

# ANTI PLATELET DRUGS and FIBRINOLYTIC DRUGS

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# Platelet action

- **Attachment** – exposure of subendothelial matrix
- **Spreading** – change in shape, release of TXA<sub>2</sub> and ADP
- **Secretion** – contents of intracellular granules
- **Aggregation** – binding of fibrinogen or fibrin to surface through glycoprotein IIb/IIIa (αIIb/β3) receptors.

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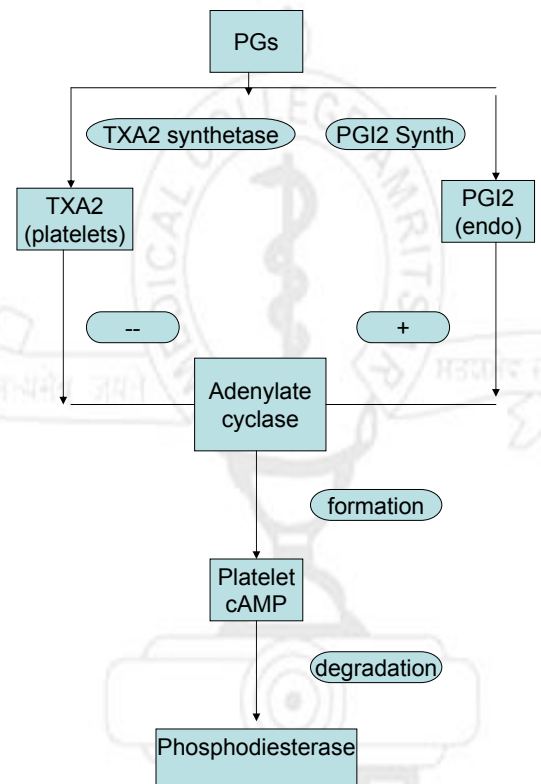
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# Platelet function regulation

- Agents generated outside the platelet and interacting with platelet memb. receptor
  - CA, Collagen, Thrombin, PGI<sub>2</sub>
- Agents generated within the platelet and interact with platelet memb. receptor
  - ADP, PGD<sub>2</sub>, PGE<sub>2</sub>, serotonin
- Agents generated within the platelet & act within the platelet
  - TXA<sub>2</sub>, cAMP, cGMP, Ca<sup>2++</sup>

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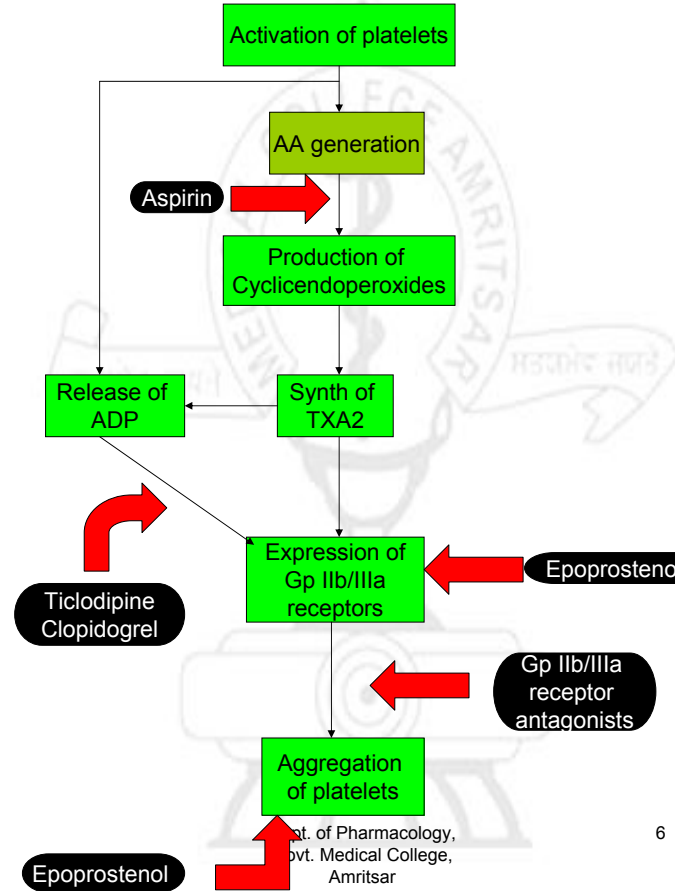


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# Antiplatelet Drugs

- Aspirin
- Phosphodiesterase inhibitors
  - Dipyridamole
  - Cilostazole
- Thienopyridine derivatives
  - Ticlopidine
  - Clopidogrel
- Gp IIb/IIIa inhibitors
  - Abciximab
  - Eptifibatid
  - Tirofiban
  - Lamifiban
- Synthetic PGI<sub>2</sub>
  - Epoprostenol



# ASPIRIN

- PG TXA<sub>2</sub> is an arachidonate product that causes platelets to change shape, to release their granules and to aggregate.
- Aspirin blocks the production of TXA<sub>2</sub> & PGI<sub>2</sub> by **covalently acetylating** a serine residue near the active site of cyclooxygenase
- Inhibition of COX-1 is **irreversible**.

# ....ASPIRIN

- Vascular endothelial cells can synthesize new PGI<sub>2</sub> but platelets **cannot** synthesize new TXA<sub>2</sub>.
- Thus action of aspirin on platelet is **permanent** lasting for the lifetime of platelet i.e. 7-10 days.
- Balance between TXA<sub>2</sub> (promoter of aggregation) & PGI<sub>2</sub> (inhibitor of aggregation) is altered.

## .... ASPIRIN

- As higher doses of aspirin are needed to inhibit COX in vascular endothelium than in platelets, antiplatelet effect can be achieved at **low doses** ( 75-150 mg per day orally)
- Other NSAIDs are reversible inhibitors.

## DIPYRIDAMOLE

- **Reversible** platelet phosphodiesterase inhibitor.
- Prevents degradation of cAMP
- **High conc of cAMP** inhibits adhesion, aggregation and release of active substances.
- Also **blocks uptake of Adenosine** leading to increased stimulation of A<sub>2</sub> receptors.
- This also increases cAMP conc. by stimulating platelet adenylyl cyclase.

## .... DIPYRIDAMOLE

- Used in combination with aspirin to prevent cerebrovascular ischaemia.
- Used in combination with warfarin for primary prophylaxis of thromboemboli in patient with prosthetic heart valve.

## THIENOPYRIDINE DERIVATIVES

- **Ticlopidine and Clopidogrel**
- Inhibit ADP dependent platelet aggregation.
- ADP acts on purinergic P2Y receptors.
- ADP causes platelet shape change, aggregation and decreases cAMP conc by inhibiting adenylyl cyclase.
- Ticlopidine and Clopidogrel block P2Y receptors.

## Ticlodipine

- Pro Drug
- 8-11 days to show maximal effect.
- Nausea, vomiting, diarrhoea.
- Thrombocytopenia
- Neutropenia
- Thrombotic Thrombocytopenic Purpura – rare.
- Due to distinct MOA combo with aspirin has **additive or synergistic effect**.
- Used for sec. prevention of stroke and unstable angina.

## Clopidogrel

- Pro Drug
- Slow onset of action
- Fewer side effects than Ticlodipine
- Dose dependent action – within 5 hrs of oral loading dose 80% of platelet activity inhibited.
- Duration of antiplatelet effect 7-10 days.

## GLYCOPROTEIN IIb/IIIa INHIBITORS

- Theoretically inhibit all pathways of platelet activation as all the pathways converge onto Gp IIb/IIIa.
- Gp IIb/IIIa complex functions as receptor mainly for **fibrinogen, von Willebrand factor and vitronectin**.
- Activation of this complex is final common pathway for platelet aggregation.

## Abciximab

- Human murine chimeric monoclonal antibody Fab fragment
- Binds with high affinity and slow dissociation rate.
- Immediate and profound inhibition of platelet activity extending for 12-36 hrs after termination of infusion.
- 0.25mg/kg bolus followed by 0.125µg/kg per min for 12hrs.

## Eptifibatide/ Tirofiban

- Prevent binding of fibrinogen to the receptor complex
- Used to treat unstable angina
- Used for angioplastic coronary interventions.
- ADRs
  - Haemorrhage
  - Thrombocytopenia

## Epoprostenol

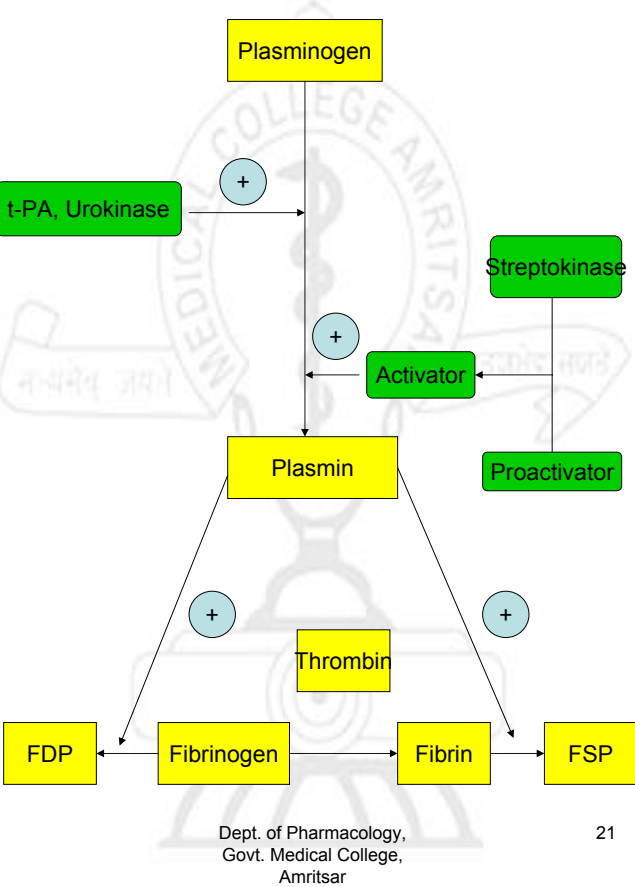
- Synthetic prostaglandin I<sub>2</sub>
- On i.v infusion acts on inositol phosphate receptors on vascular smooth muscles and platelets.
- Stimulates adenylate cyclase
- Causes vasodilatation
- Inhibits aggregation by any pathway
- Chemically unstable

## Uses of antiplatelet drugs

- MI
- Prophylaxis in high risk cases
- Following CABG
- Unstable coronary syndromes
- Following angioplasty or stenting ( Gp IIb/IIIa inhibitors)
- TIA or Thrombotic stroke – to prevent recurrence

## FIBRINOLYTICS

- Rapidly lyse thrombi by catalyzing the formation of plasmin from its precursor plasminogen.
- Streptokinase
- Alteplase
- Tissue plasminogen activator
- Urokinase
- Both protective hemostatic thrombi and target thrombi are broken down



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## Various Agents

- **Streptokinase** is a protein synthesized by streptococci that combines with proactivator plasminogen. Caution in patients with previous history of fibrinolytic therapy due to formation of antibodies.
- **Urokinase** is a human enzyme synthesized by the kidney that directly converts plasminogen to plasmin.
- Plasminogen can be activated endogenously by **t-PA**. Preferentially activate plasminogen bound to fibrin.

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## INDICATIONS

- STEMI (ST Elevation Myocardial Infarction)
- Multiple Pulmonary Emboli
- Central Deep Vein Thrombosis
- Peripheral vascular disease

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## DOSES

- **Streptokinase**- loading dose of 250,000 units followed by 100,000 units/hr for 24-72 hrs.
- **Contraindicated** in pts with previous history of infusion or antistreptococcal antibodies.
- **Urokinase**- loading dose of 300,000 units followed by 300,000 units/hr for 12 hrs.
- **Alteplase (t-PA)**- 60 mg i.v. over the first hour followed by 40 mg at a rate of 20 mg/hr.

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