Pharmacology

HLS

Sheet No. 6

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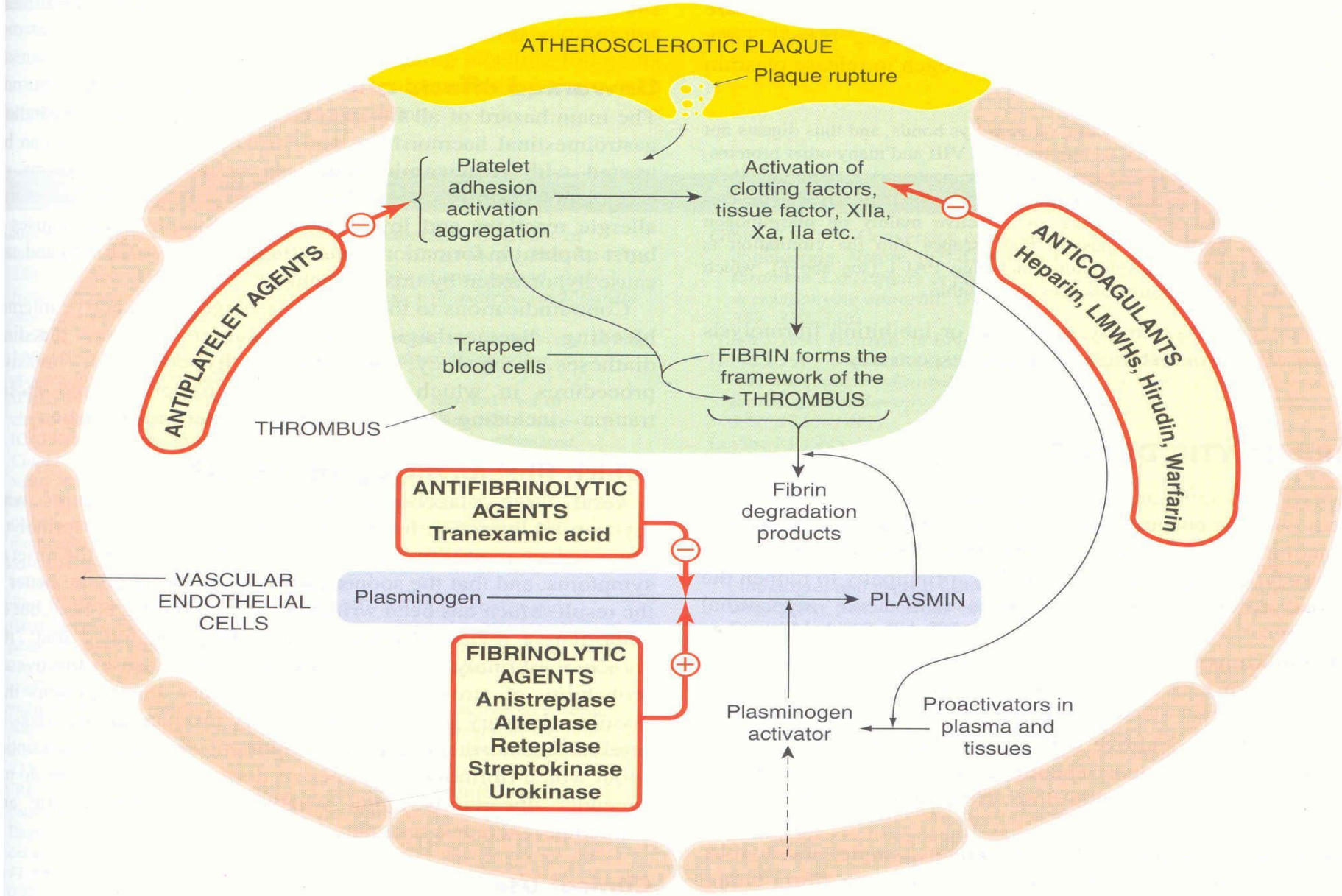
Thrombolytic Agents



Fibrinolytic system. The schematic shows interactions with coagulation and platelet pathways and sites of action of drugs that modify these systems. (LMHs, low-molecular-weight heparins.)

Thrombolytic Agents

- **The fibrinolytic system dissolves intravascular clots by the action of plasmin, a protease.**
- **Re-establish tissue perfusion.**
- **Not alternative to anticoagulants.**
- **Thrombolytic agents are plasminogen activators, including the “tissue plasminogen activator” (tPA).**

Thrombolytic Agents

- **First Generation TAs:**
  1. **Streptokinase**
  2. **Urokinase**
- **Second & Third Generation TAs:**
  1. **tPAs: Alteplase, Reteplase, Tenecteplase.**

Streptokinase

- Produced by Lancefield group C β-hemolytic streptococci.
- It is indirectly acting.
- Nonenzymatic protein, binds to plasminogen and induces a conformational change that exposes the active site which converts plasminogen to plasmin.
- Antibodies from previous streptococcal infection may neutralize activity, thus, it requires a loading dose (LD).
- Adverse Effects:

  Bleeding – systemic lytic state, Allergy, Anaphylaxis, Drug fever.

Tissue Plasminogen Activator (tPA)

- **It binds to fibrin with high affinity and activates plasminogen bound to the clot. i.e fibrin-selective activation.**
- **May activate circulating plasminogen at large doses or with long duration of therapy.**
- **Re-occlusion may be lessened by administration of heparin and antiplatelet drugs.**
- **Given by intravenous infusion.**

Adverse effects: bleeding, allergy.

Thrombolytic Agents

Therapeutic uses:

1. **Acute myocardial infarction: within 6 hours of onset, infused over 1-3 hours.**
2. **Central DVT.**
3. **Sever PE, or multiple PE.**

   Infused over 12-72 hours
4. **Acute ischemic stroke (??): within 3 hours of onset.**

Contraindications: **Similar to anticoagulants.**

Thrombolytic Agents - Antidotes

Aminocaproic acid, Tranexamic acid:

- **Bind to plasminogen and plasmin, thus preventing their action on fibrin.**
- **Contraindicated in dessiminated Intravascular coagulation (DIC), and bleeding from kidney or ureters.**

Adverse effects: Thrombosis, Myopathy, Hypotension, Nausea.

Anything written in handwriting or in red (except red headlines) is added to the slides/ mentioned by the doctor, best of luck..

Antiplatelet Drugs

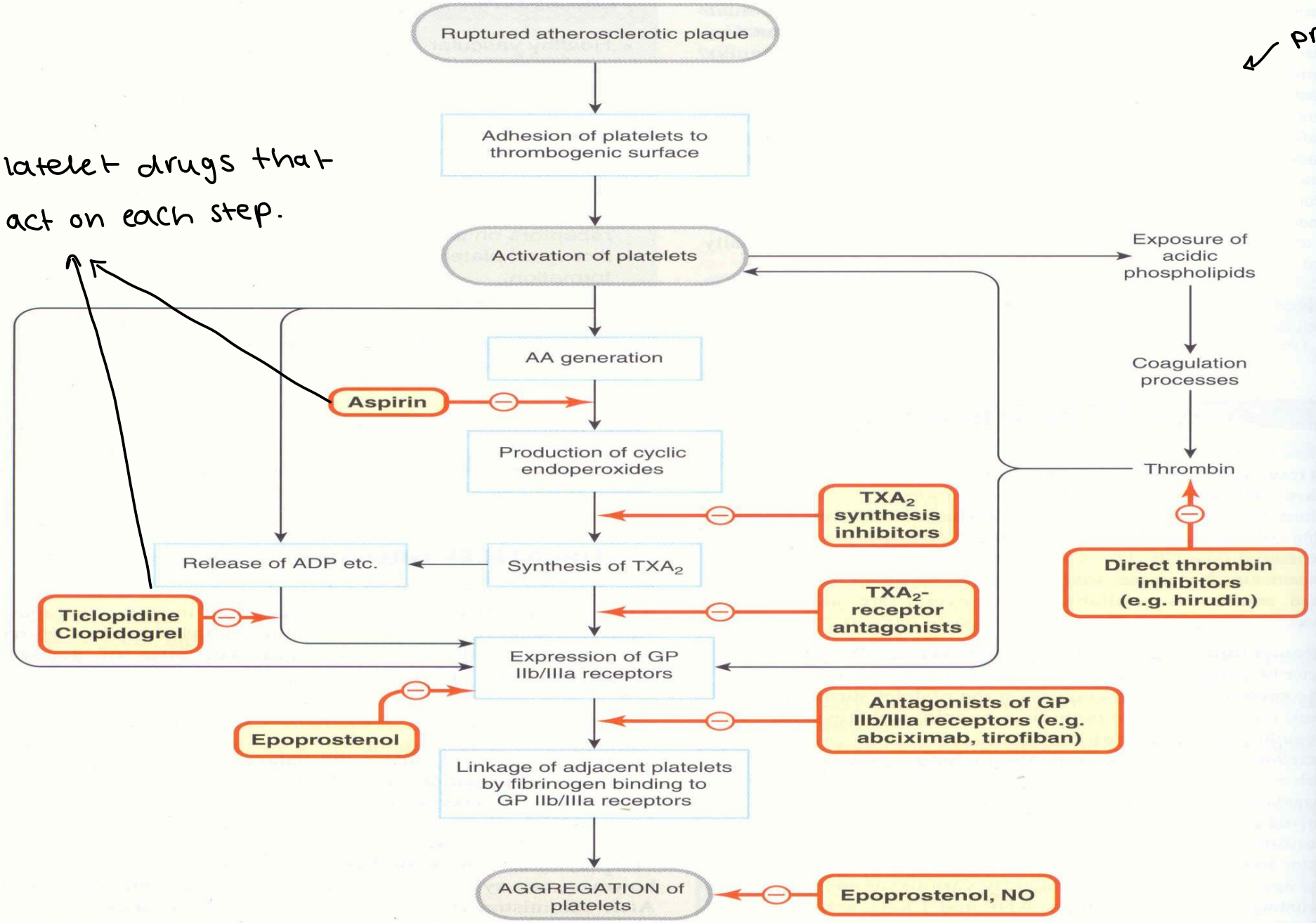
- Drugs that inhibit platelet aggregation.

- All what we discussed so far interacts with antiplatelets (anticoagulants and many others…)

* very commonly used in medicine + very important.

process الخثرة *

antiplatelet drugs that act on each step.



Platelet activation. Events involved in platelet adhesion and aggregation are shown, with the sites of action of drugs and endogenous mediators. (AA, arachidonic acid; ADP, adenosine bisphosphate; GP, glycoprotein; NO, nitric oxide; TXA_2, thromboxane A_2.)

Antiplatelet Drugs

here ↓

NSAIDS inhibit prostaglandin synthesis so بمنعوا the mucosal barrier against acid >> cause peptic alcerations.

- **Platelets provide the initial hemostatic plug at the site of vascular injury and participate in atherosclerosis.**

↳ They reduce it but they can cause bleeding.

Used for:

" might cause confusion بس مح هي ، اشطبوه "

1. **Prophylaxis of arterial thrombosis.**
2. **Prophylaxis** (لمنع حدوث) **and management** (نعالج) **of Myocardial infarction & & Ischemic stroke, Within 2 hours of onset.** + Secondary prophylaxis

Ischemic heart disease

- **Administered as adjuncts to thrombolytic therapy along with heparin to maintain perfusion and limit size of infarction.**

There's primary and secondary prophylaxis of diseases, primary is to prevent 1st occurrence while secondary is to prevent reoccurrence. Taking aspirin as an act of primary prophylaxis is proven to be dangerous as it causes gastrointestinal bleeding/ affects the function of its mucosal barrier and not beneficial for prevention of ischemic heart disease. >> up ↑↑

In ischemic stroke, with an onset of 3 hours we can use thrombolytic agents. But we must differentiate between ischemic and hemorrhagic stroke (same symptoms but hem. is more dense) because using thrombolytic agents in hemorrhagic stroke could increase the hemorrhage. → MRI

Antiplatelet Drugs

Classification:

1. **Cyclooxygenase inhibitors: Aspirin.** Most commonly used
2. **PGI_3 generators: Eicosapentaenoic acid.** One of Omega 3 fatty acids. Generates PGI2 and PGI3. → vasodilator, inhibitor of platelet aggregation
3. **ADP receptor blockers: Clopidogrel and Ticlopidine.**
4. **GPIIb/IIIa receptor blockers: Abciximab, Eptifibatide, Tirofiban,** → we'll talk about them in few slides.
5. **Others: Dipyrimadole and Cilostazol.**
   - Dipyrimadole: Works in the presence of other drugs.
   - Cilostazol: For peripheral vascular diseases.

Adp increases its expression

Aspirin

vasoconstrictor

platelet aggregator

- Irreversible inhibitor (acetylation of active site) of cyclooxygenase of platelets, thus, blocking the production of thromboxane A_2.
- The effect lasts for the life time of the platelet (7-10 days), why?
- Used at low doses (< 325 mg). Higher doses are not beneficial, because of inhibition of PGI_2 production.

62 mg

81 mg

100 mg

Because platelets can't synthesize new cyclooxygenase thus can't produce thromboxane A2.

Does that mean that we give aspirin once a week? No, once a day because everyday there's formation of new platelets.

Eicosapentaenoic Acid

- **Unsaturated fatty acid present in cold water fish.** شمال الكرة الأرضية
- **Generates PGI_3 and TXA_3.** TXA3 is not active or weekly active as a vasoconstrictor and platelet aggregator.
- **PGI_3 is an effective anti-aggregating agent like PGI_2, while TXA_3 is much less active than TXA_2.**

PGI3 is as active as PGI2 as a vasodilator and inhibitor of platelet aggregation.

Clopidogrel, Prasugrel & Ticlopidine

- **Prevent formation of platelet plug & clot retraction.**
- **These drugs irreversibly block the ADP P2Y12 receptor on platelets.**
- **This inhibits ADP-induced expression of platelet membrane GPIIb/IIIa receptor and fibrinogen binding to activated platelets.**
- **Needs 4 days to work, full effect 10 days.**
- **Clopidogrel is a prodrug that requires activation via the cytochrome P450 enzyme isoform CYP2C19.**

Why too long? Because of processes as DNA replication and transcription and protein synthesis, they take time..

Clopidogrel, Prasugrel & Ticlopidine

Therapeutic Uses:

As in renal disease, it's contraindicated.

1. **Patients who require aspirin but can not take it:**

(myocardial infarction, unstable angina pectoris, transient ischemic attacks, ischemic strokes).

2. **Patients with coronary stents, in combination with aspirin.**

Clopidogrel, Prasugrel & Ticlopidine

> 1% → common

Adverse Effects:

1. Bleeding (5%)
2. Nausea, dyspepsia, diarrhea (20%)
3. Severe Neutropenia (1%)
4. Thrombotic thrombocytopenic purpura
5. Cholestatic hepatitis

Antibodies against heparin >> HIT induced thrombocytopenia.

- Less with clopidogrel

GPIIb/IIIa Receptor Blockers

- **The platelet GP IIb/IIIa receptor functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor.**
- **Activation of this complex is the final common pathway for platelet aggregation.**
- **Used in acute coronary syndromes parenterally.**

GPIIb/IIIa Receptor Blockers

Include:

Abciximab: a humanized monoclonal antibody against the receptor.

Eptifibatide: a fibrinogen analog. ← شبيه → binds without function.

Tirofiban: similar to Eptifibatide but smaller molecule.

GPIIb/IIIa Receptor Blockers

Given with other drugs.

Dipyridamole:

- It is a vasodilator that also inhibits platelet function by inhibiting adenosine uptake and cGMP phosphodiesterase activity.
- It has little or no beneficial effect if used alone.
- It may be used in combination with aspirin to prevent cerebrovascular ischemia, or with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves.

Cilostazol:

- It is a phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation.
- It is used primarily to treat **intermittent claudication**.

pain in calf muscles while walking

عرج متقطّع

Its drug of choice is Cilostazol. Pain is due to ischemia in peripheral arteries of calf muscles.