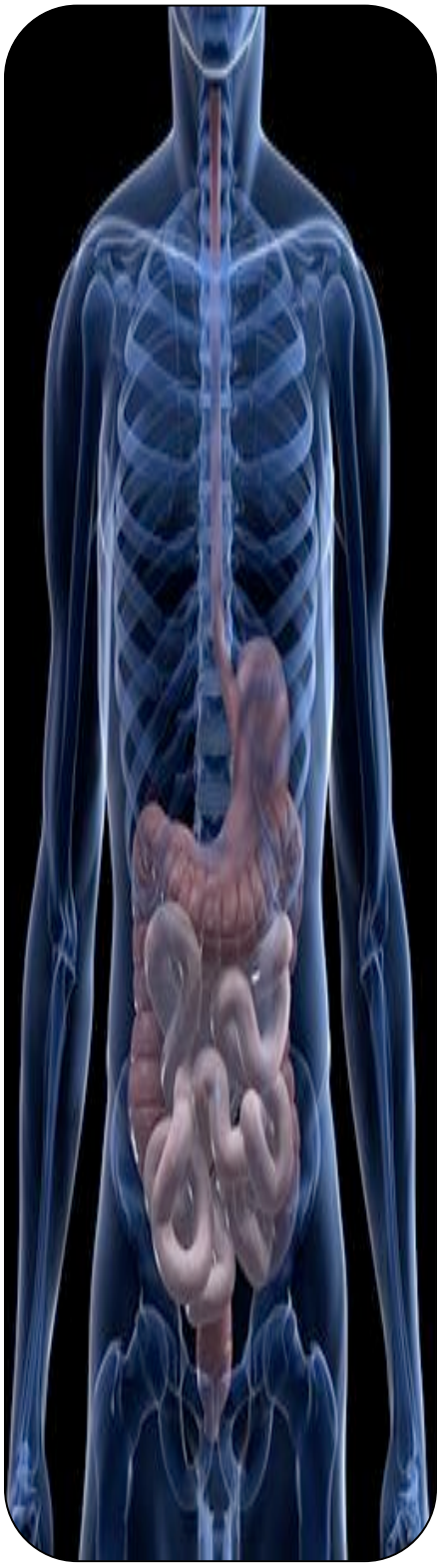
Pharmacology Team

Anti-Platelets Drugs



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Platelets and blood vessels

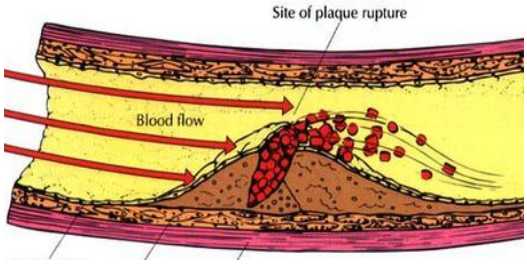
In healthy vasculature

, circulating platelets are maintained in an inactive state by nitric oxide **(NO)** and prostacyclin **(PGI2)** released by endothelial cells lining the blood vessels.

PGI2 & NO increase platelet cAMP that stabilize Glycoprotein IIb/IIIa receptors on platelets thus inhibit platelet aggregation also , it is vasodilator .

An injury to vascular system

leads to interaction between **Platelets, Endothelial system and Coagulation factors** which lead to formation of the **CLOT**



physiology:

Platelets aggregation & Arterial Thrombosis

Platelet adhesion occurs at the site of plaque rupture at exposed subendothelial surface of damaged endothelium (collagen).

Platelets recruitment, activated platelets release mediators for attraction of more platelets as **PAF, ADP, thromboxane A2 (TXA2), serotonin.**

Thromboxane A2 (TXA2) is synthesized from arachidonic acid within platelets & which stimulates aggregation & vasoconstriction.

Adenosine diphosphate (ADP): secreted from platelet, a powerful inducer of platelet aggregation

Serotonin (5HT), which stimulates aggregation & vasoconstriction.

Platelet aggregating factor (PAF) which stimulates aggregation

Platelets aggregation, mediators released by activated platelets cause increase in intracellular Ca^{2+}.

Elevated Ca 2+ causes:

Release of platelet granules

Increased synthesis of TAX2

Activation of Glycoprotein IIb/IIIa receptors

The final common pathway in platelet aggregation is cross-linking of the activated GP IIb/IIIa receptor with circulating fibrinogen and von Willebrand factor thus aggregation & formation of a platelet plug.

The coagulation system cascade is activated, thrombin generation & a fibrin clot, which stabilizes the platelet plug.

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 with in the blood vessel, producing life threatening condition.
Acute myocardial infarction
Acute ischemic stroke
Deep vein thrombosis
Pulmonary embolism

Classification of antiplatelet drugs

Arachidonic acid pathway inhibitors e.g aspirin

Phosphodiesterase inhibitors e.g. dipyridamol

ADP pathway inhibitors e.g.

Ticlopidine- Clopidogrel

Glycoprotein IIb/IIIa inhibitors e.g.

Abciximab, tirofiban

Uses

Prophylaxis of venous thrombosis.

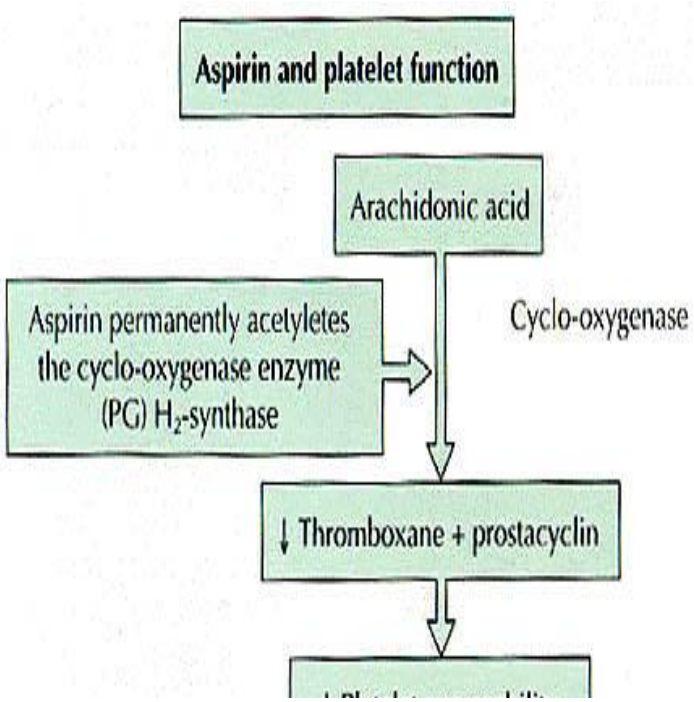
Transient cerebral ischemic attacks.

Following coronary artery bypass grafting.

Prevention of myocardial infarction.

Following coronary artery angioplasty.

Prosthetic heart valves.



Aspirin (Acetylsalicylic Acid)

Mechanism of action

Low dose of aspirin inhibit TXA2 production in platelets by inhibiting irreversibly COX-1 acetylation. We give aspirin in pediatrics dose to make it more selective

Larger dose inhibits both COX-1& COX-2

thus inhibits thromboxane synthesis in platelets (TXA2) and prostacyclin (PGI2) synthesis in endothelium.

Dose: Low dose 75 - 150 mg / day.(just for ur knowledge)

Side effects

Peptic Ulcer.

Increased incidence of GIT bleeding (aspirin

prolongs bleeding time).

Uses

Prophylaxis of thromboembolism e.g. secondary prevention of ischemic stroke, myocardial infarction and unstable angina. Patient who suffered from stroke for example u give him fibrinolytic and anticoagulant (Heparin) then as prophylaxis anti-platelet (aspirin)

can be combined with clopidogrel or heparin

ADP (Adenosine diphosphate) pathway inhibitors

Ticlopidine & Clopidogrel

Mechanism of action

Irreversibly inhibition of ADP-mediated activation of platelet aggregation.

No effect on PGs synthesis

Pharmacokinetics of ticlopidine

Given orally.

Slow onset of action (3 - 5 days).

Adverse Effects of ticlopidine

Sever neutropenia, blood count should be done during treatment.

Bleeding (Prolong bleeding time).

CYT P450 inhibitors (so remember drug- drug interaction)

G.I.T : nausea, dyspepsia, diarrhea.

Allergic reactions.

Drug interaction: increased plasma levels of drugs as phenytoin, carbamazepine.

Clopidogrel

is more potent than ticlopidine.(75 mg once daily).

Longer duration of action.

Less frequency of administration because its long duration.

Less side effects (less neutropenia).

Bioavailability is unaffected by food.

Clinical Uses of ADP inhibitors

Alternative prophylactic therapy to aspirin intolerant patients in secondary prevention of stroke, myocardial infarction and unstable angina.

Dipyridamole

Mechanism of action

Phosphodiestrase inhibitor thus ↑ cAMP in the blood platelets → inhibition of release of granules containing platelet aggregating agents.

adenyl cyclase phosphodiesterase

AMP → cAMP → 3,5 AMP

Uses of dipyridamole

Taken orally.

Has weak antiplatelet activity

If used, should be combined with aspirin

As prophylactic therapy to treat unstable angina pectoris (in combination with aspirin).

Primary prophylaxis in patients with prosthetic

heart valves (in combination with warfarin).

Disadvantages: Headache because vasodilatation action of the drug

Advantage: No excess risk of bleeding

Glycoprotein IIb/ IIIa receptor inhibitors

Include drugs as: abciximab, tirofiban

Glycoprotein IIb/ IIIa receptor is required for platelet aggregation with each others and with fibrinogen and von Willbrand factor.

The only group given by injection , Need hospitalization

Abciximab

is a monoclonal antibody directed against

glycoprotein IIb/ IIIa receptors.

It binds to IIb/ IIIa receptors thus inhibiting platelets binding to fibrinogen and von Willebrand factor, and consequently inhibiting platelet aggregation.

It inhibits all the pathways of platelet activation (Final common pathway).

Abciximab

Given I.V. infusion

is used as adjuvant to angioplasty surgery for

the prevention of cardiac ischemic

complications of angioplasty.

Heparin or aspirin is given with abciximab

Tirofiban & Eptifibatide

Tirofiban (non peptide drug)

Epitafibatide (peptide drug) .

Acts by occupancy of the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen (fibrinogen like mimetic agent).

They are given intravenously for the reduction of incidence of thrombotic complications during coronary angioplasty.

Summary

Drug	MOA	Adverse effect	Uses
Aspirin	Low dose irreversibly inhibit cox-1	Peptic ulcer GIT bleeding	Unstable angina prophylaxis of M.I 2ry prevention of ischemic stroke
Ticlopidine – clopidogrel	Irreversibly inhibit ADP	Ticlopidine :neutropenia – CTYp450 inhibitor	Ticlopidine :delayed action Clopidogrel:more potent
Dipyridamole	Increase cAMP	Headache	Unstable angina with aspirin – prosthetic valve with warfarin
GPIIb-IIIa inhibitor	Abciximab : bind to the receptor and inhibit its binding to other platelets		is used as adjuvant to angioplasty surgery for the prevention of cardiac ischemic complications of angioplasty.
	Tirofiban – eptifibatide : occupancy of site of receptor		reduction of incidence of thrombotic complications during coronary angioplasty

Questions

Which one of following drugs can cause neutropenia:

1-tirofiban

2-ticlopidine

3-clopidogrel

A 55 year old hypertensive obese male patient is suffering from infrequent anginal attacks on exertion. He was put on antiplatelet therapy since then. These days he is complaining of epigastric pain with hyperacidity. Which ONE of the following drugs is likely to produce such symptoms?

1-. Abciximab
2- Aspirin
3- Clopidogrel

Which one of the following is MOA of Aspirin ?

1- Decreases TXA2 synthesis
2- Blocks TXA2 receptor
3-Blocks GP IIb / IIIa receptor

Which one of the following is taken I.V only ?

1- Aspirin
2-Clopidogrel
3-Abciximab

Answers 2 2 1 3