PHARMACOLOGY

TEAM 432

Anti-Platelet Drugs

Objectives

Not Given

Color Guide

Slides = Black

Females slides = Green

Males slides= Blue

Explanation=Orange

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Terminology

What is a Clot ?

Blood clot a coagulum in the bloodstream formed of an aggregation of blood factors, primarily platelets.

A clot could be :

1. **THROMBUS:** is the CLOT that adheres to vessel wall
2. **EMBOLUS:** is the CLOT that floats in the blood
3. **THROMBOSIS:** is the formation of unwanted clot within the blood vessel, producing life threatening condition. Ex :

A. Acute myocardial infarction
B. Acute ischemic stroke
C. Deep vein thrombosis
D. Pulmonary embolism

Physiological Aspects

- In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide (NO) and prostacyclin (on of the prostaglandins: PGI2) released by endothelial cells lining the blood vessels

- An injury to vascular system leads to interaction between Platelets, Endothelial system and Coagulation factors which lead to formation of the CLOT.

- Injury exposes reactive subendothelial matrix proteins, platelet adherence & activation ??(see next slide) .

- Also, there is secretion & synthesis of vasoconstrictors & platelet activating molecules Such as :

I. Thromboxane A_2 (TXA_2) is synthesized from *arachidonic acid* within platelets & is platelet activator & potent vasoconstrictor. (opposite to Prostaglandin)

II. Adenosine diphosphate (ADP), secreted from platelet, a powerful inducer of platelet aggregation, Causes stickiness of the platelets

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

Physiological Aspects

- **Activation** of platelets lead to **aggregation** & **conformational change** in the **GP11b/111a,** enabling it to bind **fibrinogen**, which cross-links adjacent platelets, aggregation & formation of a platelet plug.

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

NOTE

Since that the physiological part is not the Main lecture objective, you should refer to physiology lectures for more understanding of the coagulation process. ☺

Here is a short video if you're interest

http://www.youtube.com/watch?v=0pnpoEy0eYE

Anti Platelet Drugs

- **Antiplatelets (drugs which prevent and inhibit platelet aggression)**

	Mechanism of action	Drug
(1) Orally	Inhibition of thromboxane A2 synthesis via inhibiting COX-1	Aspirin
(2) Orally	Inhibition of ADP-induced platelet aggregation (Antagonist of ADP receptors)	Clopidogrel Ticlopidine
(3) Orally	Phosphodiestrase 3 (PDE) inhibitors / adenosine uptake inhibitors	Dipyridamol Cilostazol
(4) IV	GP IIb / IIIa receptor antagonists (Inhibitors)	Abciximab Tirofiban Eptifibatide

Remember \ They are different from :

Anticoagulants drugs: which prevent clotting by inhibiting clotting factors)

Thrombolytics (Fibrinolytics) drugs: which reduce or lysis the clot.

In Acute cases (emergencies), Fibrinolytics are the drugs of choice (as treatment) Anticoagulant & Antiplatelet are for prevention mainly (that's why most of their uses are for 2dry disease or inhibiting recurrence)

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Aspirin

MOA	Uses	Adverse effects	Notes
irreversible inhibition (acetylation) of cyclooxygenase enzyme-1 (COX-1) thus inhibits the synthesis of thromboxane A 2 **Remember that :** thromboxane A 2 causes platelet aggregation.	• Prophylaxis of thromboembolism e.g.\ 1. unstable angina 2. myocardial infarction 3. ischemic stroke • Can also be used in combination with other antiplatelet aggregating drugs (Clopidogrel) and anticoagulant drugs (Heparin) **Aspirin is the most commonly prescribed antiplatelet drug (First choice)**	Hyperacidity Contraindication Peptic ulcer Route Oral	Aspirin should be given with a low dose (75-160 mg **Why ??** Because it will selectively inhibits COX-1 , decreasing synthesis of platelet TxA2 and inhibit platelet aggregation. Aspirin in low dose does NOT inhibits (spares) PGI2 synthesis by endothelium. **Remember that :** Prostacyclin (also called prostaglandin I2 or PGI2) inhibits platelet activation and is also an effective vasodilator.

Clopidogrel & Ticlopidine

Clopidogrel	Ticlopidine
MOA	
irreversibly block ADP receptors on platelets (This action inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets.)	
USES	
To prevent thrombosis. **Could be used in prevention of vascular events in patients with :** • **transient ischemic attacks** • **unstable angina pectoris** • **placement of a coronary stent**	
Adverse Effects	**Adverse Effects**
• **same but fewer than ticlopidine**	• **nausea , dyspepsia , diarrhea** • **hemorrhage** • **leucopenia** • **TTP (thrombotic thrombocytopenic purpura)**

Clopidogrel & Ticlopidine

Clopidogrel	Ticlopidine
Notes	Notes
works by reducing the "stickiness" of platelets Its recommended as an alternative for people who cannot take aspirin ========== clopidogrel is more potent than ticlopidine and has a better safety profile, clopidogrel has replaced ticlopidine. long duration of action Given once daily	Therapy with ticlopidine requires regular monitoring of WBCs for neutropenia during the first 3 monthes. Given twice Daily

Ticlopidine and clopidogrel are prodrugs that require metabolism by the hepatic cytochrome P450 (CYP) enzyme system to active form.

Monoclonal Antibodies

Abciximab	Tirofiban & Eptifibatide

MOA

GP IIb / IIIa receptor Blockers (antagonists)

Remember that : GPIIb/IIIa is found on the surface of platelets and when activated, GPIIb/IIIa binds adhesive molecules, such as fibrinogen and vWF to promote clotting.

Abciximab binds to GPIIb/IIIa and stops the clot fromation	Tirofiban and eptifibatide inhbit platelets binding to fibronogen

USES

To prevent thrombosis.

Could be used in prevention of ischemic cardiac complications in :

- Acute coronary syndrome (ACS)
- Percutaneous coronary intervention

Adverse Effects

- Bleeding
- Thrombocytopenia (immune reaction)

Clopidogrel & Ticlopidine

Abciximab	Tirofiban & Eptifibatide
Notes	**Notes**
Abciximab is non-competitive and has long duration of action	Tirofiban & Eptifibatide are competive and have short duration of action
Clinical Efficacy of abciximap: ❖ Uses in acute MI patients ❖ Abciximab is administered iv as an adjuvant to angioplasty surgery for the prevention of ischemic complications of angioplasty ========== Given parenteraly only ========== Heparin or aspirin is given with abciximab	

Cilostazole

MOA: Phosphodiesterase inhibitor (on PDE3).

increases cAMP

Promots Vasodilation

Inhibit platelet aggregation

(Phosphodiesterase normally break down cAMP, when they're inhibited→ Inc. cAMP)

**(its not more used as anti platelet drug because of is side effects on the heart, e.g. **

Tachycardia (because of increase cAMP effect)

Its used To prevent intermittent claudication

Claudication refers to the pain, aching or fatigue of the muscles of the buttocks, thigh and/or calf that occurs with exertion. This pain or cramping is caused by poor circulation due to blockage of the arteries of the lower extremity

Side notes from the lecture

- clopidogrel & aspirin may be recommended for people who have had a heart attack, a severe attack of angina, or who have undergone a coronary angioplasty & stenting.

- **Monitoring :**

Bleeding time should be monitored

(Antiplatelet drugs increase bleeding time)

Aspirin Resistance:

Resistance: recurrent thrombosis while on antiplatelet therapy.

The reported incidence of resistance varies greatly, from 5 % to 75%.

Although aspirin reduces the production of TX_{A2}, it may fail to inhibit platelet aggregation because platelets continue to respond strongly to other agonists.

TX_{A2}-induced platelet aggregation is only ONE of many factors leading to thrombus formation, which is the most common, but not the only, mechanism leading to ischemic events.

Test Your Knowledge???

Q1\ which of the following drugs could causes neutropenia :

a-- tirofiban
b-- ticlopidine
c-- clopidogrel

Q2\ which of the following is the MOA of aspirin :

a-- Decreases TXA2 synthesis
b-- Blocks TXA2 receptor
c-- Blocks GP IIb / IIIa receptor

Q3\ which of the following is taken I.V. only :

a-- Aspirin
b-- Clopidogrel
c-- Abciximab

Q4\ a 50 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 most likely to produce those symptoms :

a-- Abciximab
b-- Aspirin
c-- Clopidogrel

Answers \ (C - A - C - B)

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