Fibrinolytic and Antiplatelet Drugs

Disclaimer

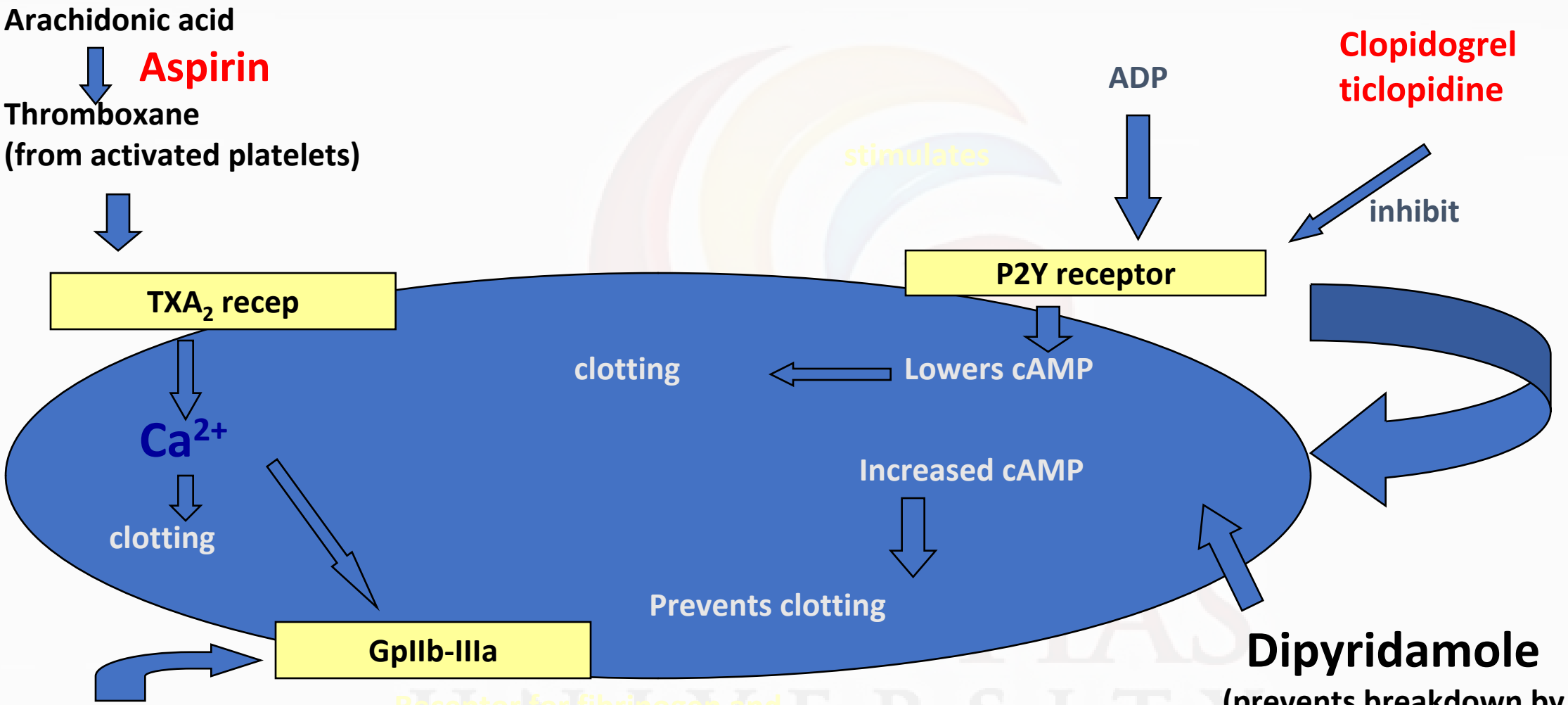
All the content material provided here is only made for teaching purpose.

Blood fluidity

- The endothelial lining is non-thrombogenic
- Balance between procoagulants (thromboxane, thrombin, activated platelets, platelet factor 4) and anticoagulants (heparan sulfate, prostacyclin, nitric oxide, antithrombin)

- 1. heparin & derivatives – stimulate natural inhibitors of coagulant proteases (antithrombin)
- 2. coumarin anticoagulants – block multiple steps in the coagulation cascade
- 3. fibrinolytic agents – lyse pathological thrombi
- 4. antiplatelet agents – aspirin

Antiplatelet drugs



Antiplatelet drugs

Ticlopidine: is a prodrug

It blocks platelet ADP receptor and prevents activation and aggregation

Is often used in combination with aspirin (synergistic action), for angioplasty and stenting surgery

Used to prevent secondary strokes and in unstable angina

Severe neutropenia – 1% of patients

Clopidogrel :
Similar to ticlopidine and used same way
Less incidence of neutropenia or thrombocytopenia
Used in combination with aspirin

Heparin

Heparin - originally isolated from the liver

Found in mast cells -storage of histamine & proteases

Rapidly destroyed by macrophages

Normally not detected in the blood

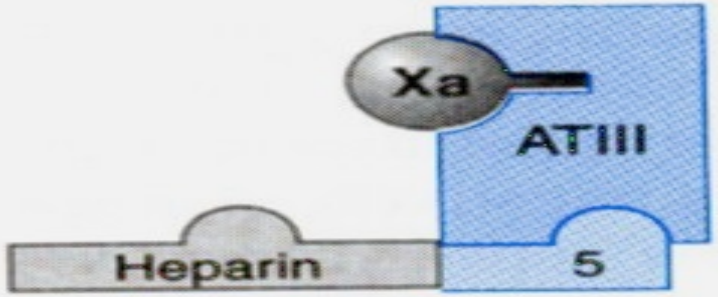
Heparan sulfate - similar to heparin but less polymerized - contains fewer sulfate groups

Found on the surface of endothelial cells and in the extracellular matrix

Interacts with circulating antithrombin to provide a natural antithrombotic mechanism

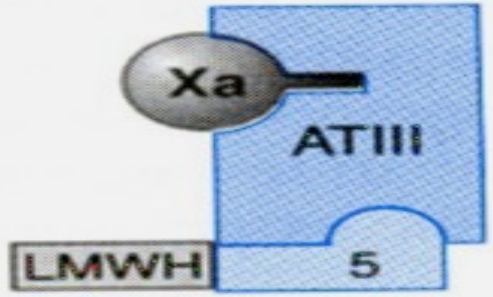
Heparin & LMW Heparins difference in action

Binds to antithrombin III (ATIII)
and thrombin (IIa)
(inactivates IIa)



Binds to antithrombin III (ATIII)
via pentasaccharide
(sufficient to inactivate Xa)

Binds to antithrombin III (ATIII)
but not to thrombin (IIa)
(poorly inactivates IIa)



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Heparin – Toxicity

- Hemorrhage – recent surgery, trauma, peptic ulcer disease, platelet dysfunction
- Life-threatening bleeding can be reversed by protamine sulfate - 1 mg of protamine sulfate for every 100 U of heparin - slow iv infusion – 50 mg over 10 min)
- Protamine sulfate interacts with platelets, fibrinogen, and other clotting factors - an anticoagulant effect – at higher doses
- Anaphylactic reactions to protamine (a basic protein isolated from Salmon sperm)

Heparin-induced Thrombocytopenia

50% decrease in platelet count - <150,000/µl)

Antibodies against complexes of heparin with platelet factor 4

In 3-5% of patients 5 to 10 days after initiation of heparin therapy

Lower incidence with low mol wt heparin

In 1/3 of pts is preceded by thrombosis

Can be life-threatening

Alternative anticoagulants – lepirudin or danaparoid

Low Molecular Weight Heparins

Avg mol. wt 4,500 daltons - 15 monosaccharide units

Better absorbed - higher bioavailability

Longer biological half-life

More predictable dose-response - does not bind to plasma proteins, macrophages, or endothelial cells

Can be given s.c. without lab monitoring in an outpatient setting

Cleared unchanged by kidney (do not use in renal failure!) rather than by the reticuloendothelial system

Lower risks of thrombocytopenia and bleeding

Safety and use during pregnancy not evaluated

LMW heparins

Dalteparin

Enoxaparin

Uses:

1. prevention of venous thromboembolism
2. Treatment of venous thrombosis, pulmonary embolism and unstable angina
3. prophylaxis following total knee arthroplasty

Other parenteral anticoagulants

Danaparoid

nonheparin glycosaminoglycans (84% heparan sulfate)

Promotes inhibition of Xa by antithrombin

Prophylaxis of deep vein thrombosis

In patients with heparin-induced thrombocytopenia

Lepirudin

recombinant derivative of hirudin (a direct thrombin inhibitor in leech)

In patients with heparin-induced thrombocytopenia

Coumarins (warfarin)

- inhibits vitamin K reduction
- efficacy measured by INR (International Normalized Ratio), the patient's PT divided by the PT in pooled plasma
- takes 4-5 days to become effective – active carboxylated factors in plasma need to be cleared
- small Vd, steep D-R curve, metabolized by CYP1A and CYP2C9 (interactions)
- Warfarin crosses placenta – is teratogenic – birth defects and abortion
- major indications: DVT, PE and atrial fibrillation

Warfarin interactions

1. the uptake or metabolism of oral anticoagulant or vitamin K
2. the synthesis function or clearance of any factor or cell involved in hemostasis or fibrinolysis
3. the integrity of any epithelial surface

Warfarin Uses

Prevent acute deep vein thrombosis or pulmonary embolism

Prevent venous throboembolism in patients undergoing orthopedic or gynecological surgery

Prevent systemic embolization in patients with myocardial infarction, prosthetic heart valves or chronic atrial fibrillation

Warfarin – Antidote

Vitamin K (oral or parenteral)

$INR = (PT_{pt} / PT_{ref})^{ISI}$ Target 2.0 to 3.0

Streptokinase

- Binds plasminogen- coverts to plasmin
- Dissolve clots after myocardial infarction, deep vein thrombosis, massive pulmonary emboli
- Side effects: Bleeding, allergic reactions, hypotension, fever.

Tissue plasminogen activator (t-PA) – (alteplase)

> activates fibrin bound plasminogen (less systemic plasmin formation)

> More expensive than streptokinase

References

1. Tripathi KD. ‘Essentials of Medical Pharmacology’, 6th edition, Jaypee Brothers Medical publications (P) Ltd., New Delhi, 2003.
2. Satoskar RS, Ainapure SS, Bhandarkar SD, Kale AK, ‘Pharmacology and pharmacotherapeutics’, 14th edition, Popular Prakashan, Mumbai, 1995.