MED438

pharmacology
Team 438

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Anti-Platelet Drugs

Objectives:

By the end of the lecture , you should know:

- describe different classes of anti-platelet drugs and their mechanism of action.
- understand pharmacological effects, pharmacokinetics, clinical uses and adverse effects of anti-platelet drugs.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Platelets and Vessels

- In **healthy** vessels, nitric oxide[1] and prostacyclin (released by endothelial cells lining the blood vessels) inhibit platelets aggregation.
- **Damage** to the vessel wall leads to interaction between Platelets, Endothelial cells and Coagulation factors which lead to formation of the **clot.**

Clot

THROMBUS

is the clot that adheres to vessel wall.

EMBOLUS

is the clot that floats in the blood .

THROMBOSIS

is the formation of unwanted clot within the blood vessel[2], producing life threatening conditions such as:

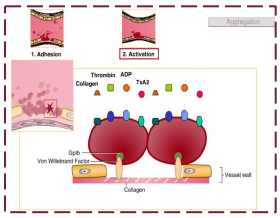
- Acute myocardial infarction[3]
- Acute ischemic stroke[4]
- Deep vein thrombosis [5]
- Pulmonary embolism

The role of platelets in Hemostasis (Clot Formation)

1
Adhesion

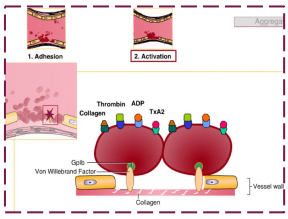
Following vascular injury, **von Willebrand factor** binds to collagen in the exposed subendothelium at the site of injury.

The other side of the "rod-formed" **von Willebrand factor binds to the platelet receptor GPIb** (Glycoprotein Ib) and platelets are thereby anchored to the site of the injured endothelium.This is called adhesion.

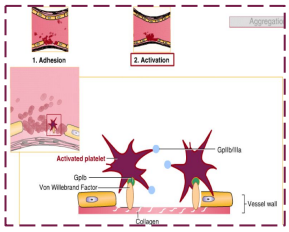


2
Activation

Following adhesion, agonists[7] such as collagen, thrombin, **adenosine diphosphate(ADP), thromboxane A2** and Serotonin (5HT), activate platelets by **binding** to their respective platelet receptors.

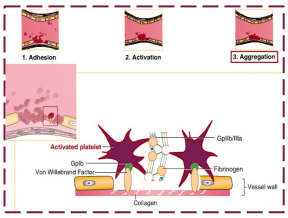


As a result of agonist binding, platelets undergo a shape change and **new structures such as phospholipids and GPIIb/IIIa[8] receptors** are exposed on the cell membrane. This is called activation



3
Aggregation

The third step of platelet response is aggregation. After activation, **binding of fibrinogen to GPIIb/IIIa** causes platelets to adhere to each other into a loose platelet plug.



1: potent vasodilator made by endothelium.
2: leading to reduced blood flow or even total blockage
3: can be fatal from the first attack especially in younger patients
4: the clinical picture depends on the area of the brain affected.
5: commonly starts from the calves muscles of the leg in (bed-bound patients, women on oral contraceptives..etc.), common complication of DVT is pulmonary embolism.
7: each binds to its corresponding receptor to contribute to platelet activation, leading to platelet shape changes and expression of new receptor (such as GPIIb/IIIa).

Drugs used in thrombosis

Anticoagulants

drugs which prevent clotting by inhibiting clotting factors (coagulation process).
used in prevention and treatment of thrombosis

Antiplatelets

drugs which prevent and inhibit platelet activation and aggression.
used as prophylactic therapy in high risk patients[1]

Thrombolytics or Fibrinolytics:

act by dissolving existing or already formed thrombi or emboli.
used in the acute treatment of thrombosis[2].

Classification of Antiplatelets

Arachidonic acid pathway inhibitors
e.g. Aspirin

Glycoprotein IIb/IIIa inhibitors
e.g. Abciximab – Eptifibatide -Tirofiban

Phosphodiesterase inhibitors
e.g. Dipyridamole

ADP pathway inhibitors
e.g. Ticlopidine - Clopidogrel
Prasugrel - Ticagrelor

Arachidonic acid pathway inhibitors

Drug	Aspirin (Acetylsalicylic Acid)
M.O.A	★ **Irreversible** inhibition of cyclooxygenase enzyme (**COX-1**) via acetylation,thus inhibiting synthesis of TXA2. • **Small dose inhibit selectively COX-1, thromboxane (TXA2) synthesis in platelets and inhibit platelet aggregation** **but not** prostacyclin (PGI2) synthesis in endothelium (larger dose).[3]
Uses	★ **Prophylaxis** of thromboembolism e.g. prevention of transient ischemic attack, ischemic stroke and myocardial infarction. • **Prevention of ischemic events** in patients with **unstable** angina pectoris[4]. • can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin).
Dose	• Low-dose aspirin (81 mg enteric coated tablet/day) is the most common dose used to prevent a heart attack or a stroke.
ADRs	• Risk of peptic ulcer. • Increased incidence of GIT bleeding[5] (aspirin prolongs bleeding time) • Hyperacidity • Allergy
C.I	• Peptic ulcer

1: used as a primary prophylactic therapy = to prevent the development of a disease in a person who is at risk for but with no prior history of the disease. (While secondary prophylaxis (AKA: maintenance therapy) means: therapy given to prevent relapse of known and appropriately treated conditions).
2: fibrinolytics have to be administered right after the insult, otherwise it is of no use. 3:because it doesn't inhibit COX-2 in small doses
4: unstable angina = patient is symptomatic (feels the anginal pain) even at rest.
5: Any patient should be asked if they are on aspirin prior to a major procedure as it should be stopped before the surgery to restore the blood's coagulability and avoid excessive bleeding.

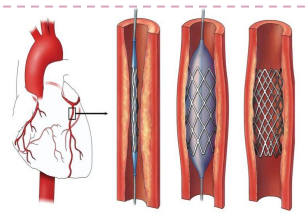
Adenosine Diphosphate (ADP) pathway inhibitors

Drug	Ticlopidine	Clopidogrel
M.O.A	★ These drugs specifically and **irreversibly inhibit ADP receptor of subtype P2Y12**, which is required for platelets activation thus prevent platelet aggregation. ○ This action inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets. ● P2Y12 is purinergic receptor and is a chemoreceptor for adenosine diphosphate (ADP).	
P.K	● given orally. ● Have slow onset of action (3 - 5 days) ● **Pro-drugs**, they have to be activated in the liver (by CYP P450) ● Bound to plasma proteins ★ **Clopidogrel** has replaced ticlopidine, because it has many advantages: ○ **Less side effects (less neutropenia),** better safety profile ○ more potent ○ Longer duration of action ○ Less frequency of administration (given once daily). ○ Bioavailability is unaffected by food.	
Uses	★ **Secondary prevention**[1] of ischemic complications after myocardial infarction, ischemic stroke and unstable angina. ● To prevent thrombosis (Prevention of vascular events) in pts with transient ischemic attacks, unstable angina pectoris, placement of a coronary stent ● **Given with aspirin** in high risk patients (Heart attack, severe attack of angina, coronary angioplasty, stenting).	
Specific Uses	-	● For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. ● For patients with **acute coronary syndrome** (unstable angina/ MI): either those managed medically[2] or with percutaneous coronary intervention(PCI) with or without stent.
ADRs	★ **Severe neutropenia** (Especially w**TICLOPIDINE**) , CBC should be done monthly during treatment,regular monitoring of WBC count during first three months ● leucopenia ● Bleeding (prolong bleeding time). ● GIT: nausea, dyspepsia, diarrhea. ● Allergic reactions. ● TTP (thrombotic thrombocytopenic purpura)	
Drug inter-action	● inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine.	

Females only

Coronary angioplasty

percutaneous coronary intervention (PCI) is a procedure used to open clogged heart arteries. Angioplasty involves temporarily inserting and inflating a tiny balloon to help widen the artery.



1: unlike aspirin that is used as a primary prophylactic.
2: = patient is managed solely through medications

Females only

New ADP Pathway Inhibitors

Drug	Prasugrel	Ticagrelor
M.O.A	★ **Irreversible** inhibitor of the P2Y12 receptor	★ **Reversible** inhibitor of the P2Y12 receptor
P.K	• both have **more rapid** onset of action than clopidogrel. • both drugs **do not need** hepatic activation .	
Uses	• to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed by PCI.	
ADRs	• both increase bleeding risk. • Ticagrelor causes dyspnea.	

Glycoprotein IIb/ IIIa receptor inhibitors

(Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each others and with fibrinogen and von Willebrand factor)

Drug	Abciximab	Tirofiban (non-peptide drug)	Eptifibatide (peptide drug)
M.O.A	• **GPIIb/IIIa receptor Receptor Blockers** (stop clot formation)		
	• inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules **to GPIIb/IIIa receptor**[1] sites on activated platelets[2].	• Act by occupying the site on **GP IIb/IIIa receptor**[1] that is required to bind the platelet to fibrinogen (act as fibrinogen-mimetic agents[3]).	
P.K	Given I.V. infusion[4].	Given intravenously (short half life)	
Uses	• used with **heparin and aspirin** as adjunct to PCI for the prevention of cardiac ischemic complications[5].	• Used for the reduction of incidence of thrombotic[6] complications during coronary angioplasty (PCI) and acute coronary syndrome.	
ADRs	• Bleeding and Thrombocytopenia		

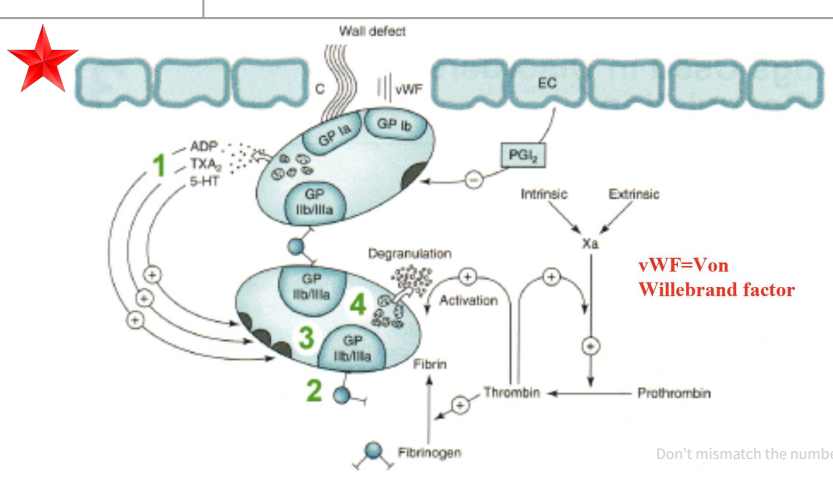
1: the last step in clotting process
2: works on different molecules in the clotting pathway = **The most potent antiplatelet**
3: act like fibrinogen by binding to its receptor = prevents fibrinogen binding.
4: does not need to be activated by the liver hence suitable as an IV.
5: using combinations will also increase bleeding risks.
6: that could happen due to the introduction of a foreign body (the stent)

Phosphodiesterase inhibitor (Not very Potent)

Drug	Dipyridamole	Males only, but important! Cilostazol
M.O.A	★ **It is a vasodilator** ★ **Inhibits phosphodiesterase** (an enzyme that normally break down cAMP) thus increases cAMP and **decreased synthesis of thromboxane A2** and other platelet aggregating factors. • Inhibits platelet function by inhibiting adenosine uptake & and inhibits cAMP metabolism by inhibiting phosphodiesterase activity	★ **Phosphodiesterase inhibitor (PDE3) ,promotes vasodilation or inhibits platelets aggregation**
P.K	• Given orally.	-
Uses	• Adjunctive therapy for prophylaxis of thromboembolism in cardiac valve replacement (with warfarin). • Secondary prevention of stroke and transient ischemic attack (with aspirin), when given alone it has little or no beneficial effect. Thus given in combination with aspirin to prevent cerebrovascular ischemia	★ Prevent intermittent claudication
ADRs	• due to vasodilating effect: ○ Headache ○ Postural hypotension	-
Caution	★ Due to dipyridamole vasodilatory properties, it should be used in caution in **coronary problem** (because the vasodilation will cause reflex tachycardia), clopidogrel is a better choice.	

Summary from Doctor's Slides

Drug	No. in the Pic	M.O.A	R.O.A
Aspirin	**1**	Inhibition of thromboxane A2 synthesis via inhibiting COX-1	Oral
Ticlopidine Clopidogrel Prasugrel Ticagrelor	**2**	Inhibition of ADP-induced platelet aggregation (ADP receptor antagonists)	Oral
Abciximab Eptifibatide Tirofiban	**3**	GP IIb / IIIa receptor antagonists	I.V
Dipyridamole Cilostazol	**4**	Phosphodiesterase (PDE) inhibitor	Oral



Don't mismatch the number as what happened in the CNS ...

Quiz

MCQ

1- Which of the $P2Y_{12}$ ADP receptor antagonists reversibly binds the receptor?

A- Clopidogrel B- Prasugrel C- Ticagrelor

2- A patient was taking an antiplatelet drug, on CBC we found that the patient developed a severe neutropenia. What's the most likely drug the patient was taking?

A- Clopidogrel B- Ticlopidine C- Dipyridamole

3- Which one of these can be used concurrently (at the same time) with warfarin (Coumadin) ?

A- Ticlopidine B- Aspirin C- Dipyridamole

4- 72 year old male comes for a subdural hematoma evacuation. He has been on antiplatelet therapy(aspirin and clopidogrel) for coronary stent placement. Which of the following is false with regards to antiplatelet medications?

A- Aspirin inhibits COX-1 B- Both clopidogrel and ticagrelor are P2Y12 antagonists
C- Prasugrel is a glycoprotein-2b3a inhibitor

5- Which of the following is used as a secondary prevention in MI patients?

A- Clopidogrel B- Aspirin C- Tirofiban

SAQ

1-2.A 46-years-old patient with unstable angina came to the clinic complaining of increased GIT bleeding, tests confirmed a prolonged bleeding time, while taking medical history the patient mentioned that he was prescribed an antiplatelet drug.
Q1-Which antiplatelet drug was most likely used in this case?
Q2-What is the M.O.A of that drug?

3-4.A 59-year-old female presents to the emergency room and diagnosed with Myocardial infarction. She requires PCI immediately.
Q3-Which Antiplatelet can be used in her case during surgery ?
Q4-What is the M.O.A of that drug?

Q5-Mention 2 indications of Clopidogrel.

Answers:

MCQ

Q1	C
Q2	B
Q3	C
Q4	C
Q5	A

SAQ

Q1	Aspirin
Q2	Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation.
Q3	Tirofiban \ Eptifibatide
Q4	Glycoprotein IIb/ IIIa receptor inhibitors
Q5	Patient with recent stroke- acute coronary syndrome

Share with us your ideas !

Good Luck , Future Doctors!

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