Revised & Approved

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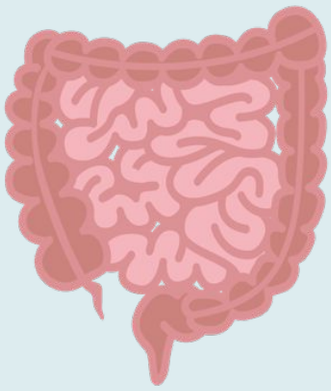
Pharmacology 439

MED439



Gastrointestinal Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Anti-Platelet Drugs

We highly recommend studying physiology of platelets before this lecture

Objectives:

- Basic concept of Activation of platelets and aggregation
- Anti-platelet drugs:
  A. Inhibition of thromboxane A2 synthesis via inhibiting COX-1: Aspirin
  B. Antagonist of ADP receptors: Clopidogrel, Ticlopidine
  C. GP IIb/IIIa receptor antagonists: Abciximab,Tirofiban and Eptifibatide
  D. Phosphodiesterase 3 (PDE) inhibitors/adenosine uptake inhibitors
- Pharmacotherapeutic profile of the individual classes (mechanism, indications, adverse drugs reactions)

Editing file | Summary

Platelets and clots formation

Platelets and vessels

- In healthy vessels, circulating platelets are maintained in an inactive state by **nitric oxide (NO) and prostacyclin (PGI2)** released by endothelial cells lining the blood vessels.
- Injury to the vessel wall leads to interaction between **platelets, endothelial system and coagulation factors** which lead to formation of the **CLOT**.

Activation of platelets after vascular injury

- ❖ Injury exposes reactive subendothelial matrix proteins, platelet adherence & activation, + secretion & synthesis of vasoconstrictors & platelet activating molecules.
- ❖ Thus, **Thromboxane A2 (TXA2)** is synthesized from arachidonic acid within platelets & is platelet activator & potent vasoconstrictor.
- ❖ **Adenosine diphosphate (ADP)**, secreted from platelet, a powerful inducer of platelet aggregation
- ❖ **Serotonin (5HT)**, which stimulates aggregation & vasoconstriction.
- ❖ Activation of platelets, → aggregation & conformational change in the GPIIb/IIIa, enabling it to bind fibrinogen, which cross-links adjacent platelets → aggregation & formation of a platelet plug.
- ❖ Simultaneously, the coagulation system cascade is activated → thrombin generation & a fibrin clot, which stabilizes the platelet plug.

Clot

- ➔ **Thrombus:** CLOT that adheres to vessel wall.
- ➔ **Embolus:** CLOT that floats in the blood.
- ➔ **Thrombosis:** Formation of unwanted clot within the blood vessels, producing life threatening condition such as:
  - Acute myocardial infarction (MI)
  - Acute ischemic stroke (AIS)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)

Drugs used in thrombosis

#CVS

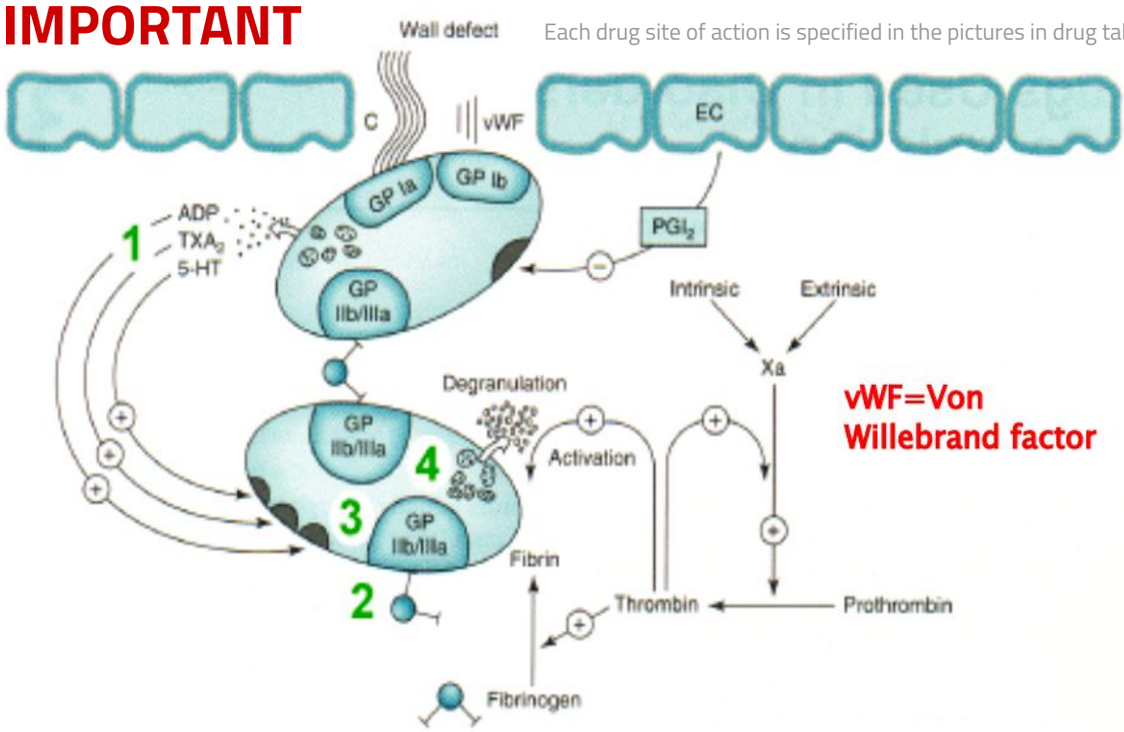
Anticoagulants:
drugs which prevent clotting by inhibiting clotting factors
(coagulation process).
used in prevention and treatment of thrombosis.

Antiplatelets:
drugs which prevent and inhibit platelet activation and aggression.
used as prophylactic therapy in high risk patients.

Thrombolytics or Fibrinolytics:
Drugs which reduce or lysis the clot. used in the acute treatment of thrombosis.

IMPORTANT

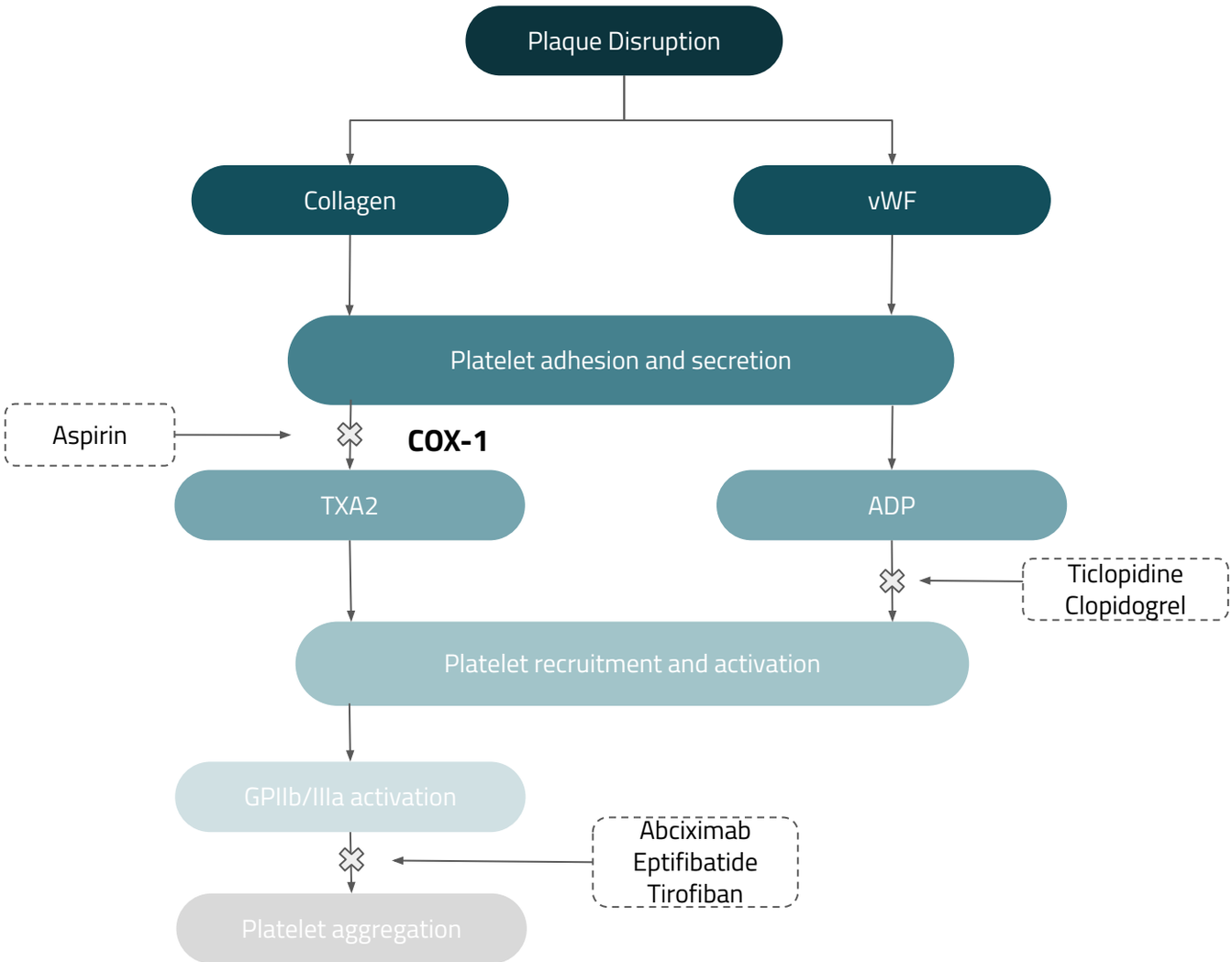
Each drug site of action is specified in the pictures in drug tables



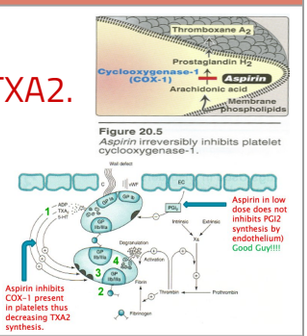
Drugs target for platelet inhibition

M.O.A	Drug	R.O.A
Inhibition of thromboxane A2 synthesis via inhibiting COX-1	Aspirin	Oral
Inhibition of ADP-induced platelet aggregation (ADP receptor antagonists)	Clopidogrel Ticlopidine	Oral
GP IIb/IIIa receptor antagonists (Inhibitors)	Abciximab Tirofiban Eptifibatide	**I.V**
Phosphodiesterase 3 (PDE) inhibitor/adenosine uptake inhibitors	Dipyridamole Cilostazol	Oral

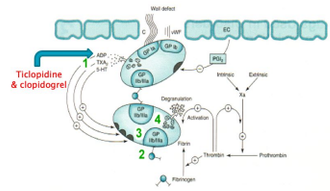
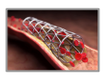
MOA of Antiplatelet Drugs (Extra)



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. **Ishfaq:** Make sure to mention COX-1 in the answer ● Low dose (75-160 mg) selectively inhibits COX-1, Decreasing synthesis of platelets thromboxane (TXA2) and inhibit platelet aggregation, but spares the protective PGI2 synthesis 
Uses	● Prophylaxis of thromboembolism e.g. unstable angina, myocardial infarction, ischemic stroke. ● Combined with other antiplatelet aggregating: (clopidogrel) and anticoagulants (heparin).
ADRs	● Hyperacidity (Risk of peptic ulcer) ● **Allergy** ● Increased incidence of GIT bleeding (aspirin prolongs bleeding time)
Contraindication	Peptic ulcer

ADP Pathway Inhibitors

Drug	Ticlopidine T= more Toxic	Clopidogrel
M.O.A	**- Irreversibly block ADP receptor of platelets** - Inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets. - ADP causes Direct aggregation of platelets and indirectly increases GPIIb/IIIa receptor expression 	
P.k	**- Pro-drugs** - Require metabolism by the hepatic cytochrome p450 (CYP) enzyme system to active form	
Uses	- Prevent thrombosis (unlike aspirin that is used as a primary prophylactic) - Prevention of vascular events in pts with: • Transient ischemic attacks • Unstable angina pectoris • Placement of a coronary stent دعامة 	
Specific Indications		- Patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease. - Patients with acute coronary syndrome (unstable angina/ MI): either those managed medically or with percutaneous coronary intervention (PCI) with or without stent.
ADRs	- **GIT:** nausea, dyspepsia, diarrhea. - Hemorrhage (prolong bleeding time) - **Leukopenia** - **TTP** (thrombotic thrombocytopenic purpura) **Precaution:** Regular monitoring of WBC count during first three months (Therapy with ticlopidine requires regular monitoring for **neutropenia**)	- Same but fewer than ticlopidine - Longer duration of action (once daily dosing, ticlopidine given twice daily) **Clopidogrel has replaced ticlopidine:** - More potent - Better safety profile

Antiplatelet Drugs:

- Prevent blood clots from forming in the arteries.
- Monitoring: Bleeding time (Antiplatelet drugs increase bleeding time)
- Aspirin is the most commonly prescribed antiplatelet drug.

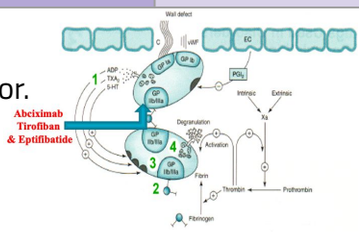
Aspirin-Clopidogrel:

- Clopidogrel works by reducing the "stickiness" of platelets in a similar way to aspirin & is often recommended as an alternative for people who cannot take aspirin.
- **Given together in high risk patients**
- May be recommended for people who have had a heart attack, a severe attack of **angina**, or who have undergone a coronary angioplasty & stenting.

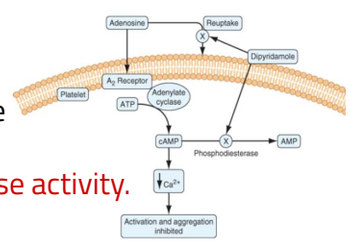
Aspirin Resistance:

- Resistance: recurrent thrombosis while on antiplatelet therapy.
- The reported incidence of resistance varies greatly, from 5 % to 75%.
- Although aspirin reduces the production of TXA2, it may fail to inhibit platelet aggregation because platelets continue to respond strongly to other agonists.
- TXA2-induced platelet aggregation is only ONE of many factors leading to thrombus formation, which is the most common, but not the only, mechanism leading to ischemic events.

Glycoprotein IIb/IIIa receptor Inhibitors (Monoclonal Antibodies)

Drug	Abciximab	Tirofiban (non-peptide drug)	Eptifibatide (peptide drug)
M.O.A	**- GP IIb/IIIa receptor Blockers (antagonists)** GPIIb/IIIa is found on the surface of platelets and is the most abundant receptor. Activated, GPIIb/IIIa binds adhesive molecules, such as fibrinogen and vWF to promote clotting. Abciximab binds to GPIIb/IIIa and stops the clot formation. 		
P.k	**- Given parenterally only** (doesn't need to be activated by the liver) Abciximab has **long** half life while Tirofiban & Eptifibatide have **short** half life.		
Uses	- In acute MI patients - Administered IV as an adjuvant to angioplasty surgery for the prevention of ischemic complications of angioplasty. - With heparin or aspirin (using combinations will also increase bleeding risks)		
	To prevent thrombosis (Prevention of vascular events in pts with): - Acute coronary syndrome - Percutaneous coronary intervention: (angioplasty with stent) a procedure used to open clogged heart arteries. Angioplasty involves temporarily inserting and inflating a tiny balloon to help widen the artery.		
ADRs	- Bleeding - Thrombocytopenia (immune reaction)		

Phosphodiesterase (PDE) Inhibitor

Drug	Dipyridamole	Cilostazol
M.O.A	- Vasodilator - Inhibits platelet function by inhibiting adenosine uptake - Inhibits cAMP metabolism by inhibiting phosphodiesterase activity. - cAMP for anti Platelet action 	Phosphodiesterase (PDE3) inhibitor, promotes vasodilation & inhibits platelet aggregation.
Uses	When given alone it has little to no beneficial effect. Thus given in combination with aspirin to prevent cerebrovascular ischemia.	**Prevention of intermittent Claudication:** muscle ischaemia during exercise caused by obstruction to arterial flow. **Ishfaq:** C for claudication
Precaution	Due to its vasodilatory properties it should be used in caution in coronary problems (because the vasodilation will cause reflex tachycardia), clopidogrel is a better choice.	

Summary

Class	Drug	M.O.A	Uses	ADRs/ Precautions
Arachidonic acid pathway inhibitors	**Aspirin** (Acetylsalicylic Acid)	Low dose selectively and Irreversibly inhibits COX-1 via acetylation, decreasing synthesis of platelets thromboxane (TXA2) and inhibit platelet aggregation, but spares the protective PGI2 synthesis.	• Prophylaxis of thromboembolism e.g. unstable angina, myocardial infarction, ischemic stroke. • Combined with other antiplatelet aggregating: (clopidogrel) and anticoagulants (heparin).	• Hyperacidity (Risk of peptic ulcer) • **Allergy**
ADP Pathway Inhibitors	**Ticlopidine** **Clopidogrel**	**- Irreversibly block ADP receptor of platelets** - Inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets. - ADP causes Direct aggregation of platelets and indirectly increases GPIIb/IIIa receptor expression	Prevent thrombosis Prevention of vascular events in pts with: TIA, Unstable angina pectoris, Coronary stent **Clopidogrel:** - Patients with a history of recent MI, stroke, or established peripheral arterial disease. - Patients with acute coronary syndrome	**Ticlopidine:** - GIT - Hemorrhage - Leukopenia - TTP **Precaution:** Regular monitoring of WBC count during first three months (for **neutropenia**)
Glycoprotein IIb/IIIa receptor Inhibitors	**Abciximab** **Tirofiban** (non-peptide drug) **Eptifibatide** (peptide drug)	**GP IIb/IIIa receptor Blockers (antagonists)** GPIIb/IIIa is found on the surface of platelets and is the most abundant receptor. Activated, GPIIb/IIIa binds adhesive molecules, such as fibrinogen and vWF to promote clotting. Abciximab binds to GPIIb/IIIa and stops the clot formation.	To prevent thrombosis (Prevention of vascular events in pts with): Acute coronary syndrome, Percutaneous coronary intervention **Abciximab:** - In acute MI patients - Administered IV as an adjuvant to angioplasty surgery - With heparin or aspirin (but it increase bleeding risks)	- Bleeding - Thrombocytopenia (immune reaction)
Phosphodiesterase (PDE) Inhibitor	**Dipyridamole**	- Vasodilator - Inhibits platelet function by inhibiting adenosine uptake - Inhibits cAMP metabolism by inhibiting phosphodiesterase activity. - cAMP for anti Platelet action	When given alone it has little to no beneficial effect. Thus given in combination with aspirin to prevent cerebrovascular ischemia.	**Precautions:** Due to its vasodilatory properties it should be used in caution in coronary problems, clopidogrel is a better choice.
	Cilostazol	Phosphodiesterase (PDE3) inhibitor, promotes vasodilation & inhibits platelet aggregation.	**Prevention of intermittent Claudication** **Ishfaq:** C for claudication	

MCQs

Q1: A man who is taking omeprazole for his hyperacidity is in a very high risk of myocardial infarction and came to the clinic and the doctor prescribed him an antiplatelet agent, which one of the following drugs is contraindicated in this patient?			
A-Cilostazol	B-Ticlopidine	C-Aspirin	D-Dipyridamole
Q2: A 56-year old woman started to take an antiplatelet agent two months ago, she came back to the clinic due to an infection. CBC showed decreased neutrophils count, which drug is she most likely on?			
A- Ticlopidine	B-Aspirin	C- Abciximab	D-Clopidogrel
Q3: Which of the following is an ADR for Glycoprotein IIb/IIIa receptor Inhibitors?			
A- Dyspnea	B-Thrombocytopenia	C-Leucopenia	D-Hyperacidity
Q4: What is the MOA of Dipyridamole?			
A- PDE inhibitor	B-ADP pathway inhibitor	C-Glycoprotein IIb/IIIa receptor Inhibitors	D-Arachidonic acid inhibitor
Q5: A patient came to you in the emergency department with MI, you wanted to prescribe aspirin but she said she's allergic to it, what is the best alternative drug in her case?			
A-Clopidogrel	B-Prasugrel	C-Abciximab	D-Tirofiban
Q6:A 55 year-old diabetic man went to the clinic due to severe distal leg pain, you diagnosed him with intermittent claudications, which one of the following drugs will you prescribe?			
A- Eptifibatide	B-Aspirin	C-Dipyridamole	D-Cilostazol
Q7: A patient is undergoing a percutaneous coronary angioplasty, which one of the following drugs can be administered parenterally?			
A- Clopidogrel	B-Cilostazol	C-Abciximab	D-Ticlopidine
Q8: Which enzyme does a small dose of aspirin block?			
A- COX-1	B- COX-2	C- PGI2	D- A&B

1	2	3	4	5	6	7	8
C	A	B	A	A	D	C	A

SAQ

Q1)What is the mechanism of action of ticlopidine?

Q2) List two Glycoproteins IIb/IIIa receptor inhibitors drugs and two ADRs:

Q3.1) Mention two drugs used in Acute Coronary Syndrome?

Q3.2) Mention their MOAs

Q3.3) Mention two ADRs for each class

Answers

A1) inhibition of ADP induced platelets aggregation (ADP receptor antagonist).

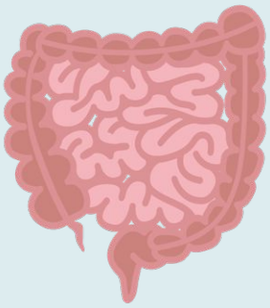
A2) Abciximab,tirofiban. ADRs: bleeding, thrombocytopenia

A3.1) A) Clopidogrel B) Abciximab

A3.2) A) Irreversible blocking of ADP receptors B) GP IIb/IIIa receptor blocker

A3.3) A) TTP and Leukopenia B) Bleeding and thrombocytopenia

Feedback Form



Gastrointestinal Block

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