THE UNIVERSITY OF WESTERN AUSTRALIA

DENT 3005:Introduction to Pharmacology

Haematology

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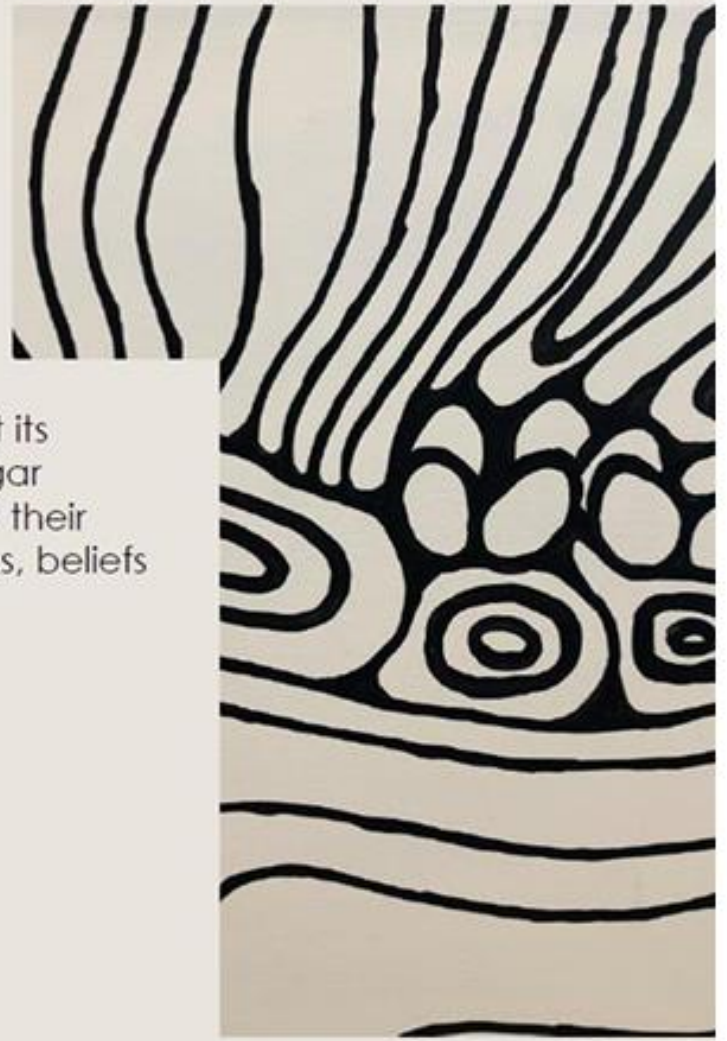
Acknowledgement of country

The University of Western Australia acknowledges that its campus is situated on Noongar land, and that Noongar people remain the spiritual and cultural custodians of their land, and continue to practise their values, languages, beliefs and knowledge.



Artist: Dr Richard Barry Walley OAM

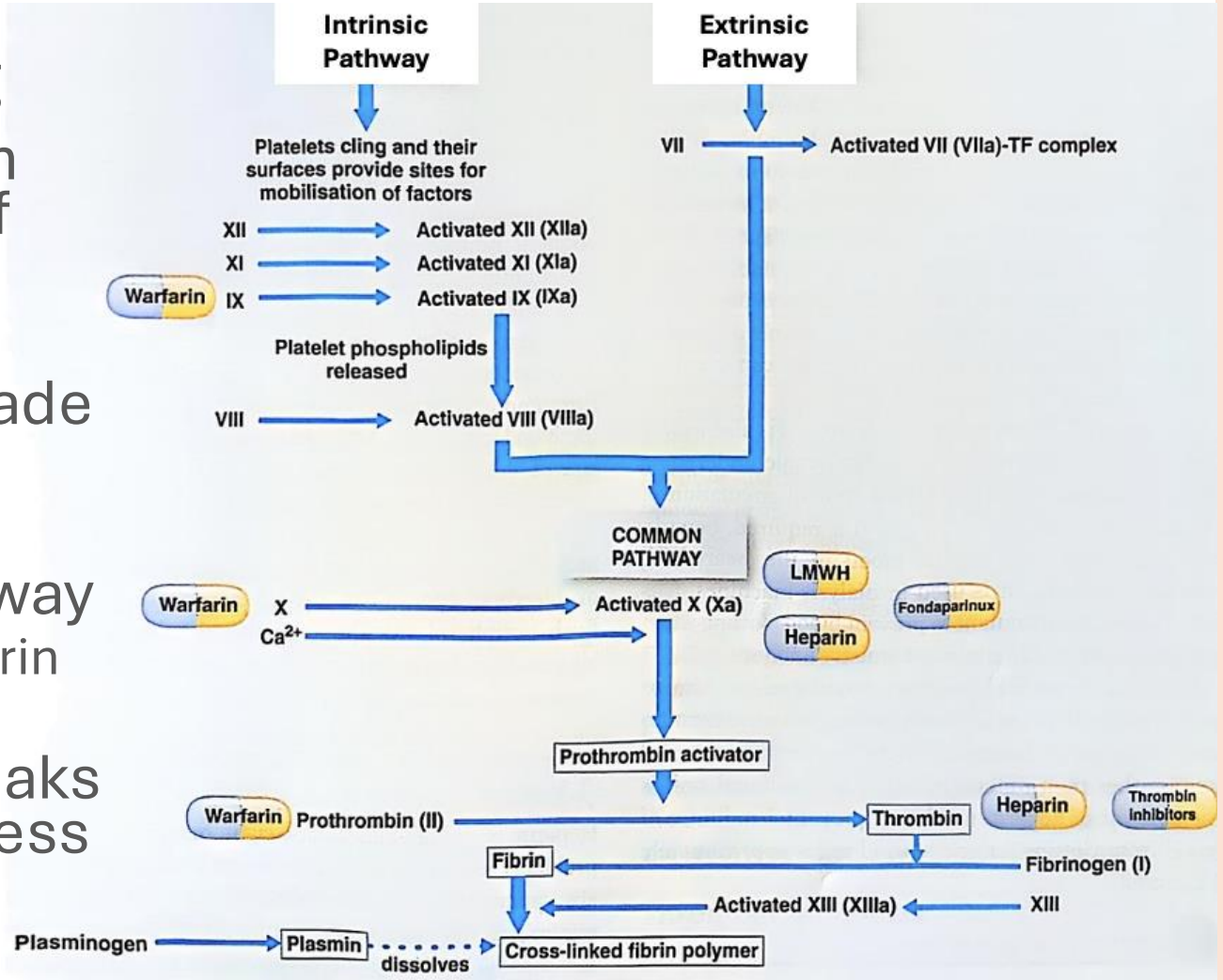
Learning Outcomes

Learning objectives

1) Understand the classes and mechanisms of haematological drugs
2) Identify common classes of haematological drugs: anticoagulants, antiplatelets, fibrinolytics, haemostatic agents, drugs used in blood disorders
3) Understand how these drugs impact coagulation and bleeding risks
4) Recognise risks for bleeding in relation to dental treatments and adjust management accordingly
5) Recognise when INR monitoring is necessary
6) Understand local haemostatic measures
7) Know the implications of haematological drugs and interactions in the dental setting

Normal Coagulation

- Haemostasis: to stop bleeding
- Primary haemostasis: forms an unstable platelet plug at site of injury
- Secondary haemostasis: activation of coagulation cascade to stabilize the plug
- Intrinsic & extrinsic pathway converge at the common pathway
  - Activation of factor X → Xa → fibrin clot
- Plasmin from plasminogen breaks down the clot after repair process is completed



Anticoagulants

- ‘Blood thinners’
  - Delay clotting of blood
- Interfere w/ coagulation cascade
- Reduce fibrin formation → prevent clot forming & growing
- **Indication**
  - Px & tx of venous thromboembolism
  - Ischaemic stroke & TIA
  - ACS

Antiplatelets

- Blood platelets are inactive until injury → clump & form thrombus
- Inhibit platelet aggregating
- **Indications**
  - Px & tx of ACS, ischaemic stroke & TIA

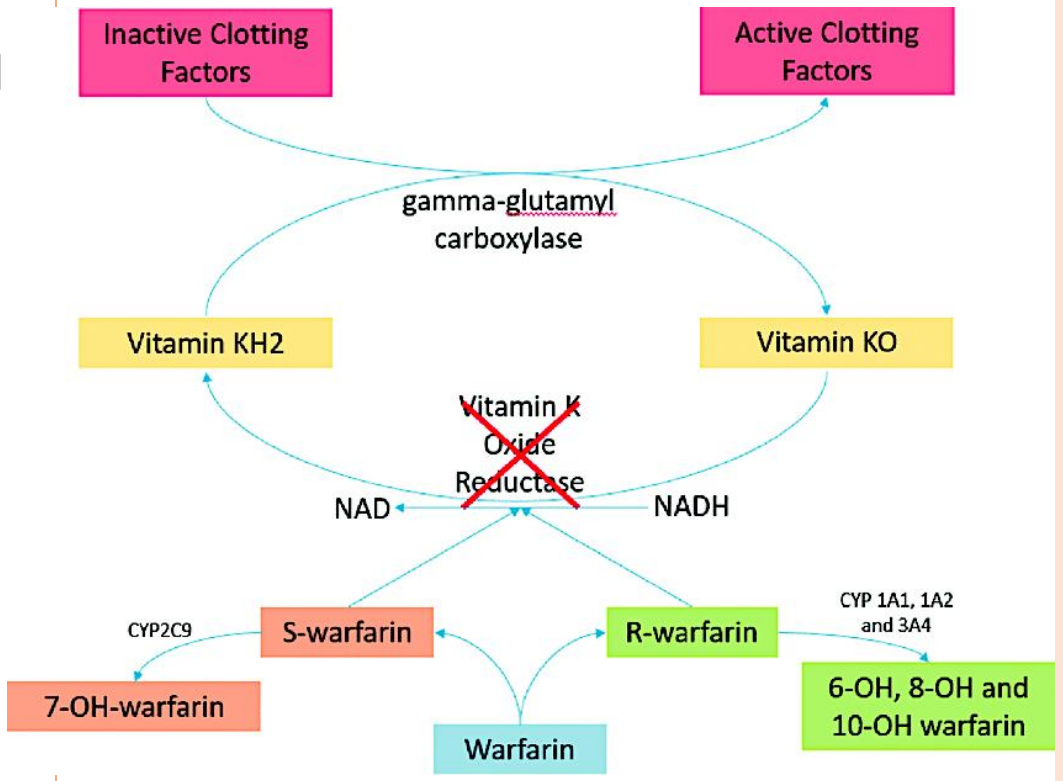
Anticoagulants

- **Heparins**
  - Binds ATIII→ inactivate clotting factors IIa (thrombin) & Xa
- **Direct Thrombin inH**
  - Reversibly inhibit both free and fibrin-bound thrombin
- **Factor Xa inH**
  - Selectively inhibit factor Xa, blocking thrombin production
- **Warfarin**
  - Vit K antagonist
  - Inhibits synthesis of vitamin K-dependent clotting factors (II, VII, IX, X)

Generic name	Brand Name
Heparins	
Dalteparin	Fragmin inj
Danaparoid	Orgaran inj
Enoxaparin	Clexane inj
Heparin	Heparin inj
Direct thrombin inhibitors	
Bivalirudin	Bivalirudin inj
Dabigatran	Pradaxa
Factor Xa inhibitor	
Apixaban	Eliquis
Fondaparinux	Arixtra inj
Rivaroxaban	Xarelto
Warfarin	Coumadin Marevan

Warfarin

- **MOA:** competitively inhibits the vitamin K epoxide reductase complex subunit 1 (VKORC1
- **Drug interactions (many)**
  - Aspirin, azoles, dicloxacillin, flucloxacillin, macrolides, metronidazole, NSAIDs, paracetamol, tetracyclines, tramadol
- **Dental implications: invasive procedures!**
  - Interruption only if advised by MGP
  - CHECK INR
    - Before procedure & recheck w/i 24hrs
    - INR < 3.5: perform procedure
    - INR >3.5: defer & refer



Antiplatelets

- **Glycoprotein IIb/IIIa inH**
  - Occupy glycoprotein IIb/IIIa receptor
  - Prevent binding of fibrinogen to platelet
  - Block platelet aggregation
- **$P2Y_{12}$ antagonists**
  - Binds to the platelet $P2Y_{12}$ receptor
  - Inhibits platelet aggregation
- **Aspirin**
  - Irreversibly inhibiting cyclo-oxygenase
  - Inhibits platelet aggregation
  - Reducing the synthesis of thromboxane A_2
- **Dipyridamole**
  - Inhibiting phosphodiesterase → increase platelet cAMP → inH platelet function

Generic name	Brand Name
Glycoprotein IIb/IIIa inhibitors	
Eptifibatide	Only through SAS
Tirofiban	Aggrastat inj
$P2y_{12}$ antagonists	
Clopidogrel	Clovix, Plavix
Prasugrel	Presugrel
Ticagrelor	Brilinta
NSAID	
Aspirin	Aspirin, Solprin
PDE inH	
Dipyridamole	Persantin inj

Thrombolytics

- **Alteplase & Tenecteplase**
  - Converts plasminogen →plasmin
  - Catalyses breakdown of fibrin
- **Indications**
  - Acute STEMI
  - Acute ischaemic stroke
  - Acute massive VTE in patients who are hemodynamically unstable

Generic name	Brand Name
Alteplase	Actilyse inj
Tenecteplase	Metalyse inj

Other

- **Other drugs affecting haemostasis**
  - **Tranexamic acid:** Blocks binding of plasminogen and plasmin to fibrin
  - **Vitamin K:** reverses effect of vitamin K antagonists
    - Essential cofactor in the synthesis of blood clotting factors II, VII, IX and X, and proteins C and S
- **Drugs for reversing anticoagulation**
  - **Vitamin K**
  - **Andexanet alfa:** Binds to apixaban or rivaroxaban → reduce their action
  - **Idarucizumab:** Binds w/ dabigatran and its metabolites → stable inactive complex
  - **Protamine :** Combines w/ heparin to → stable inactive complex

Generic name	Brand Name
Drugs affecting hemostasis	
Tranexamic acid	Cyklokapron
Vitamin K	Konakion inj
Reversing anticoagulation	
Andexanet alfa	Andexxa inj
Idarucizumab	Praxbind inj
Protamine	Protamine inj

Drugs for anemia

- **Erythropoietin agonists**
  - Recombinant glycoproteins that bind to erythropoietin receptors on erythroid progenitor cells → stimulate erythropoiesis
- **Folic acid**
  - Required for synthesis of purine and pyrimidine bases (DNA) and for amino acid metabolism and normal erythropoiesis
- **Iron**
  - Essential element required for the formation of haemoglobin and myoglobin.
- **Vitamin B_{12}**
  - Essential for nerve development, nucleic acid synthesis and normal erythropoiesis.

Generic name	Brand Name
Erythropoietin agonists	
Darbepoetin alfa	Aranesp inj
Epoetin Alfa	Eprex inj
Epoetin beta	NeoRecormon inj
Methoxy pegepoetin beta	Mircera inj
Other	
Folic acid	
Iron	
Vitamin B12	

Hematology Dental implications

Oral manifestations of hematopoietic disorders

- Pale oral mucosa (anaemia)
- Glossitis (inflamed, smooth tongue)
- Angular cheilitis (cracked mouth corners)
- Oral mucositis (painful sores, erythema, swelling)

Management of oral complications

- Oral mucositis: good oral hygiene, antiseptic rinses, topical anaesthetics
- Viral outbreaks: antiviral medications, self-care
- Fungal infections (candidiasis): antifungal agents
  Bacterial infections (periodontal disease): scaling, root planning, antibiotics

Role of dental professionals

- Early recognition of oral signs
- Multidisciplinary management approach
- Awareness of pharmacological implications

Hematology drugs-drug interactions

Direct thrombin & factor xa inhibitors

- Dabigatran, apixaban, rivaroxaban → PGP substrates
- Macrolides (clarithromycin, erythromycin), azole antifungals (ketoconazole, itraconazole) → increase bleeding risk

Warfarin interactions

- High interaction potential with:
  - Antibiotics: macrolides, tetracyclines, metronidazole
  - Antifungals: azoles (fluconazole)
  - NSAIDs, aspirin, paracetamol, tramadol
- Monitor INR levels, consult with physician

P2Y12 antagonists & opioids

- Prasugrel, ticagrelor → metabolized by CYP3A4
- Clarithromycin, erythromycin, azole antifungals → increase bleeding risk
- Opioids: delay platelet inhibition → consider delaying if pain is manageable

Key considerations for dental practice

- Review medication history for interactions
- Be cautious with antibiotics and antifungals
- Monitor bleeding during/after procedures
- Coordinate with medical providers for safe management

Antithrombotic drugs: considerations for oral & dental procedures

- **Recap**
  - ***Antithrombotic drugs:*** *oral anticoagulants, injectable anticoagulants, antiplatelets*
- **Risk Assessment:** Balance bleeding vs. thromboembolic risks
- **Specialist Referral:** Consider for high bleeding risk or complex procedures
- **Patient Guidance:** Seek help for persistent/restarting/concerned bleeding
- **NSAIDs:** Avoid; increase bleeding risk—use **paracetamol** instead
- **Conclusion:** Ensure safe management through clear communication and careful risk balancing

Figure 13.30 Important patient-related factors that increase the risk of prolonged bleeding from an oral or dental procedure in patients taking antithrombotic drugs

Patients with multiple risk factors have an additive risk of prolonged bleeding. Risk factors include:

- elevated blood pressure
- abnormal kidney or liver function
- prior stroke
- history of bleeding (particularly if this occurred with a similar procedure)
- pre-existing bleeding disorder
- poor anticoagulant control (eg labile INR)
- older age or frailty
- other drugs that predispose to bleeding [NB1], including NSAIDs (eg nonprescribed NSAIDs, low-dose aspirin)
- hazardous alcohol consumption.

INR = international normalised ratio; NSAIDs = nonsteroidal anti-inflammatory drugs

NB1: Many other prescription, over-the-counter and complementary medicines can affect haemostasis, either directly or through drug interactions.

Oral and dental procedures that are unlikely to cause prolonged bleeding	
examination and diagnostic procedures (eg periodontal examination, impressions)	
restorative treatments (eg restorations, root canal therapy)	
orthodontic treatment	
Oral and dental procedures that are likely to cause prolonged bleeding	
Lower risk of prolonged bleeding	**Higher risk of prolonged bleeding [NB2]**
extraction of a small number of teeth (eg 1 to 3 teeth) that are not adjacent	extraction of a large number of teeth (eg 4 or more teeth) or extraction of adjacent teeth that creates a large wound
periodontal procedures (eg subgingival debridement)	any procedure where a mucoperiosteal flap is used (eg surgical extractions, implant placement, periapical surgery, periodontal surgery)
incision and drainage of swellings	extensive soft tissue biopsies
limited or small soft tissue biopsies	hard tissue biopsies

NB1: The bleeding risk associated with these procedures is based on the consensus opinion of the Oral and Dental Expert Group. Risk assessment requires clinical judgment of the individual procedure-, patient- and drug-related risks of bleeding, and the practitioner's competency to manage prolonged bleeding, should it occur.

NB2: Consider specialist referral for procedures with a higher risk of prolonged bleeding in patients taking antithrombotic drugs.

Figure 13.31 Local haemostatic measures for oral and dental procedures in patients taking antithrombotic drugs

- Apply pressure to the wounds—pressure is the most important factor in achieving haemostasis.
- Minimise tissue trauma.
- Place cellulose and collagen, if indicated.
- Place sutures to ensure closure of the wounds, if indicated.
- Consider using tranexamic acid 4.8% mouthwash as an adjunctive measure for patients taking warfarin—tranexamic acid mouthwash can stabilise a blood clot in patients taking warfarin. There is no evidence on the use of tranexamic acid mouthwash in patients taking DOACs. Apply tranexamic acid mouthwash topically just before surgery. After the procedure, give the patient tranexamic acid 4.8% mouthwash with instructions for use (10 mL rinsed in mouth for 2 minutes then spat out, 4 times daily for 2 days) [NB1].

DOACs = direct-acting oral anticoagulants

NB1: Tranexamic acid 4.8% mouthwash can be compounded by a pharmacy. If it is not available, a suitable alternative solution can be made by crushing a 500 mg tablet and dispersing it in 10 mL of water immediately before administration.

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