دفعة يقين 2025

HLS

PHARMACOLOGY فارما

LECTURE المحاضرة

4

BY إعداد

Shereen Abu Saif

EDITED تعديل

النادي الطبي

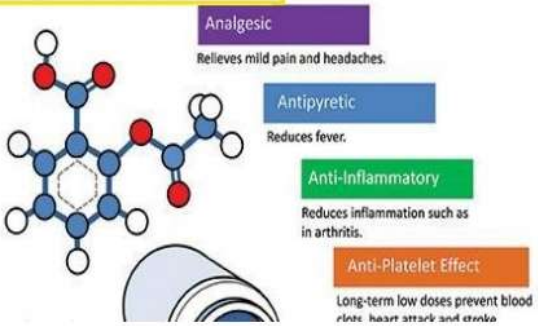
#معكم_خطوة_بخطوة

Aspirin

مهم تحكي انه recurrent MI ،،لانه الموضوع فيه debate عالي ،، بمعنى هل الاسبرين لازم يندعطى للناس الي صار عندهم MI او كمان للناس الي ما عندهم MI لكن عندهم استعداد لذلك (عندهم risk factor لل MI)

Therapeutic Uses

1. Reduce incidence of recurrent MI
2. Decrease mortality resulting from MI
3. Prophylactic treatment of transient cerebral ischemia → it's called "TIA" , it doesn't reach to be complete CVA
4. Others
   - 75mg/day: complete platelet inactivation



*we can use aspirin for a wide range of cases not just as antiplated effect , such as: -analgesic effect : with the same mechanism (COX-1 inhibitor) by this it stops the synthesis of prostaglandins which cause pain in certain conditions.
-antipyretic effect: with the same mechanism
-anti inflammatory: such as rheumatoid arthritis and infections that cause inflammation like rheumatic fever

*the action of aspirin is determined by it's dose
**the dose that is enough to make it work as antiplatelate is in average 75 mg daily (range from 50 to 325 mg daily)
** baby aspirin usually contains 75 -90 mg

Aspirin

Pharmacokinetics

- Oral (or rectally)
- Absorbed by passive diffusion from GIT
- Hydrolyzed to *salicylic acid* in the liver
- Half-life: → it's also functional as antiplatelate **So, both aspirin and its metabolite are active

Aspirin: 15-20 mins
Salicylic acid: 3-12 h

depending on above, the majority of aspirin effect is mediated by the effect of metabolite
its metabolism and excretion are very fast

Aspirin (prodrug) Salicylic acid

aspirin is a prodrug consists from salicylic acid binds with acetyle group

Drug Interactions

***ketorolac*—increased bleeding**
***cidofovir*—nephrotoxicity**
***probenecid*—decreased uricosuric effects**

remember that, t1/2 of aspirin based on it's metabolism and excretion (how much time it still in blood stream) .however, it's overall effect lasts for days because it works in irreversible mechanism.

Aspirin

the most common problem with aspirin is with pts who have peptic ulcer or gastric irritation. these pts should not get aspirin because it inhibits the synthesis of useful prostaglandins (gastro protectiveprostaglandins), and by this the risk of bleeding from GIT will be increased.

Adverse effects

- Bleeding (bleeding time is increased)
  - GI bleeding
  - Cerebral
  - increased risk if combined with NSAIDs

Adverse Effects

Angioedema
Bleeding
Bronchospasm
GI disturbances
Reye syndrome
SJS

* it's a hypersensitivity reaction

so that pts with asthma should not get it.

* it happens to children under 12 yrs old , so they should not get aspirin.

Aspirin

Salicylate Toxicity

Clinical		Laboratory
CNS	Tinnitus, decreased hearing, agitation, somnolence, confusion, seizure, cerebral edema, coma.	Metabolic acidosis Respiratory alkalosis Transaminitis
Pulm	Tachypnea, ARDS, respiratory failure.	Hypoglycemia Coagulopathy
CV	Hypotension, CHF, cardiovascular collapse.	
GI	Nausea, vomiting, gastritis, hepatitis.	
Renal	Volume depletion, proteinuria, AKI	

No specific **antidote** for salicylate poisoning is available so that , salicylic toxicity is treated by supportive therapy and renal dialysis .

$P2Y_{12}$ Receptor Antagonists

$P2Y_{12}$ Receptor Antagonists

Ticlopidine
Clopidogrel
Prasugrel
Ticagrelor
Cangrelor
Elinogrel

$P2Y_{12}$ Receptor Antagonists

Mechanism of Action

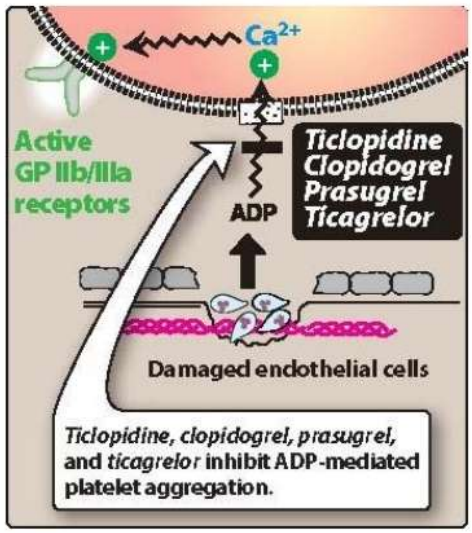
Inhibit binding of ADP at $P2Y_{12}$ →

inhibit the activation of GP IIb/IIIa →

inhibit fibrinogen binding →

platelet aggregation

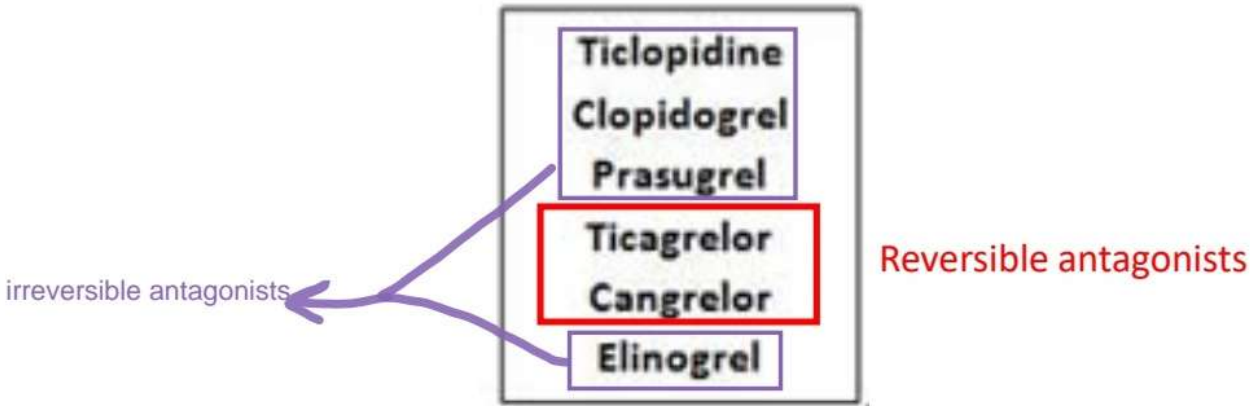
during the synthesis of thrombus, in step no.5 ,we have said that " activating platelets, as they are being active and able to activate other platelets, they secrete many meiators such as thrompoxin, A2 ,thrombin,serotonin, ADP...etc. ADP wo rks as signalling molecule,binds with resting platelets in order to activate it , also ADP has an ability to increase intracellular calcium.....the action of P2Y12 is "brakeing ADP" to stop further activation of platelets.



* ADP has a special receptors on resting platelets, this called "P2Y12 receptors"

$P2Y_{12}$ Receptor Antagonists

Mechanism of Action



$P2Y_{12}$ Receptor Antagonists

Duration of Action

they are different in duration of action :

Ticlopidine	3-4 days
Clopidogrel	3-5 days
Prasugrel	2-4 hours
Ticagrelor	1-3 hours
Cangrelor	2 minutes (IV)
Elinogrel	

$P2Y_{12}$ Receptor Antagonists

Therapeutic Uses

Clopidogrel → most common one, usually associated with aspirin

1. the prevention of atherosclerosis associated with MI/acute coronary syndrome/stroke/peripheral artery disease → all of them are related to abnormal formation of thrombus.
2. Prevention of thrombosis during PCI → "peripheral coronary intervention", by this we enter from peripheral blood vessels and reach to coronary artery to open a stenosis there. during this process, pts are at risk of thrombus formation , because there is a foreign body (prope) move inside the BV , so we should give antithrombotic to pts.

Ticlopidine

1. Prevention of stroke/TIA

$P2Y_{12}$ Receptor Antagonists

Therapeutic Uses

Prasugrel

1. the prevention of thrombotic events in patients with ACS (unstable angina, ST- and non-ST- elevation MI, MI after PCI) NOT STROKE

Ticagrelor

1. the prevention of thrombotic events in patients with ACS NOT STROKE

Cangrelor

1. Adjunct to PCI

**prasugrel and ticagrelor aren't used for stroke , because they increase the cerebral bleeding which is life threatening.

$P2Y_{12}$ Receptor Antagonists

Pharmacokinetics

- Require oral loading doses (except cangrelor)
- Heavily protein-bound in plasma
- Metabolized by CYP450
- Eliminated renally/fecally

it's a prodrugs , need metabolism by CYP2C19" in order to convert it into active form (i.e it's metabolite is the active form)

Medication	Drug Interactions
Clopidogrel	Strong CYP2C19 inhibitors reduce antiplatelet effect (e.g., *omeprazole*)
Prasugrel	Anticoagulants Other antiplatelets
Ticlopidine	Antacids—decreases levels *Cimetidine*—reduces clearance
Ticagrelor	Strong CYP3A4 inhibitors (e.g., *ketoconazole*) Strong CYP3A4 inducers (e.g., *rifampin*)

$P2Y_{12}$ Receptor Antagonists

*pts could be poor or high metabolizer depending on genatic varies to CYP2C19.
*pts with polymorphism in CYP2C19, and they are poor metabolizer---> these aren't able to convert clopidogrel into it's active form sufficiently.
so that before give clopidogrel to pts , its too important to make pharmacogenetic tests.

Pharmacokinetics

Clopidogrel

- Prodrug
- Metabolized into active metabolite by CYP2C19
- Poor metabolizers due to polymorphism in CYP2C19→reduced response
- Screening

What happens if you combine clopidogrel with omeprazole?
other drugs that inhibit CYP2C19 such as omeprazole and esomeprazole should not be administered concurrently with dopidogrel.

$P2Y_{12}$ Receptor Antagonists

Adverse effects

reduce the no. of leukocytes in blood stream.

- Bleeding (no antidote)

Ticlopidine → agranulocytosis, TTP, aplastic anemia

Prasugrel , ticagrelor→ contraindicated in patients with stroke/TIA

so that, these drugs have a black box warning that food and drugs organization put it on their leaflet (these boxes are shown next slide)

Medication	Adverse Effects
Clopidogrel	Bleeding SJS
Prasugrel	Angioedema Bleeding Headache Hyperlipidemia Hypertension
Ticlopidine	Abnormal LFT Bleeding Dizziness GI disturbances SJS
Ticagrelor	Bleeding Dyspnea Headache Raised SCr

$P2Y_{12}$ Receptor Antagonists

Black Box Warnings

Potential for significant, sometimes fatal, bleeding

- Do not use in patients with active bleeding or a history of transient ischemic attack (TIA) or stroke
- Generally not recommended for age >75 years (increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients [diabetes or prior MI])
- Do not initiate in patients undergoing urgent coronary artery bypass grafting (CABG); if possible, discontinue at least 7 days before any surgical procedure
- If possible, manage bleeding without discontinuing (risk of subsequent cardiovascular events is increased if prasugrel stopped, particularly in first few weeks after ACS)

Additional risk factors for bleeding

- Weight <60 kg
- Propensity to bleed (eg, recent trauma, recent surgery, recent or recurrent GI bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate-to-severe renal impairment)
- Concomitant use of other drugs that increase bleeding risk

Prasugrel

Black Box Warnings

Like other antiplatelet agents, can cause significant, sometimes fatal, bleeding

Do not use with active pathological bleeding or a history of intracranial hemorrhage

Do not start in patients planned to undergo urgent coronary artery bypass graft surgery (CABG); when possible, discontinue at least 5 days prior to any surgery

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures after starting ticagrelor

If possible, manage bleeding without discontinuing; stopping ticagrelor increases risk of subsequent cardiovascular events

Aspirin dose and ticagrelor effectiveness

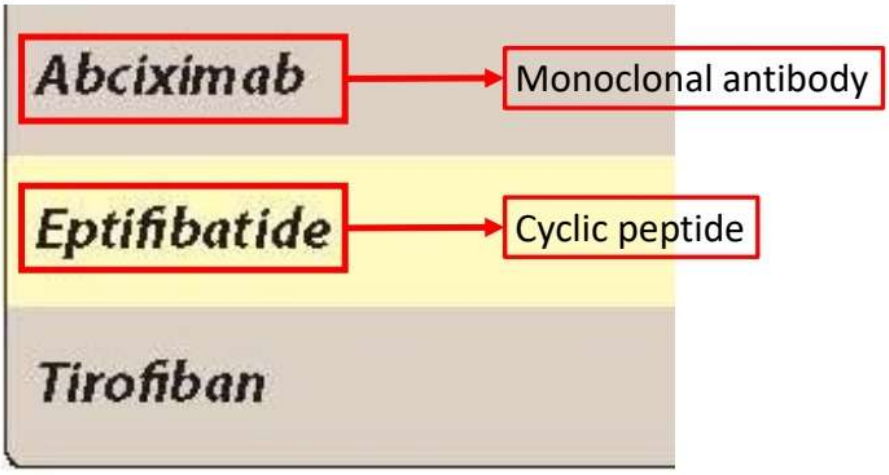
- Aspirin maintenance dose >100 mg reduces the effectiveness of ticagrelor and should be avoided
- After any initial loading dose, use with aspirin 75-100 mg/day

Ticagrelor

Glycoprotein IIb/IIIa Inhibitors

Generally, they prevent linkage btw platelets through GP IIb/IIIa receptor.

Glycoprotein IIb/IIIa Inhibitors

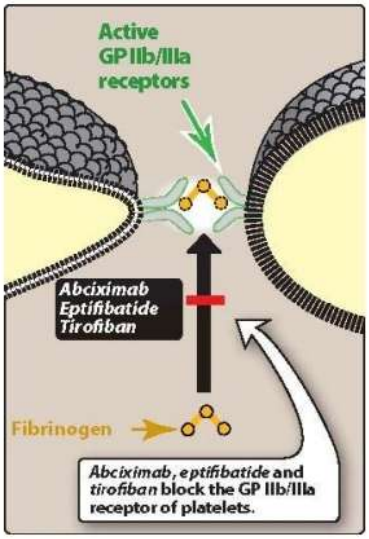


Glycoprotein IIb/IIIa Inhibitors

Mechanism of Action

- Block GP IIb/IIIa → prevent the binding of fibrinogen and VWF

platelet aggregation



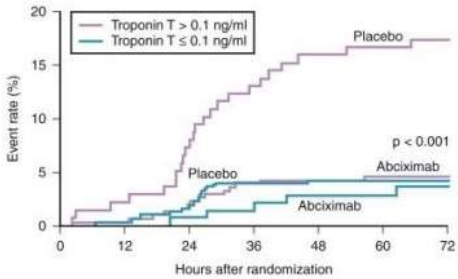
Glycoprotein IIb/IIIa Inhibitors

Therapeutic uses

- given as an adjunct to PCI for the prevention of cardiac ischemic complications
- Abciximab is approved for unstable angina not responding to conventional therapy

not MI

given IV



Glycoprotein IIb/IIIa Inhibitors

Pharmacokinetics

- Given IV
- Rapidly degraded in plasma
- Platelet function is restored within 24-48 hours

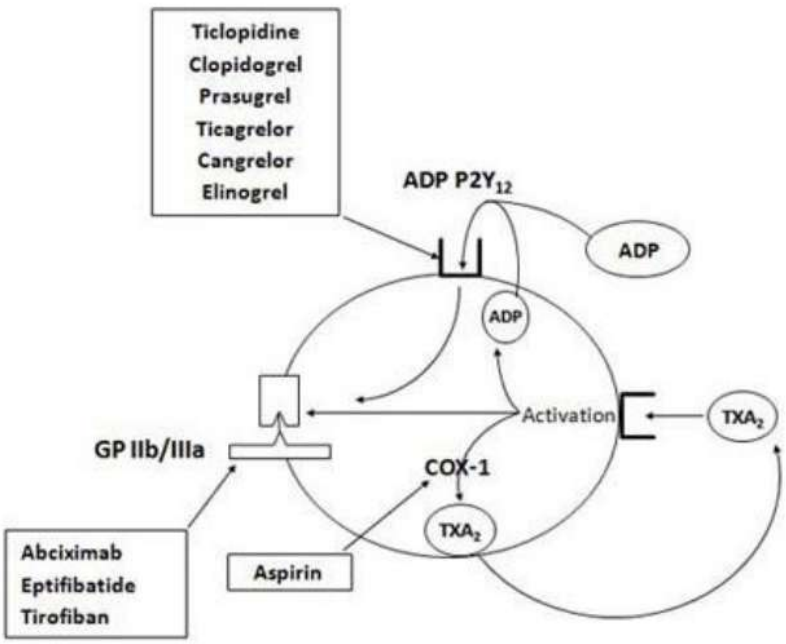
Medication	Drug Interactions
Abciximab	For all agents: Increased bleeding: *Ginkgo biloba* Antiplatelets Salicylates SSRIs and SNRIs
Eptifibatide	
Tirofiban	

Glycoprotein IIb/IIIa Inhibitors

Adverse effects

- Bleeding

Medication	Adverse Effects
Abciximab	For all agents: Hypotension Nausea Vomiting Thrombocytopenia
Eptifibatide	
Tirofiban	



Dipyridamole

Dipyridamole

this is the enzyme that is responsible of stop degradation of cAMP , and high cAMP level means that platelets still in rest state (i.e prevent activation of platelets)

Mechanism of action

- Coronary vasodilator
- Phosphodiesterase inhibitor → ↑ platelet cAMP levels
- ↓ thromboxane A_2 synthesis
  - ↓ platelet adhesion to thrombogenic surfaces

Therapeutic uses

1. Stroke prevention (with aspirin)

Dipyridamole is contraindicated in unstable angina because it causes coronary vasodilation (coronary steal phenomenon)

Cilostazol

Cilostazol

Mechanism of action

Phosphodiesterase III inhibitor → ↑ platelet cAMP levels

(prevent degradation of cAMP ---> increase cAMP level ---> resting platelets)

Therapeutic uses

Treatment of intermittent claudication

Contraindicated in patients with heart failure

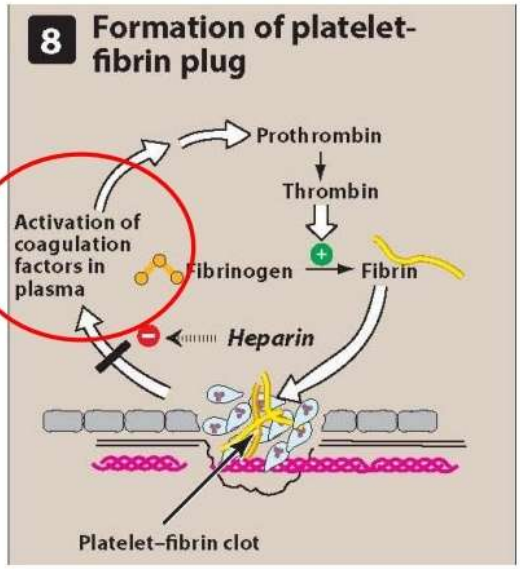
Anticoagulants

Pharmacology and Toxicology
HLS Module
Second Year Medical Students
Tareq Saleh, MD, PhD
Faculty of Medicine
The Hashemite University

Plug (Clot) Formation

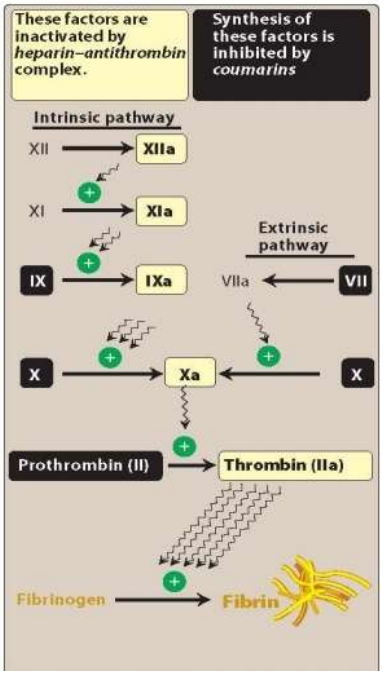
- From previous lecture

during synthesis of thrombus, we have said that in step no.8 ,a plug of activated platelets activate coagulation pathways which at the end activate prothrombi (II)into thrombin (IIa) ,and this will convert soluble fibrinogen found in blood into insoluble fibrin fibrin that deposide into plug of platelets abd form



Blood Coagulation

- Intrinsic pathway
- Extrinsic pathway

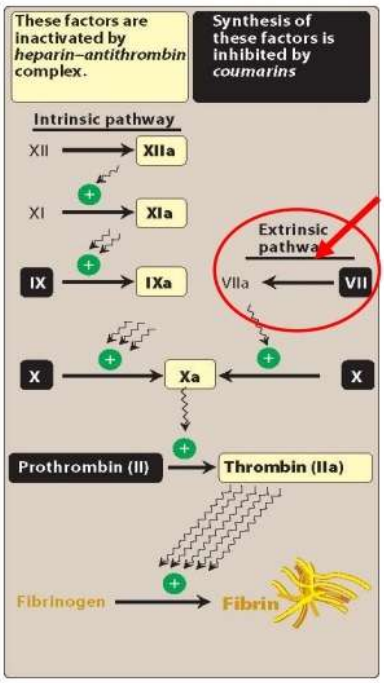


Blood Coagulation

- Intrinsic pathway
- **Extrinsic pathway**

both pathways are activated by different factors, for example: - extrensic pathway is achieved by tissue factor(thromboplastin) which is transmembrane receptor hidden under the endothelium , it is exposed upon endothelial injury.

** in case of endothelial injury, thromboplatstin will expose to the blood, and convert factor VII into it's active form which will convert factor X into Xa and this will convert prothrombin(II) into thrombin(IIa) and this us the main target for both intrinsic and extrinsic pathways.

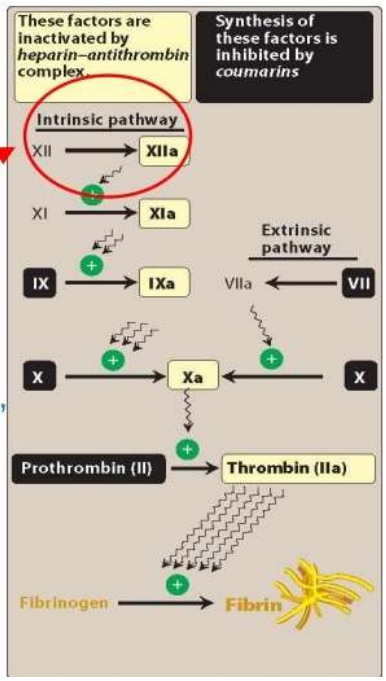


Tissue Factor (thromboplastin) Transmembrane receptor that becomes exposed upon endothelial injury

Blood Coagulation

- **Intrinsic pathway**
- Extrinsic pathway

Contact with exposed collagen



*it usually happens when there is a direct connect btw blood and exposed subendothelial collagen .

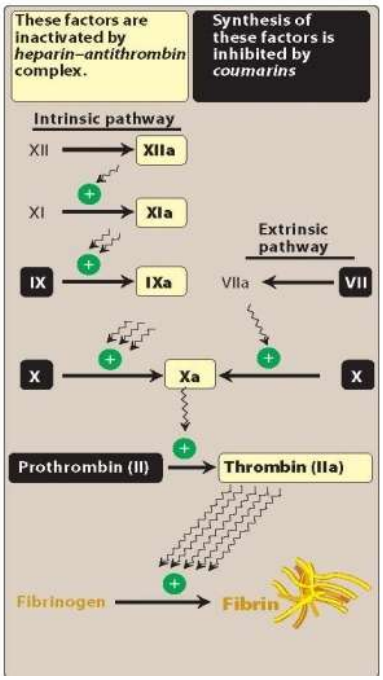
**it starts with factor XII which is converted into XIIa , and this will activate XI into XIa then XIa activates X into Xa which help in converting prothrombin into thrombin and at the end thrombus will be formed.

Blood Coagulation

- Intrinsic pathway
- Extrinsic pathway

- Coagulation factors are serine proteases (zymogens)

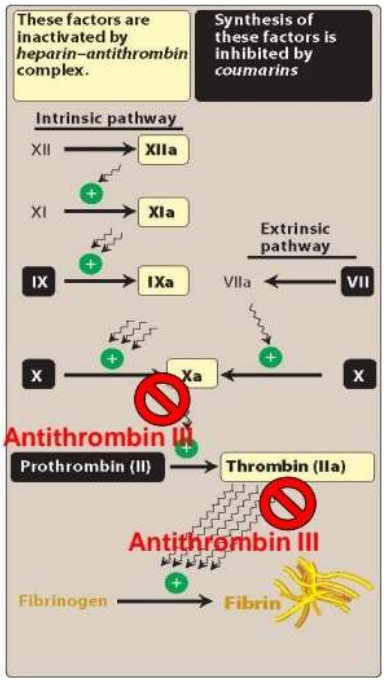
means that these factors are found normally in blood stream "in inactive form", when it is activated, it will be effective and able to do action (clevage effect).



Formation of Fibrin

- Intrinsic pathway
- Extrinsic pathway

- Both pathways result in the activation of factor X which cleaves prothrombin into thrombin
- Antithrombin III inactivates thrombin and factor Xa



Inhibitors of Coagulation

- In addition to **antithrombin III**, what are other inhibitors of coagulation?

❑Protein C

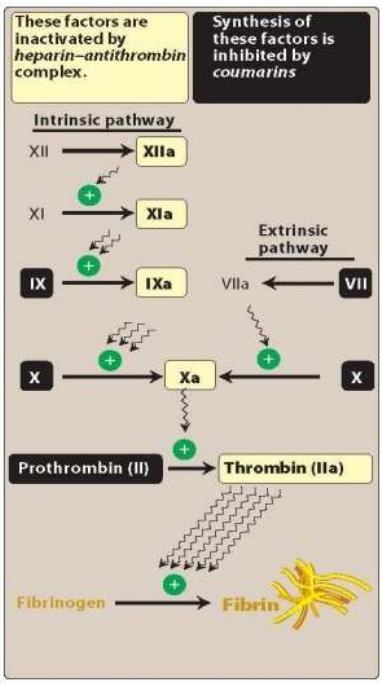
❑Protein S

❑Tissue factor pathway inhibitor

* people with protein S or C deficiency are at risk of forming thromboembolism disorders and frequent miscarriage for pregnant women

What are possible mechanisms to interfere with the coagulation pathway?

→ this will discuss during lecture

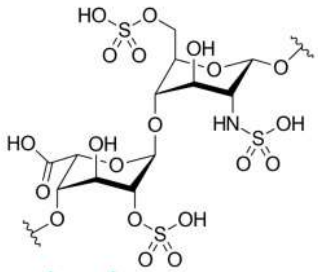


Parenteral Anticoagulants

→ can be given IM , IV and SC

Heparin is the most common one.

- Rapid acting
- Injectable
- Naturally-derived macromolecule (complexed with histamine in mast cells)
- Extracted from porcine intestinal mucosa



*it is glycosaminoglycan (suger and protein)

Heparin has 2 forms:

- **Unfractionated heparin:** mixture of straight-chain, anionic, highly acidic glycosaminoglycans (wide range of molecular weights).

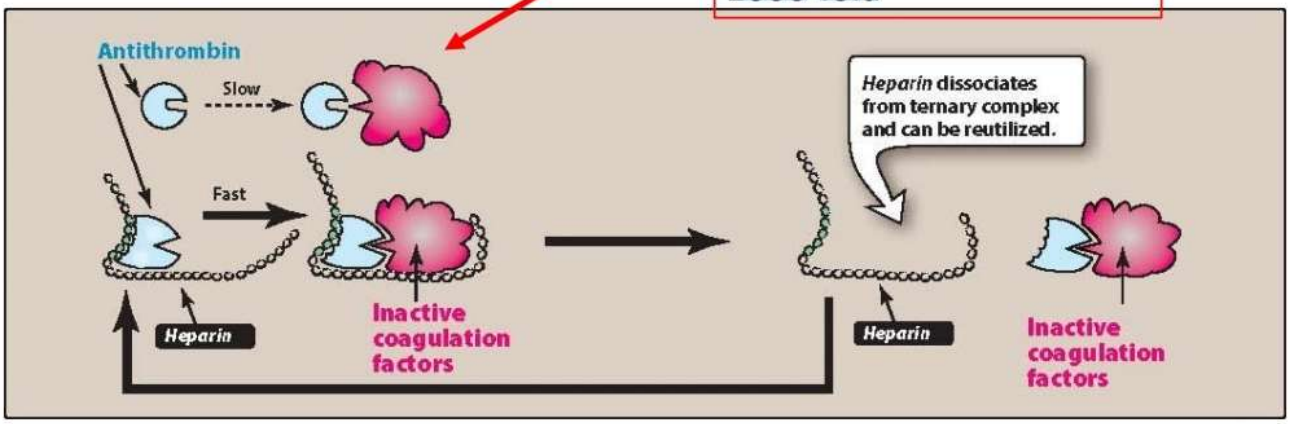
- **Low Molecular Weight forms of Heparin (LMWH):** heterogenous compounds about one-third the size of unfractionated heparin.
  - enoxaparin
  - dalteparin

*Generally, heparin increases the effect of antithrombin III which works against the function of thrombin by inactive coagulation factors.

Heparin

Mechanism of action

Heparin results in a conformational change that catalyzes the inhibition of thrombin 1000-fold

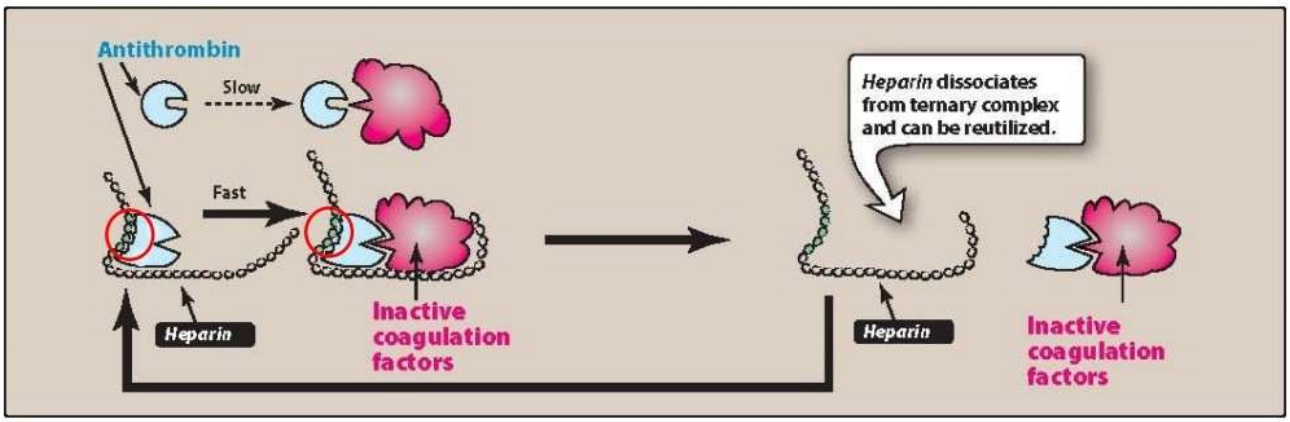


Heparin

Mechanism of action

~~5 glucose residues~~

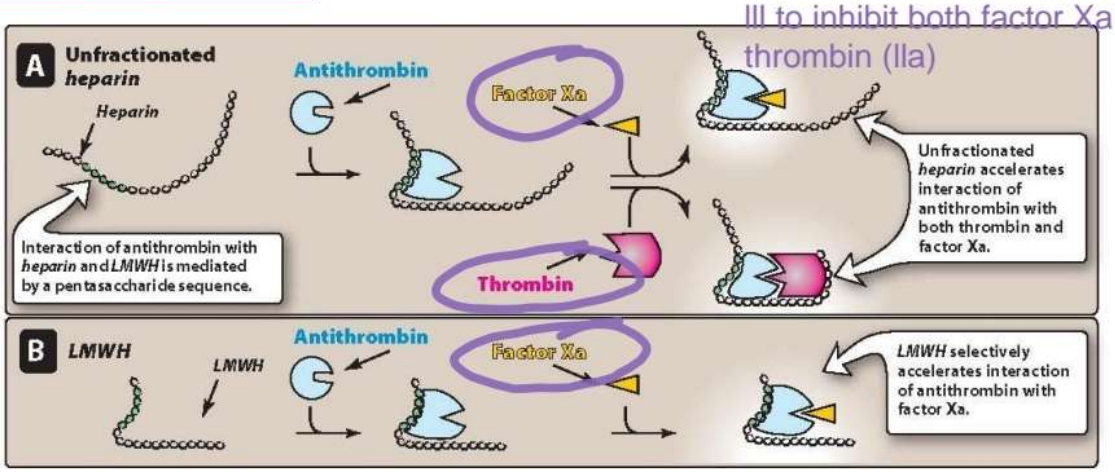
A unique pentasaccharide permits the binding of heparin to antithrombin III



Heparin

LMWH association with antithrombin III only inhibits **Xa** , but according to unfractionated heparin, it activates antithrombin III to inhibit both factor Xa and thrombin (IIa)

Mechanism of action



Heparin

Therapeutic uses

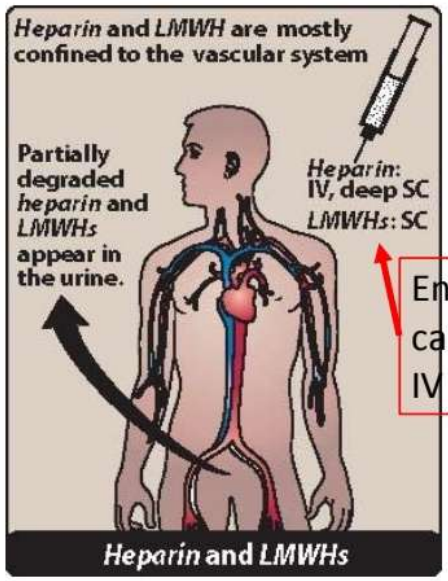
A. Treatment of acute venous thromboembolism (DVT and PE).
B. Prophylaxis of postoperative venous thrombosis e.g., hip replacement and MI
C. Treatment of choice for thrombotic disease in pregnant women.
   Why? because it can't pass through placenta, so it doesn't have teratogenic effect.

- LMWH do not require monitoring and can be given in the outpatient setting.

Heparin

Pharmacokinetics

- Given IV, SC
- Bolus (initial)
- maintenance: low doses, continuous infusion, titrated based on aPTT or anti-Xa levels
- LMWH requires 4 h to achieve maximum anticoagulation



Enoxaparin can be given IV for MI

Heparin

Pharmacokinetics

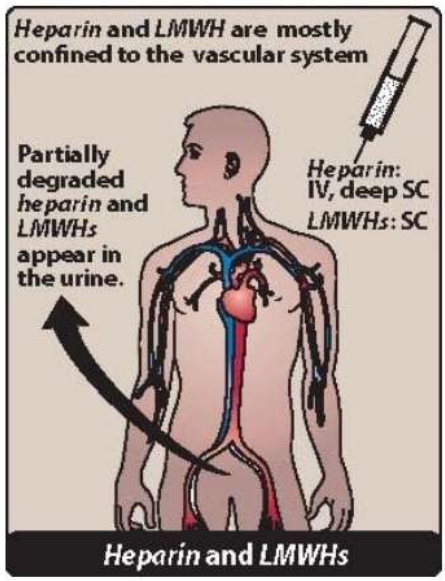
Unfractionated heparin:

heavily protein-bound; unpredicted pharmacokinetics

-requires monitoring

because there is a risk of bleeding

* also it is usually given in hospital



Heparin

Pharmacokinetics

LMWH:

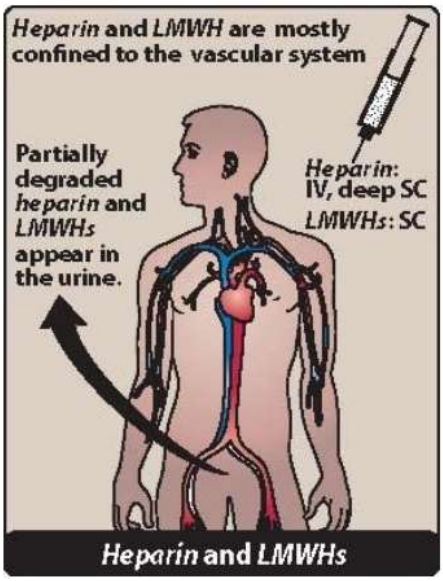
More predictable pharmacokinetics

-does not require monitoring of coagulation values

HOWEVER

Monitor in cases of:

Renal impairment, pregnancy, obesity

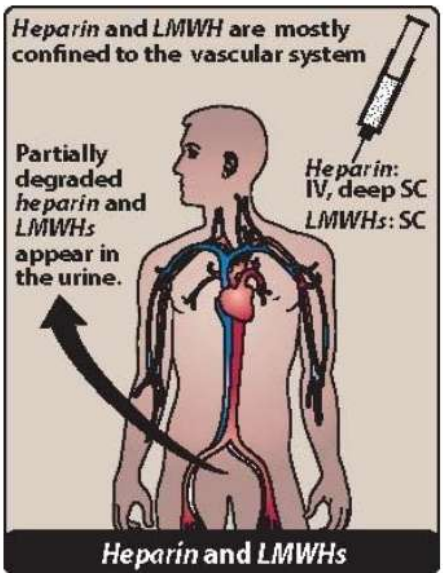


Heparin

Pharmacokinetics

Degradation:

Heparin is taken up/degraded by monocyte/macrophage system



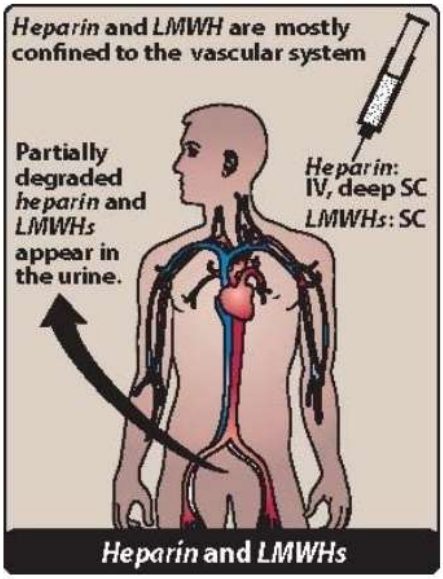
Heparin

Pharmacokinetics

Elimination:

LMWH and inactive, degraded heparin are eliminated by renal clearance.

What happens in cases of kidney disease?



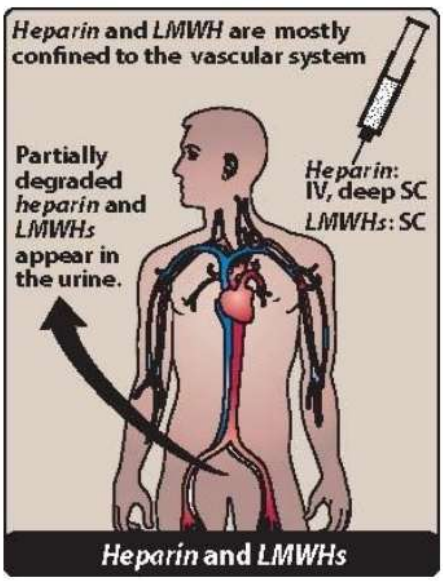
Heparin

Pharmacokinetics

Half-life:

Unfractionated: 1.5 h

LMWH: 3-12 h



Heparin

has a similar structure with heparin , it binds with heparin in order to inactive it and stop it's action.

Adverse effects

❑**Bleeding**

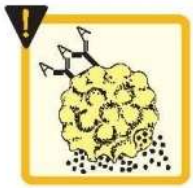
- Requires monitoring
- Treatment: discontinue heparin, give antidote

Antidote: protamine sulfate

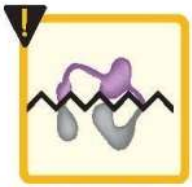
- Forms stable 1:1, inactive complexes with heparin
- Titrated slowly (1 mg for 100 unit of heparin). Why?

because if it is given rapidly and in high dose , this could increase bleeding (work as heparin because both have the same structure)

Bleeding



Hypersensitivity



Thrombo-cytopenia

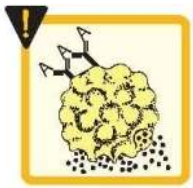
Heparin

Adverse effects

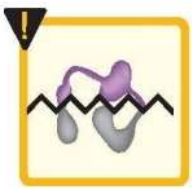
❑**Hypresensitivity, antigenicity**

- chills, fever, urticaria, anaphylactic shock
- Why? because it is naturally derived

Bleeding



Hypersensitivity



Thrombo-cytopenia

THE END

BEST WISHES 😊😊🌹🌹