B. 18 Drugs used in coagulation disorders

a. Classify the anticoagulants.

oral agents inhibiting vitamin K metabolism
warfarin

parenteral anticoagulants
heparin, low-molecular-weight fractions, hirudin

platelet inhibitors
aspirin, NSAIDs, dipyridamole, ticlopidine, abciximab

thrombolytics
tPA, streptokinase, urokinase

fibrinogen-depleting agents
ancrod

in vitro agents
citrate, EDTA

pro-coagulants
† clotting factor synthesis
vitamin K

platelet activators
DDAVP

plasminogen activation inhibitors
EACA, tranexamic acid

plasmin inhibitors
aprotinin (EACA, tranexamic acid)

b. Describe the pharmacodynamic and pharmacokinetics of heparin and low-molecular-weight heparins including their side effects.

heparin
parenteral anticoagulant
used IV and SC
derived from porcine & bovine gut and other tissues
anionic mucopolysaccharides synthesized in mast cells
MW 5000-30000
up to 50 saccharides
quantitated by anticoagulant activity
bioassay of anticoagulant effect on animal blood
1 ml sheep blood with 0.2 ml 1% CaCl₂ anticoagulated for 1 hour

pharmacokinetics
not absorbed orally
t1/2 of effect 0.5-3 h saturable kinetics
taken up by reticuloendothelial cells (high affinity, low capacity)
absorbed by epithelium
hepatic metabolism by heparinase
some renal clearance
administered by IV infusion (rate according to APTT) following loading dose
active subcutaneously at low dose (5000 U bd - 7500 U tds) for DVT prophylaxis
late rise in heparin levels observed after reversal with protamine

pharmacodynamics
binds to antithrombin III, greatly increasing its affinity for thrombin
thrombin activity rises rapidly from 8-13 saccharides
increases anti factor Xa activity of antithrombin III
only 5 saccharides required for Xa activity
some antiplatelet activity
adverse actions
bleeding
hypersensitivity
thrombocytopenia
dose-related in prolonged use
immune-mediated HITS
osteoporosis
alopecia

Low molecular weight heparins (dalteparin “Fragmin”, enoxaparin “Clexane”, nandroparin “Fraxiparine”, danaparoid “Orgaran”)

- low molecular weight fractions of heparin produced by depolymerization
  - MW 2000-9000
  - polysaccharide with 13-22 sugars
  - quantitated by anti factor Xa activity
  - used in prophylaxis and heparin sensitivity

pharmacokinetics
- 90% available by subcutaneous injection
- $t^{1/2} \beta$ 2 h IV (3-4 h sc)

pharmacodynamics
- binds antithrombin
  - promotes inactivation of factors IXa, Xa, XIa and kallikrein
  - little effect on thrombin
  - little platelet binding
  - anti factor Xa activity is not reversed by protamine

adverse actions
bleeding
hypersensitivity
osteoporosis
thrombocytopenia

hirudin
- leech anticoagulant prepared by rDNA techniques
- direct antithrombin activity

**c. Describe the mode of action and side effects of protamine**

protamine
- basic protein (cationic)
- derived from salmon testes

pharmacokinetics
- administered slowly IV
- binds heparin immediately in circulation

pharmacodynamics
- binds heparin in circulation to form inactive complexes (1.3 mg protamine to 100 U heparin)
- complexes are cleared by the reticuloendothelial system

adverse actions
hypotension
- systemic vasodilation from rapid administration, especially via CVC
due to histamine release from cationic drug
- minimized by slow injection (5 mg/min) into peripheral line

type I hypersensitivity
- more common in patients with fish allergy and diabetics using protamine-containing insulin
theoretical risk in vasectomized men
anaphylactoid reactions
complement activation by heparin-protamine complexes in lungs
possible role of IgG
protamine inhibits plasma carboxypeptidase
responsible for inactivating many cytokines
increased risk if ACE is also inhibited
transient pulmonary vasoconstriction due to TXA₂ release
anticoagulant activity in large overdose
? mechanism

d. Describe the chemistry, mechanism of action and toxicity of the coumarin anticoagulants.

![Chemical structures of Warfarin and Vitamin K](image)

warfarin
- discovered accidentally in spoiled sweet clover silage
- oral anticoagulant of choice
- racemic mixture (L-warfarin is four times as potent as D-warfarin)

pharmacokinetics
- 100% bioavailable
- 99% protein bound
- V_d small
- t₁/₂β 36 h
- hepatic metabolism

pharmacodynamics
- a competitive inhibitor of the reduction of vitamin K from epoxide to hydroquinone form
- vitamin K hydroquinone is required for γ-carboxylation in the synthesis of factors II, VII, IX and X (and protein C)
- factors II, VII, IX and X have half-lives of 60, 6, 24 and 40 h, resulting in a clinical effect from about 30 h and full effect from about 72 h
- antagonism with vitamin K (dietary and intentionally administered)
- can also be reversed with FFP

interactions
- pharmacokinetic
  - enzyme induction or inhibition
  - protein binding

- pharmacodynamic
  - other inhibitors of clot formation, especially NSAIDs which interact via displacement from protein binding, impaired metabolism and synergistic anti-
  - platelet activity (phenylbutazone)
  - some patients (and rats) have a hereditary abnormality of vitamin K metabolism and are resistant to warfarin

adverse actions
- bleeding
- teratogenicity
  - warfarin crosses the placenta readily
  - γ-carboxylation is required in the normal synthesis of bone and other tissues in...
the foetus
protein C deficiency can result in hypercoagulability in some patients, with skin
carcinosis and multiple infarcts
alopecia
The other oral anticoagulants include dicoumarol and phenindione. They have less
predictable absorption and phenindione causes hepatic and renal impairment in some
patients.

e. Describe the fibrinolytic pathway and mechanisms of action of thrombolytic
agents.

Plasminogen is a plasma protein which is trapped in the formation of a clot. Tissue
plasminogen activator (tPA) is slowly released from injured endothelium and tissues and
activates plasminogen to form plasmin. Plasmin is a protease which degrades fibrin, factors
V, VIII and XII, thrombin and fibrinogen, causing lysis of the clot. This typically occurs over
hours to days following clot formation.

The action of plasmin is limited by circulating alpha_2-antiplasmin which prevents
any low levels of circulating plasmin from lysing clots.

Fibrinolytic agents include streptokinase and anisoylated plasminogen-streptokinase
activator complex (derived from bacteria), urokinase (derived from the kidney) and
recombinant tPA and SCU-PA. All act by binding to proactivator plasminogen which then
catalyzes the formation of plasmin from plasminogen.

Streptokinase and urokinase bind to circulating as well as bound plasminogen and so
result not only in clot lysis but depletion of circulating fibrinogen. APSAC binds to fibrin
and is deacylated to yield active streptokinase. r-tPA and r-SCU-PA preferentially activate
bound plasmin, theoretically producing more selective fibrinolysis, but in practice there is
little difference between their fibrinolytic effects.

Streptokinase and APSAC differ from the human-derived agents in that they are
more antigenic. An immune response typically begins within 5 days of administration and
hypo-sensitivity reactions can result from sensitization by streptococcal infection.

Benefit from thrombolytic therapy is proven in early treatment of suitable patients
with AMI. There is no proven advantage in using any one agent. Treatment for cerebral
infarcts, pulmonary embolism and DVT is indicated under specific circumstances. Use in
clearing clot from long-term CVCs is safe and effective.

f. Describe the action of antifibrinolytic agents such as ε-aminocaproic acid
(EACA).

EACA and tranexamic acid are competitive inhibitors of plasminogen activation and
have minor anti-plasmin activity. EACA is H_2N(CH_3)_5COOH.

pharmacokinetics
- high oral bioavailability
- rapid renal clearance unchanged
- V_d ~0.5 l/kg
- t_1/2_β ~2 h
- EACA dosage: 5 g over 30 minutes, 1 g/h for therapeutic plasma levels (130 mg/l)
- post-TURP: 0.25 g/h as EACA is concentrated in urine

pharmacodynamics
- binds plasminogen activator and plasmin

clinical application
- useful in the treatment of bleeding postoperatively due to primary fibrinolysis
- bleeding in DIC (secondary fibrinolysis) is greatly exacerbated by EACA
g. Describe the action and pharmacological role of anti-platelet drugs

aspirin and other NSAIDs
discussed previously (2.B.4)

dipyridamole
- phosphodiesterase inhibitor
- increases platelet cAMP
- impairs adhesion and activation
- increases myocardial oxygen requirement

ticlopidine
- inhibits ADP-mediated platelet activation
- proven benefit over placebo in TIAs, unstable angina
- not demonstrated to be better than aspirin
- adverse effects
  - 20% nausea, diarrhoea
  - 5% bleeding
  - 1% leukopenia

abciximab
- preparation for intravascular use in PTCA
- Fab fragment directed against platelet receptors
- inhibits platelet aggregation by binding IIIa receptors

h. Describe the actions of aprotinin

Plasma prekallikrein is activated by trypsin, factor XIIa and kallikrein itself to form kallikrein which activates high-molecular-weight kininogen to form bradykinin. This promotes activation of the intrinsic pathway and mediates a vasodilator and chemotactic response. Kinins act via B₁ and B₂ receptors (B for bradykinin). There are multiple B₂ subtypes, which are G-protein linked. Bradykinin promotes tissue release of t-PA. Kallikrein also converts prorenin to renin, C₁ to C₁ and plasminogen to plasmin.

Aprotinin inhibits kallikrein, reducing production of bradykinin and plasmin. It also inhibits plasmin’s fibrinolytic activity and reduces the inactivation of PAI by protein C.

additional

Classify and describe transfusion reactions.

haemolytic
- acute
  - ABO incompatibility causes immediate intravascular haemolysis
  - 0.004% incidence
  - recipient IgM binds to donor RBC antigens
  - complement activation, CMI activation, chemotactic factors
  - life-threatening: 25% mortality
  - shock
  - DIC
  - renal failure
  - usually due to clerical error
  - volume dependent
  - management
    - cease transfusion, return to blood bank with recipient sample
    - support circulation
    - maintain renal function
    - detect and treat DIC
    - maintain ventilation
delayed
minor recipient Ab to donor antigens causes extravascular haemolysis
e.g. Rhesus
0.06%
IgG coating of RBC, haemolysis in reticuloendothelial system
gradual onset
fever, malaise
jaundice, haemoglobinuria
fall in haematocrit

not haemolytic
acute
anaphylaxis
IgA-deficient recipient Ab to donor IgA
0.005%
tiny volume required
type I hypersensitivity
pulmonary oedema
donor Ab to recipient lymphocytes
complement activation
rare
urticaria
recipient Ab to donor plasma proteins or other constituents (e.g. food, drugs)
2-3%
type I or III hypersensitivity
fever
recipient Ab to donor granulocytes
1% with packed cells, 20% with platelets
complement and recipient leukocyte activation
treated with pethidine, steroids
delayed
purpura
recipient antiplatelet Ab
rare
GVH disease
engraftment of donor lymphocytes in immunosuppressed recipient
life threatening