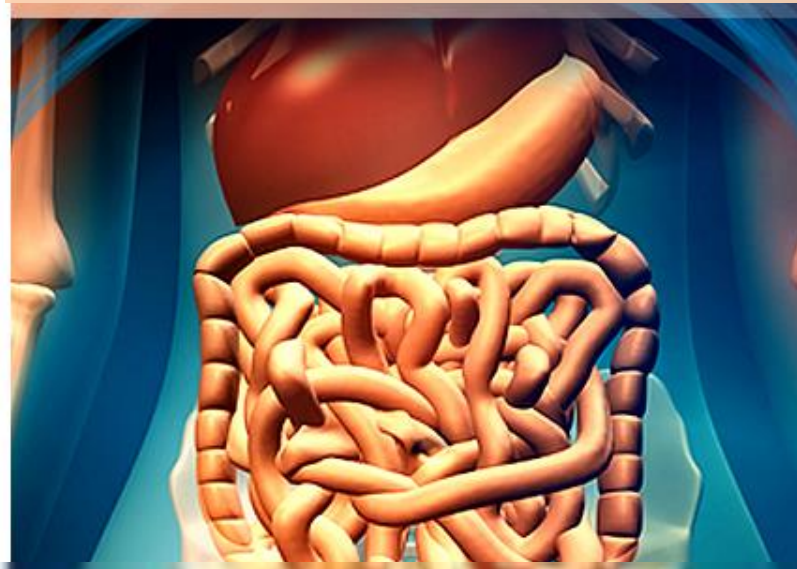
King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

PHARMACOLOGY 433

MED 433 Teams



Lecture 10:
Anti-platelets drugs

objectives

- **Describe different classes of anti-platelet drugs and their mechanism of action.**

- **Understand pharmacological effects, pharmacokinetics, clinical uses and adverse effects of anti-platelet drugs.**

Mind map

ANTIPLATELET DRUGS

Arachidonic acid pathway inhibitors

Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation
Ex.
Aspirin

ADP pathway inhibitors

specifically and irreversibly inhibit ADP receptor of subtype P2Y12
Ex.
Ticlopidine & Clopidogrel

Glycoprotein IIb/IIIa inhibitors

inhibits platelet aggregation
Ex.
Abciximab

act as fibrinogen like mimetic agents
Ex.
Tirofiban & Eptifibatide

Phosphodi-esterase inhibitors

Inhibits phosphodiestrase thus increase cAMP
Ex.
dipyridamole

Platelets and vessels

introduction

In healthy person, nitric oxide and prostacyclin are released from endothelial cell of blood vessel to inhibit aggregation of platelet and formation of CLOT !

In contrast , when the blood vessel injured , (Platelet + Endothelial system + coagulation factors) got activated to form Clot , that lead to prevent escape of blood out of vessel !

Clot

Thrombus	**CLOT that adheres to vessel wall . (Stable)**
Embolus	**CLOT that floats in the blood . (moveable)**

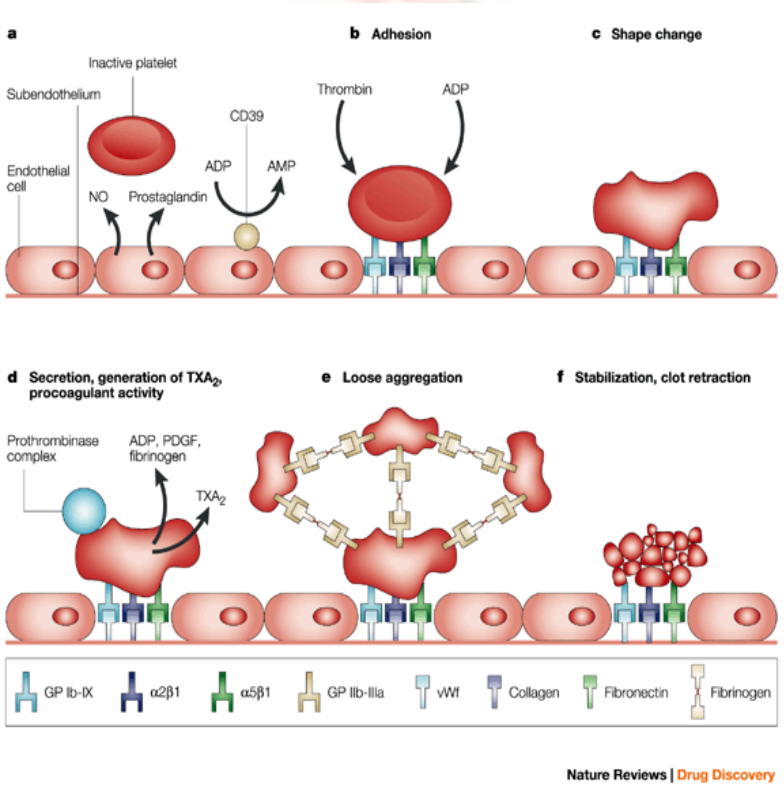
Thrombosis : formation of unwanted clot within the blood vessel, producing life threatening conditions such as: Acute myocardial infarction, Acute ischemic stroke, Deep vein thrombosis, Pulmonary embolism.

Refresh your mind : 

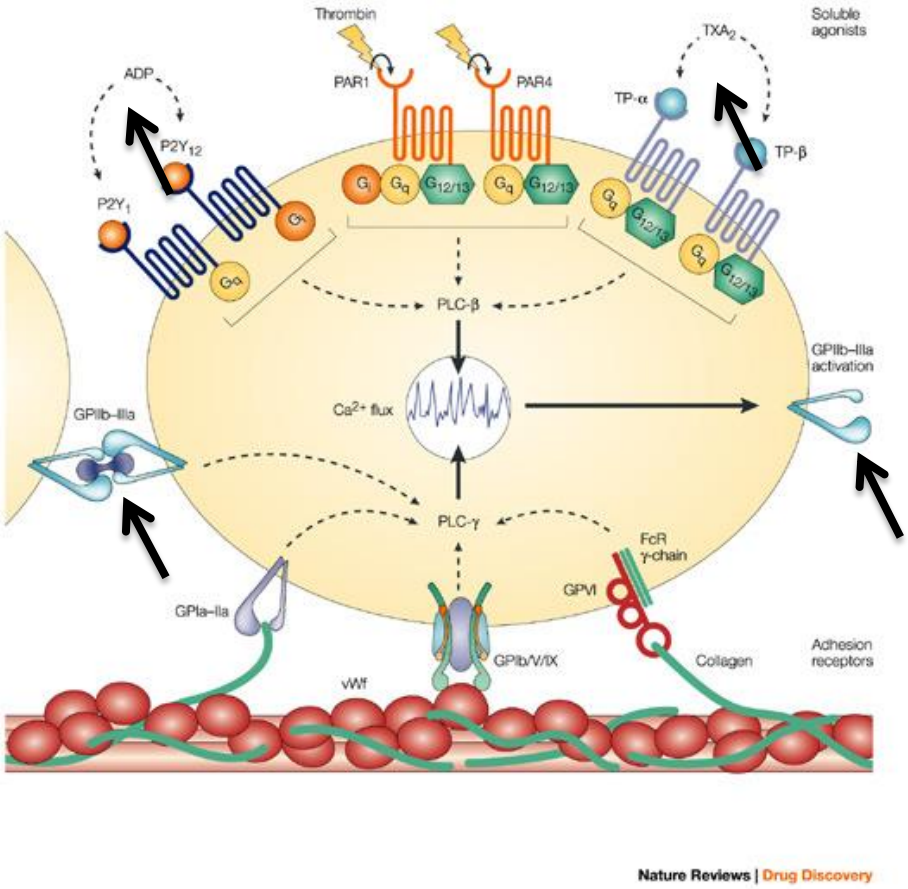
Role of platelet

introduction

Platelet adhesion then activation then aggregation.



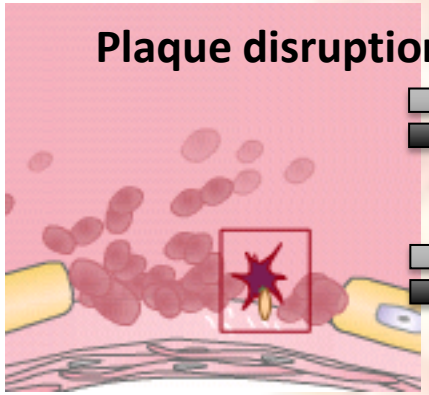
Platelet receptors that play role in clot formation.



When we inhibit those pathways, we will <u>prevent</u> adhesion or activation or aggregation of platelets ..

Mechanism of action of Anti-platelets drugs

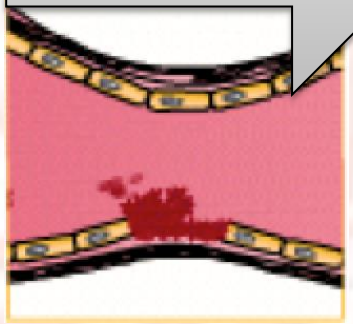
introduction



Collagen

vWF*

Platelets adhesion and secretion



Aspirin

COX1 Release TXA2

Release ADP

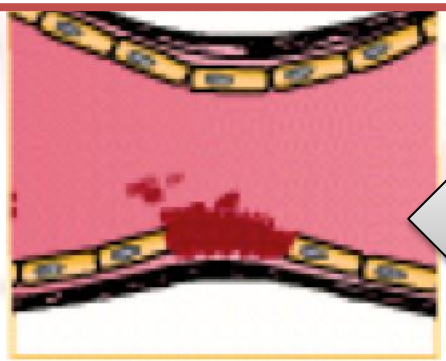
Clopidogrel
Ticlodipine

Platelets recruitment and activation

Active GP IIb\IIIa

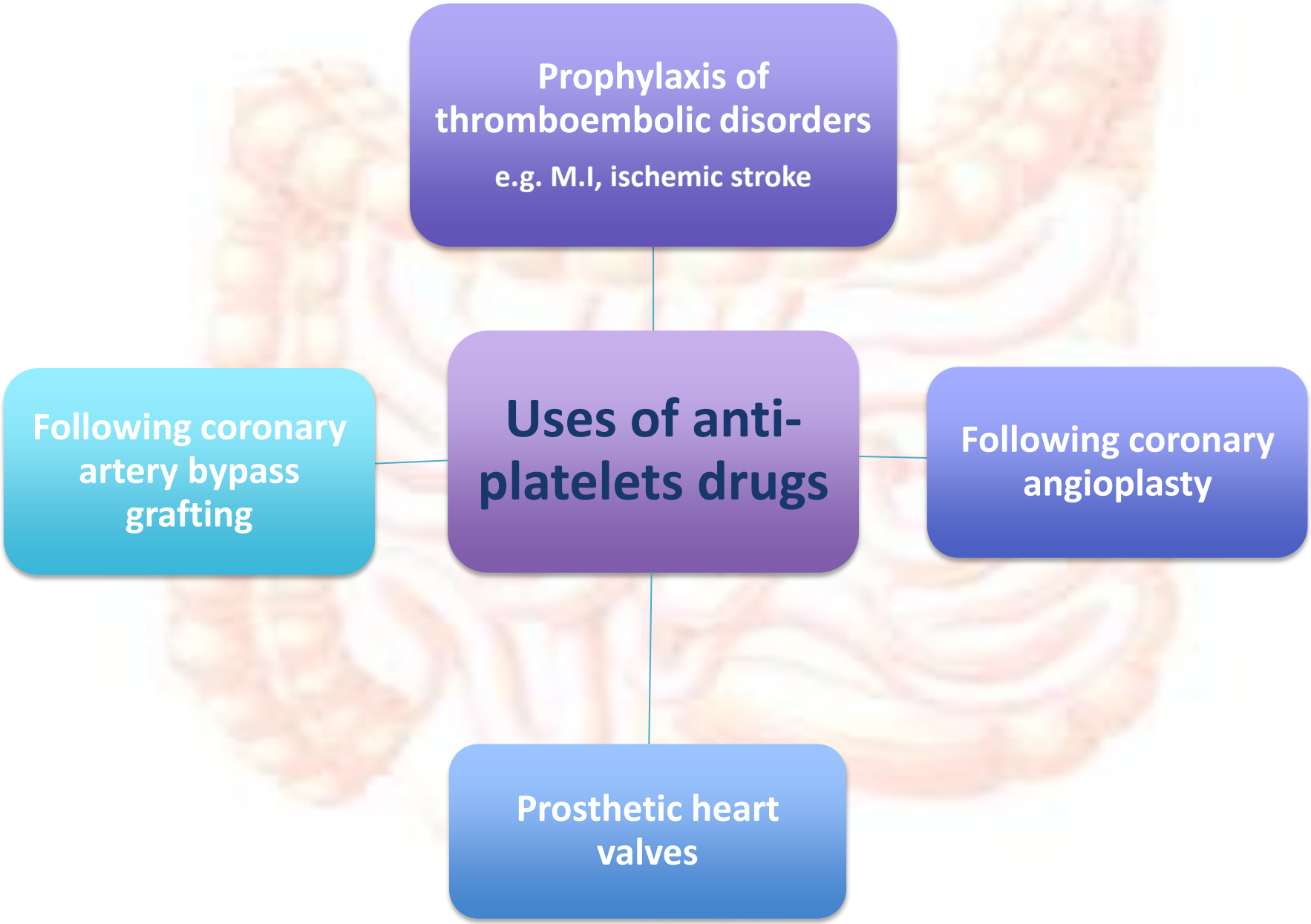
Abciximab, Tirofiban, Eptifibatide

Platelets aggregation



*von willebrand factor

slide | doctor's note | important | explanation



slide doctor's note important explanation

Drugs used in thrombosis

Thrombolytics or Fibrinolytics: act by dissolving existing or already formed thrombi or emboli (used in the acute treatment of thrombosis).

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).

CLASSIFICATION OF ANTIPLATELET DRUGS

- ARACHIDONIC ACID PATHWAY INHIBITORS: E.G ASPIRIN
- ADP PATHWAY INHIBITORS: E.G. TICLOPIDINE - CLOPIDOGREL
- PHOSPHODIESTERASE INHIBITORS: E.G. DIPYRIDAMOLE
- GLYCOPROTEIN IIB/IIIA INHIBITORS: E.G. ABCIXIMAB – EPTIFIBATIDE -TIROFIBAN

1-Arachidonic Acid pathway inhibitors : Aspirin (Acetylsalicylic Acid)

M.O.A	- Irreversible inhibition of cyclooxygenase enzyme (COX-1) via acetylation. Small dose inhibits thromboxane (TXA2) synthesis in platelets But not prostacyclin (PGI_2) synthesis in endothelium (larger dose)
Dose	commonly 81 mg enteric coated tablet/day
Uses	➢ Prophylaxis of thromboembolism ➢ e.g. prevention of transient ischemic attack, ischemic stroke and myocardial infarction. ➢ Prevention of ischemic events : in patients with unstable angina pectoris. ➢ can be combined with other antiplatelet drugs (clopidogrel) or anticoagulants (heparin).
Side effect	➢ Risk of Peptic Ulcer. ➢ Increased incidence of GIT bleeding (aspirin prolongs bleeding time)

slide | doctor's note | important | explanation

2- ADP pathway inhibitors

1-Ticlopidine & 2-clopidogerl (more potent)

***MOA:**

Block all the receptors P2Y12 (purinergic receptor and is a chemoreceptor for adenosine diphosphate (ADP).) in the platelets' surface **"irreversibly"** which inhibit platelets aggregation & activation.

***Pharmacokinetic:**

- Given orally & it is a pro-drug (requires activation)
- Slow onset of action 3-5 days
- Bound to plasma proteins
- Microsomal "CYTP450" inhibitor > inc. plasma levels of phenytoin and carbamazepine "Anti-epilepsy"

***Drug interaction of ADP inhibitors :**

inhibit CYT P450 causing increased plasma levels of drugs such as phenytoin and carbamazepine.

*2ry prevention: prevent reoccurrence of the attacks "prophylaxis"

USES

- **2ry prevention* of ischemic complication after Myocardial infarction, ischemic stroke and unstable angina.**
- Pt. sensitive to aspirin due to G.I problems.

Adverse reactions

- **Severe neutropenia "CBC should be done regularly"**
- **Bleeding:** prloong bleeding time
- **G.I problems (nausea, dyspepsia, diarrhea)**
- **Allergic reaction**

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2-Clopidogrel: "has replaced ticlopidine"

- More potent than ticlopidine.(75mg to 250mg)
- Longer duration of action & Less frequency of administration. (given once daily).
- Less side effects (less neutropenia).
- Bioavailability is unaffected by food

Indication: *As prophylactic to prevent reoccurrence*

- patient with history of recent myocardial infarction, stroke or established peripheral arterial disease.
- Acute coronary syndrome "ACS" (Angina & M.I): those managed medically or with percutaneous coronary intervention "PCI" with or without stent.

3-New ADP pathway inhibitors

Prasugrel:	Ticagrelor:	Uses:
Irreversible inhibitor of P2Y12 receptors	Reversible inhibitor of P2Y12 receptors	Prophylactic: reduce the rate of thrombotic cardiovascular events in patients with ACS who are managed by PCI

- Both have rapid onset of action than clopidogrel
- They do not require any hepatic activation
- Given orally

Adverse reaction:

- Increase the bleeding of risk
- Ticagrelor causes dyspnea "difficulty in breathing"

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4-Glycoprotein IIb\IIIa receptor inhibitors

Abciximab – Tirofiban & Eptifibatid (the only drugs administrated as I.V infusion)

MAO:

They bind to & block GPIIb\IIIa receptors on platelets surface to inhibits their aggregation.

1) Abciximab:

Prevent the binding of fibronigen, von Willebrand factor, and other adhesive molecules to all GPIIb/IIIa receptors sites on activated platelets.

Pharmacokinetic:

Given I.V. infusion

Indication:

- **Prevention of ischemic cardiac complications in patients undergoing percutaneous coronary intervention (PCI) "emergency".**
- **Can be used in combination with aspirin and heparin. "risk of bleeding"**

2) Tirafiban & Eptifibatide:

Occupy the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen (act as fibrinogen mimicry agents*).

Pharmacokinetic:

Given I.V. infusion

Indication:

- **Reduce the incidence of thrombotic complication during coronary angioplasty "PCI".**

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

***Mimicry agent:** they hace the same structure as fibrinogen but antagonist in action.

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5-Dipyridamole:

Vasodilator & phosphodieterase inhibitor

MAO:

Inhibits phosphodiestrase > increase cAMP > decrease the Ca2+ influx > decrease the synthesis of thromboxane A2 and other platelet aggregating factors.

Given orally

Indications: (As adjunctive therapy; never given alone)

- **Prophylaxis: with warfarin (vit.K antagonist) of thromboembolism in cardiac valve replacement patients.**
- **2ry prevention with aspirin of stroke and transient ischemic attack.**

Adverse reation:

-Headache.

-Postural hypotension >> it was used as anti-hypertension drug when 1st discovered .

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Summary

Classification	Drugs	Mechanism of action	Uses	Side effects
Arachidonic acid pathway inhibitors	Aspirin (orally)	- Irreversible inhibition of COX-1 via acetylation - Small dose inhibits TXA2 synthesis in platelets - Larger dose inhibits PGI2 synthesis in endothelium	- Prophylaxis of thromboembolism - Prevention of ischemic events in unstable angina pectoris	- Peptic Ulcer. - GIT bleeding
ADP pathway inhibitors	Ticlopidine (orally)	specifically and irreversibly inhibit ADP receptor of subtype P2Y12 to prevent platelet aggregation	Secondary prevention of ischemic complications after MI, ischemic stroke and unstable angina.	- Sever neutropenia (less in Clopidogrel) - Bleeding - G.I.T - Allergic reactions
	Clopidogrel (orally)		- Recent MI, Recent Stroke or Established Peripheral Arterial Disease - Acute Coronary Syndrome	
PDE inhibitors	Dipyridamole (orally)	Inhibits phosphodiestrase → ↓TXA2	- prophylaxis of thromboembolism in cardiac valve replacement with warfarin - Secondary prevention of stroke and transient ischemic attack with aspirin.	- Headache - Postural hypotension
New PDE inhibitors	Prasugrel	Irreversible inhibitor of the P2Y12 receptor	reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are to be managed by PCI.	- increase bleeding risk - Ticagrelor causes dyspnea
	Ticagrelor	Reversible inhibitor of the P2Y12 receptor		
Glycoprotein IIb/IIIa inhibitors	Abciximab I.V	inhibits platelet aggregation by preventing the binding of fibronigen to GPIIb/IIIa receptor	Prevention of ischemic cardiac complications in patients undergoing PCI	
	Tirofiban I.V	occupying the site on glycoprotein IIb/ IIIa receptor that is required to bind the platelet to fibrinogen	reduction of incidence of thrombotic complications during PCI	
	Eptifibatide I.V			

Quiz yourself

Answers 1.A , 2.C , 3.B , 4.A , 5.A , 6.C , 7.B , 8.B

Q1: A 30-year-old female who underwent mitral valve replacement. She is taking drug A in addition to warfarin. What is drug A ?
A- dipyridamole
B- aspirin
C- abciximab

Q2: Which one of the following can cause dyspnea ?
A- eptifibatide
B- abciximab
C- ticagrelor

Q3: What's the mechanism of action of Prasugrel ?
A- Inhibit P2Y12 receptor reversibly
B- Inhibit P2Y12 receptor irreversibly
C- Inhibit PDE

Q4: A 45- year-old male who came to the ER with MI and underwent PCI. From history, he is on phenytoin. Which is the best protective drug to give in this case ?
A- Prasugrel
B- ticlopidine
C- clopidogrel

Q5: which one of the following could cause neutropenia ?
A- Ticlopidine
B- ticagrelor
C- tirofiban

Q6: one of Dipyridamole side effect is :
A- peptic ulcer
B- hypertension
C- postural hypotension

Q7: one of the differences between clopidogrel & ticlopidine is
A- clopidogrel has shorter duration of action
B- clopidogrel is more potent
C- ticlopidine has less side effect

Q8: A 55-year- old male came to GP with severe abdominal pain after meals & hyperacidity . Endoscopy shows gastric ulcer. From history, he is a heavy smoker for 25 years and taking drug A as cardio protection. What's drug A that can be the cause of his illness ?
A- dipyridamole
B- aspirin
C- abciximab

Done by

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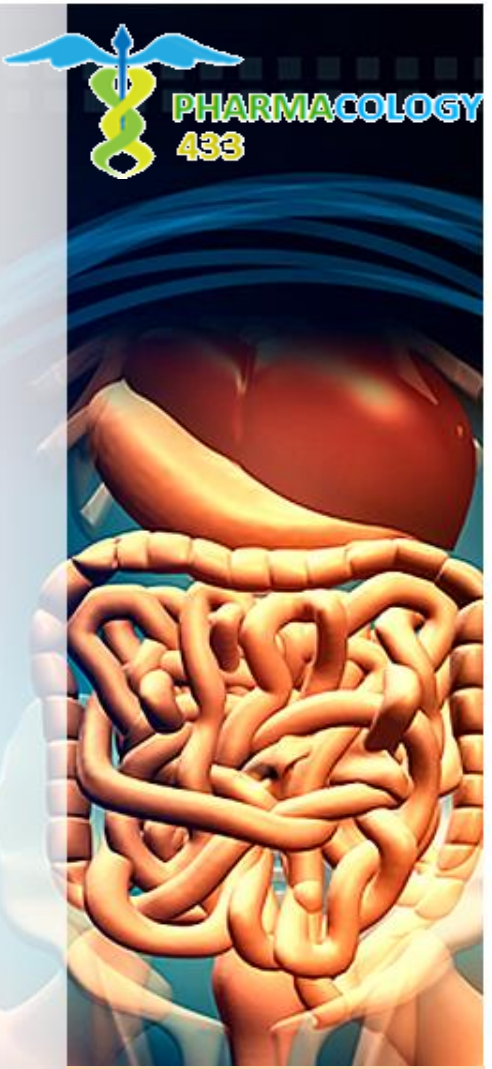
Munira AL Mehsen	

It always seems impossible until it is done

BEST OF LUCK



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Good luck ☺