HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	1
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Cardiovascular diseases are major medical conditions that are found in almost all populations and are considered one of the most fatal diseases worldwide. One type of these diseases **is the unwanted clotting (thrombosis) of the blood** that is caused by many factors like hyperlipidemia, hypertension and smoking. Our topic today is clot-reducing drugs; this family includes:

1- ***Anti-platelets***: which are generally used ***prophylactically*** with patients who are at risk of developing thrombosis. (Smokers, hypertensive patients …etc.)
Remember: platelets aggregation is the first step of clot formation, so once the clot is formed, these drugs are useless (usually).

2- ***Thrombolytic drugs (emergentic drugs)****:* which act on the already formed thrombus and dissolve it. These drugs have serious side effects (such as bleeding) that might cause death, so their prescription is highly controlled. Doctors only prescribe them when there is no other choice.

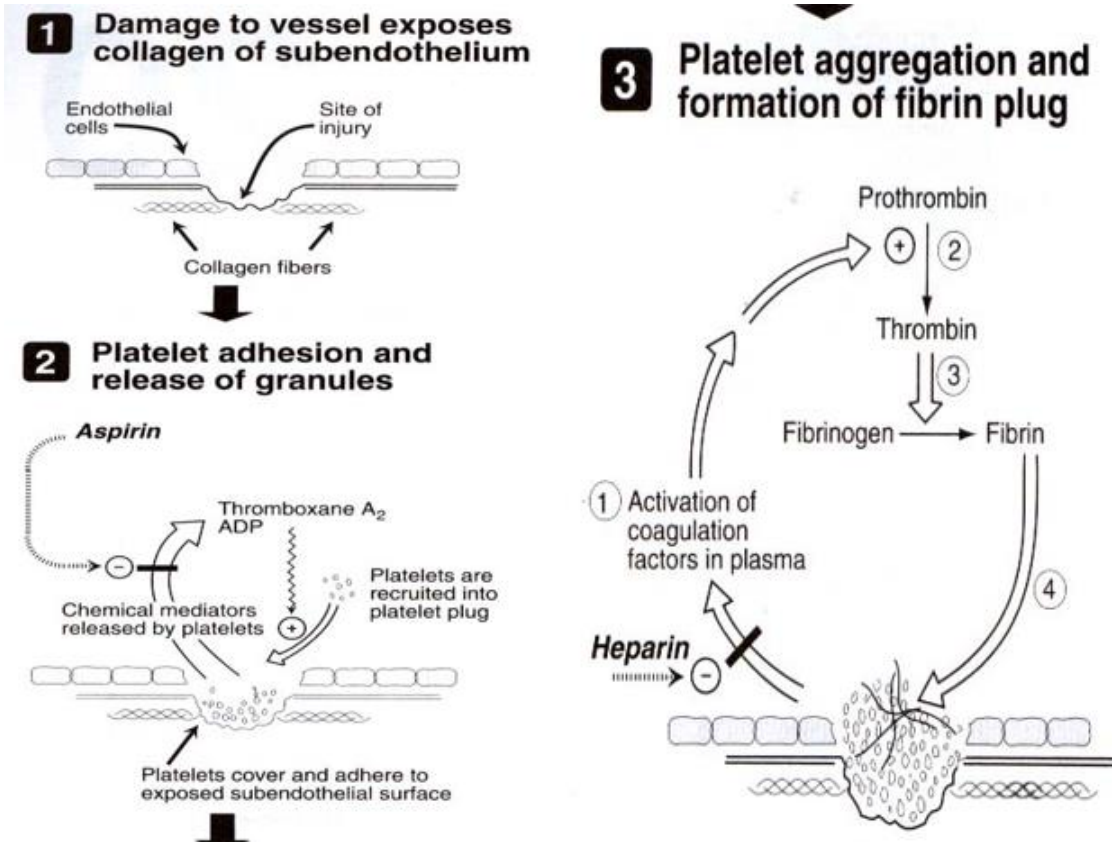
3- ***Anti-coagulants*****:** we use these drugs when the prophylactic therapy fails and the thrombus forms.

A common adverse effect among this family is **bleeding**.

Anti-platelets drugs

Platelets are neither always active nor always inactive; they are in a state of balance provided by **prostaglandins** (prostacyclin or PGI2) that are platelet inhibitors, and **thromboxanes** (particularly TXA2), which are platelet activators. So, our main idea is to maintain and re-establish this balance if it's interrupted (if it goes towards thrombosis).
Thrombi formation: when the endothelial cells are injured, **sub-endothelial collagen** is exposed so platelets can adhere to it, releasing their **granular content (ADP and TXA2 mainly)** which **attracts more platelets to aggregate** and finally get **cross-linked** and joined together by **fibrinogen through their IIb/IIIa receptors**.
Platelets have receptors affected by platelet activators & platelet inhibitors.
Chemical signals that oppose platelets activation include:

1- **Elevated prostacyclin levels:** prostacyclins bind to their receptors on the platelets increasing the production of **cAMP that prevent degranulation of platelets**.
2- **Decreased plasma levels of thrombin and thromboxanes:** they induce degranulation, so their absence means no degranulation.



Anti-platelet drugs work on different steps of this pathway, we are going to discuss **four mechanisms** of anti-platelet drugs:

(1) Inhibition of prostaglandin synthesis (aspirin),
(2) Inhibition of ADP-induced platelet aggregation (Clopidogrel, ticlopidine),
(3) blockade of glycoprotein IIb/IIIa receptors on platelets (abciximab, tirofiban, and eptifibatide).
(4) phosphodiesterase inhibitor (Dipyridamole ?? and cilostazol).

- Aspirin:

This drug shows its anti-platelet activity by **inhibiting the enzyme cyclooxygenase (COX), which produces thromboxanes from arachidonic acid**. So, this drug inhibits the production of platelets' activator **(TXA2).**

Aspirin is a **non-steroidal anti-inflammatory drug (NSAID)** that is used in:
1- in high doses to treat inflammation
2- as an **anti-platelet** drug in low doses (100mg).
* It is contraindicated in children because it causes **Reye's syndrome**.

-> There are many non-steroidal anti-inflammatory drugs, but the most commonly used for its anti-platelets activity is aspirin, why?

Because it's the only NSAID that binds **irreversibly** to the enzyme (COX), and thus producing **a long-lasting effect** compared to others (other NSAID inhibit cyclooxygenase but reversibly, so they have shorter duration of action).

Note: when aspirin binds irreversibly to the enzyme, the only way for the platelets system to be active again is to produce new platelets, which takes 7-10 days. **So, if you're going to do a major surgery and your patient is under aspirin therapy, you must stop the aspirin and wait for at least 4-5 days.**

Remember: we are not inhibiting the whole platelets' activity, we are only inhibiting the synthesis of thromboxane A2, other pathways for platelets' activity are still available.

Aspirin is not considered a strong drug compared to other drugs of this family, but its effect is enough to inhibit platelets aggregation in patients with a ***clean history*** *of previous thrombotic incidence (stroke, myocardial infarction and embolism) and at high risk of developing one.*
Important Note: aspirin is given before the event. If the cardiovascular event already happened we give aspirin with Other drugs like **Clopidogrel (Plavix)**.

Aspirin is used **prophylactically** in:

1- **Hyperlipidemic** and **hypertensive** patients (usually in old patients).
2- **Angina**: angina is the medical term for chest pain or discomfort usually caused by coronary artery disease (thrombosis). In this case, aspirin is given in combination with other drugs.
3- To prevent **recurrence of Myocardial infarction**.

Side effects of aspirin: hemorrhagic stroke and GIT bleeding, but they are **very rare**.
*****We usually don't give aspirin to peptic ulcer patients, because it might cause bleeding.

• Clopidogrel (and Ticlopidine):

Clopidogrel (Plavix) **inhibits the action of ADP by blocking its receptors on the platelet membrane**. As we said earlier, *this drug is used when there is an event (i.e. transient ischemic attack*) to prevent thrombosis from happening. It's also used in coronary stent plantation.
Useful in patients who cannot tolerate aspirin or who failed aspirin.
Remember: ADP induces platelets aggregation and adhesion.

Coronary stent plantation:

Atherosclerosis caused by some factors might form a thrombus, which occludes the artery and causes angina. Patients with this condition undergo coronary stent plantation. The coronary stent is usually either a metal or plastic stent, so during the surgery, its edges may injure the vessel and start the clotting cascade again forming another thrombus. To prevent this scenario from happening, clopidogrel is given after the operation.

Clopidogrel dose in coronary stent (oral): after the surgery, we give the patient **a loading dose** of clopidogrel (300-600mg) to achieve the steady state, then the patient administers a maintenance dose (75-150mg) for a few years to prevent the stent-induced clotting from occurring.

Clopidogrel is a prodrug, which means that it needs to be activated inside the body to produce its effect. The enzyme that does the activation is **cytochrome p450/CYP2c19** and this enzyme is susceptible to mutations that alter its function and produce polymorphism. Therefore, there is that variation in the loading (300-600mg) and maintenance (75-150mg) doses. A device called multiplate measures the functionality of CYP2c19, and according to its results, the dose is determined. To stay away from this issue, we give another more expensive drug called **prasugrel**; it's also a prodrug, but unlike clopidogrel**, it has many enzymes that can activate it, so one deficient enzyme won't affect its efficiency.**

So, Clopidogrel uses are:

1- Prevention of vascular events in patients with transient ischemic attacks.
2- Unstable angina.
3- Prevention of thrombotic stroke.
4- to prevent thrombosis in patients undergoing placement of a coronary stent.

Side effects: **neutropenia** (uncommon) and **thrombotic thrombocytopenic purpura (TTP)**, not serious.

- Abciximab (eptifibatide and tirofiban):

-Abciximab is a humanized monoclonal antibody directed against IIb/IIIa complex.
-Eptifibatide & Tirofiban inhibit ligand binding to IIb/IIIa receptor by their occupancy of the receptor.
- Those drugs are way stronger than clopidogrel and aspirin and all three are administered parentally.

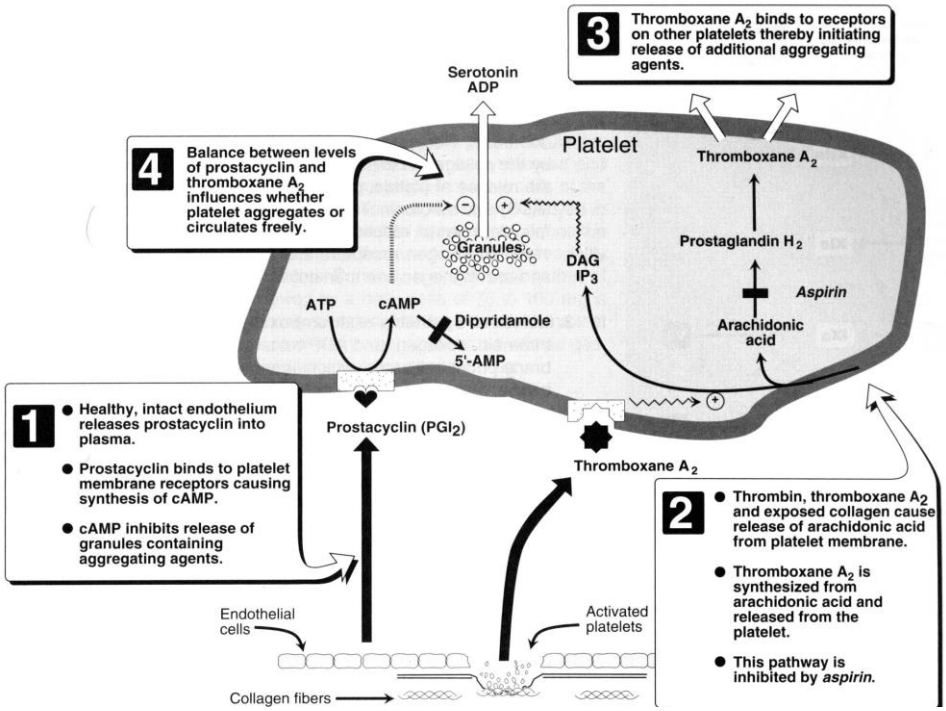
They can be used in coronary stent plantation. **Abciximab** has a different mechanism of action than clopidogrel; it **inhibits the bridging of platelets by fibrinogen through blocking IIb/IIIa receptors of the platelets**. It's the most active drug in inhibiting platelets

aggregation since it works on **the final and the most important step of the pathway**. This drug is *administered parenterally*, and because of *its very high efficacy*, this drug isn't commonly used.
Note: As you increase the efficacy of the drug, its adverse effects also increase in intensity and become serious issues that must be taken into consideration.

Abciximab injection is given 1-2 hours before the **stent** surgery to prevent the aggregation of platelets during the surgery (the most common use).
Uses:
1- Unstable angina.
2- Percutaneous coronary intervention (Percutaneous transluminal coronary angioplasty-PTCA).
3- Acute coronary syndromes (ACSs).
4- Coronary stent plantation.

- Dipyridamole

It is not active by itself (must be used in combination to produce its effect), so usually we add it to aspirin or warfarin. This drug **inhibits the phosphodiesterase enzyme, rendering more available cAMP, which in turn potentiates the effects of prostacyclin in inhibiting platelets aggregation**.
-dipyridamole is also a coronary vasodilator
Uses:
1- in combination with aspirin for prophylaxis in angina.
2- with warfarin to prevent embolization from prosthetic heart valves.
You need to know it as a drug, but clinically it is not used anymore.



Summery:

Drug Name	Is given	MOA	Adverse effects	uses
Aspirin	orally	COX inhibitor (irreversible) Prevents the Formation of TXA2	Hemorrhagic stroke/ and GIT bleeding	Prophylaxis in **Hyperlipidemic** and **hypertensive** patients Angina, prevention of MI recurrence
Clopidogrel (prasugrel is used in case of CYP2A19 mutations)	orally	inhibits the action of ADP by blocking its receptors on the platelet membrane.	Neutropenia, **thrombotic thrombocytopenic purpura (TTP)**	Prevention of vascular events in patients with transient ischemic atta Unstable angina, Prevention of thrombotic stroke, coronary stent.
Abciximab	Parentally	inhibits the bridging of platelets by fibrinogen through blocking IIb/IIIa receptors of the platelets	More adverse effects since they are more potent	ACSs, PTCA, unstable angina and Coronary stent.
Eptifibatide				
Tirofiban				
Dipyridamole	Orally	Inhibits phosphodiesterase more cAMP, more prostacyclin activity and less aggregation	-	in combination with aspirin for prophylaxis in angina with warfarin to preve embolization from prosthetic heart valves

Good luck ^_^