotein IIb/IIIa	
eptifibatide (Integrilin)		
tirofiban (Aggrastat)		

*Brand names listed in (parentheses)

Key points:

- Aspirin
  - Dosing: 75-325 mg by mouth once daily
  - Produces a 25% reduction in the risk of cardiovascular death, MI, and stroke!
  - Most common side effects: GI distress, peptic ulcers
- Clopidogrel and Prasugrel
  - Clopidogrel dosing: 75 mg by mouth once daily, loading doses can be given
  - Prasugrel dosing: 10 mg by mouth once daily after loading dose
  - These drugs require metabolic activation by the hepatic cytochrome P450
  - Prasugrel has 10x the potency of clopidogrel
  - Produces an 8.7% reduction in cardiovascular death, MI, and stroke, by in patients with recent ischemic stroke, MI, or peripheral arterial disease
- Ticagrelor
  - Dosing: 90 mg by mouth twice daily after loading dose
  - Does not require metabolic activation (compared to clopidogrel and prasugrel)
  - Similar efficacy to clopidogrel as it pertains to stroke, with significant reduction in MI and cardiovascular death
- Dipyridamole
  - Typically combined with low-dose aspirin in Aggrenox

- Both oral and intravenous (IV) forms available

- Abciximab
  - Dosing: typically used as an IV infusion 0.125 mcg/kg/min for 12 hours
  - Monitor aPTT (goal is to keep elevated prior to percutaneous coronary intervention)
- Eptifibatide
  - Dosing: typically used as an IV infusion 2 mcg/kg/min
  - In acute coronary syndrome, may be given until discharge or CABG surgery (up to 72 hrs)
  - May see used with aspirin or heparin
- Tirofiban
  - Dosing: Initial IV bolus of 25 mcg/kg, then 0.15 mcg/kg/min IV for up to 18 hours
  - Used in acute coronary syndrome NSTEMI
  - Monitor platelet count during therapy

Anticoagulant Drugs

Vitamin K Antagonists

The clotting factors II, VII, IX, and X as well as protein c and s are all dependent on vitamin K for their synthesis. Something called vitamin K epoxide reductase (VKOR) is the enzyme that converts these factors to active clotting proteins. Warfarin is a drug that inhibits VKOR, thus making the clotting factors less or completely ineffective. It is important to note that the clotting factors have a lifespan, and therefore it takes time to achieve the full antithrombotic effect. For this reason, you will often see simultaneous use of heparin or LMWH for several days when a patient first starts taking warfarin.

Key Points:

- Warfarin
  - Dosing: 2-5 mg by mouth daily for 2-4 days, followed by 1-10 mg by mouth daily as indicated by measurements of the international normalized ratio (INR)
  - Typically used with heparin or LMWH for at least 5 days (see explanation above)
  - The anticoagulant effect is impacted by genetic factors, diet, other drugs and disease states
  - Requires frequent monitoring of PT/INR
  - Antidote: Vitamin K, typically given 5-10 mg by slow IV infusion
  - Should NOT be given during pregnancy, as it crosses the placenta

Note: What is INR? INR stands for international normalized ratio and is quite simply a ratio of the patient's blood sample value compared to a reference value. This should normally be 1.0. When a patient is being treated with warfarin, the INR will be elevated and the dosage titrated to keep the INR within a therapeutic range. The typical target INR is 2.0-3.0.

Direct Factor Xa Inhibitors

As the name indicates, these drugs directly inhibit factor Xa. No laboratory monitoring is required, but it is important to know there are no antidotes for these drugs.

- Rivaroxaban
    - Dosing: 10 mg by mouth daily
- Abixaban
    - Dosing: 5 mg by mouth twice daily

Indirect Thrombin Inhibitors

Antithrombin is a substance naturally occurring in the body that inhibits various coagulation factors, thrombin, factors IXa and Xa. These drugs indirectly affect thrombin through their interaction with antithrombin. Heparin binds to both antithrombin and thrombin and increases the interaction with factor Xa. Low molecular weight heparin (LMWH) is a smaller molecule that is too small to bind both thrombin and antithrombin; it binds only to antithrombin and inhibits factor Xa. Fondaparinux has the same activity as LMWH, but is an even smaller molecule and does not have any inhibition of thrombin.

All these drugs have a more rapid onset of action as compared to warfarin, which may take days to achieve a full therapeutic effect. The therapeutic effect of heparin can be monitored by the activated partial thromboplastin time (aPTT or PTT) and is typically kept at 1.5-2.5 times the baseline lab value. However, the aPTT is not standardized like PT/INR, thus limiting its usefulness. LMWH and fondaparinux do not require frequent lab monitoring and are thus more useful in the outpatient management of patients.

Key Points:

- Heparin
    - Dosing: very dependent on clinical situation; continuous IV infusion dosed in units/kg/hr. Subcutaneous administration is typically 5000 units 2-3 times daily.
    - The risk of bleeding increases with dose increase
    - Can cause heparin induced thrombocytopenia (HIT)
    - Antidote: Protamine, 1 mg for every 100 units of heparin by slow IV infusion
    - Heparin, LMWH, and fondaparinux do not cross the placenta (in contrast to warfarin)
- LMWH - enoxaparin
    - Dosing: dependent on clinical situation; dosing ranges from 1mg/kg subcutaneously every 12 hours to 40 mg/day for DVT prophylaxis
    - Use caution with renal insufficiency
    - Antidote: Protamine only partially reverses the anticoagulation effects of LMWH
    - If necessary to monitor the effects of LMWH, assess anti-factor Xa concentrations (therapeutic levels with LMWH are 0.5-1.2 mg/mL)
- Fondaparinux
    - Dosing: typically 2.5 - 10 mg subcutaneously once daily, dosing may be weight dependent
    - Does not cause HIT
    - Antidote: none available, although factor VII may reduce some of the anticoagulant effects

Application

For learning purposes, it may be helpful to classify drugs according to clinical use and FDA indications. It is also important to remember that all antithrombotic drugs increase the patient's risk of bleeding! Therefore, many of these medications must be stopped prior to a patient having surgery to avoid excessive bleeding during and after surgery. The following table helps to summarize these points.

Table 1. Common Antithrombotics According to Clinical Use*

Drug	DVT Prophylaxis	ACS	MI Prevention	TIA/Stroke Prevention	Other Thrombotic Event Prevention	Surgical Considerations - When to Stop Administration
aspirin (Bayer, Ecotrin)		✓	✓	✓		Not typically stopped, but if patient at high risk for bleeding hold 5 days
clopidogrel (Plavix)		✓	✓	✓	✓	Hold 5 days prior to surgery
prasugrel (Effient)		✓				Hold 7 days prior to surgery
ticagrelor (Brilinta)		✓	✓			Hold 5 days prior to surgery
dipyridamole (Persantine; with aspirin, Aggrenox)					✓	Depends on bleeding risk of patient
abciximab (Reopro)			✓			Depends on bleeding risk of patient
eptifibatide (Integrilin)		✓				Depends on bleeding risk of patient
tirofiban (Aggrastat)		✓ (NSTEMI)				Depends on bleeding risk of patient
warfarin (Coumadin)	✓		✓	✓	✓	Hold 5 days prior to surgery
enoxaparin (Lovenox)	✓	✓			✓	Typically continued until surgery
heparin	✓	✓			✓	Typically continued

						until surgery
rivaroxaban (Xarelto)	✓			✓	✓	Hold > 24 hrs prior to surgery
apixaban (Eliquis)	✓			✓	✓	Hold 48 hrs prior to surgery

*Brand names listed in (parentheses)
DVT = deep vein thrombosis
ACS = acute coronary syndrome
MI = myocardial infarction
TIA = transient ischemic attack

This concludes your introduction to antithrombotic drugs!

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"Aminocaproic acid (AMICAR, generic) is a lysine analog that competes for lysine binding sites on plasminogen and plasmin, blocking the interaction of plasmin with fibrin. Aminocaproic acid is thereby a potent inhibitor of fibrinolysis and can reverse states that are associated with excessive fibrinolysis."

(Do not include: cp bypass circuits and catheters activate factor XII, which can cause clotting of the oxygentator and catheter. Heparin is used for surgery requiring CPB becauseit can be reveresed. Have to be careful with renal impairment!
Notes: High doses of heparan can affect platelet aggregation (LMWH and fondaparinux do not)

otamine is a highly basic, positively charged peptide that combines with negatively charged heparin as an ion pair to form a stable complex devoid of anticoagulant activity.

"This amount is approximately 1 mg of protamine for every 100 units of heparin remaining in the patient; protamine (up to a maximum of 50 mg) is given intravenously at a slow rate (over 10 minutes)."Protamine only binds long heparin molecules. Therefore, protamine only partially reverses the anticoagulant activity of LMWHs and has no effect on that of fondaparinux.

Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given IV. Anaphylactoid reactions to protamine sulfate can occur, and drug administration by slow IV infusion is recommended to reduce the risk.