4. Drugs Used in Disorders of Coagulation

Classification
1. Hemostatic drugs
2. Antithrombotic drugs
   - Anticoagulants
   - Antiplatelet drugs
   - Fibrinolytic drugs

1. HEMOSTATIC DRUGS
Hemostasis is the cessation of blood loss from a damaged vessel.

Classification of hemostatic products
1.1. Topical products to treat active compressible, localized bleeding
1.2. Infusible products to treat non-compressible, internal bleeding or prevent bleeding

Indications: mild to moderate bleeding from capillaries and small venules

1.1. Topical products to treat active compressible, localized bleeding (hemostatic drugs with local effect):

- Mechanical haemostatics (passive haemostats):
  - **Mechanism of action**: mechanisms of absorption, pressure, vasoconstriction
    - vasoconstrictor effects: Adrenaline, Noradrenaline,
    - absorbable hemostatic drugs: Gelatin (can absorb many times its weight of blood)
  - **Indications**:
    - Adrenaline: haemostatic in superficial hemorrhages of the skin or mucosa
    - Gelatin: haemostatic in surgical procedures (as an absorbable film/spoenge)

- Haemostatics inductors of coagulation
  - **Mechanism of action**:
    - Biotransformation of fibrinogen in fibrin (accelerate fibrin formation through exogenous thrombin and fibrinogen): Trombin, Fibrin
    - Matrix for coagulation: Celulose (applied to a bleeding surface, they swell to form a gelatinous mass which aids in the formation of a clot)
  - **Indications**: to control haemorrhage from capillaries and small venules during surgical procedures

- Others:
  - **Hydrogen peroxide**
    - **Mechanism of action**: it is an oxidising agent which release oxygen when applied to tissues (the effect lasts only as long as the oxygen is released) = short duration of action. The antimicrobial effect of the liberated oxygen is reduced in the presence of organic matter.
    - **Pharmacodynamic effects**:
      - antiseptic, disinfectant, and deodorant,
      - antibacterial activity and is also effective against viruses, including HIV.
• mild haemostatic action. It owes its antiseptic action to its ready; in addition. The mechanical effect of effervescence is probably more useful for wound cleansing than the antimicrobial action.

- **Indications**
  - to cleanse wounds and ulcers in concentrations of up to 6%;
    - adhering and blood-soaked dressings may be released by the application of a solution of hydrogen peroxide.
  - mouthwash in the treatment of acute stomatitis and as a deodorant gargle as a 1.5% solution
  - removal of wax from ears
  - disinfect soft contact lenses
  - for bleaching hair.

- **Adverse effects**
  - irritating 'burns' on the skin and mucous membranes with a white eschar,
  - mouth ulceration if used as hydrogen peroxide 3%.

1.2. Infusible products to treat non-compressible, internal bleeding or prevent bleeding (hemostatic drugs with systemic effect)

- **Classification**
  - hemostatic drugs efficient for the coagulation of blood:
    - Vitamin K,
    - Protamin sulfate,
    - factor VIII fraction, factor IX fraction, factor I fraction (fibrinogen), factor XIII fraction (stabilizing fibrine);
  - hemostatic drugs that increase blood capillary resistance:
    - Etamsylate,
    - Carbazocrome,
    - calcium;
  - antifibrinolytic drugs (inhibit fibrin disolution):
    - Tranexamic acid,
    - epsilon-aminocaproic acid,
    - Aprotinin.

**Vitamin K**

**Sources**
- plant sources: vitamin K1 (phytomenadione);
- intestinal flora: Vitamin K2 (menaquinone);
- synthetic: vitamin K3 (menadione).

**Mechanism of action**: Vitamin K is reduced to vitamin K-epoxide that acts as a cofactor in the hepatic synthesis of factors II (prothrombin), VII (proconvertină), IX (B antihemofilică globulin) and X (Stuart-Prower factor) coagulation. Subsequently, the action of epoxide reductase, vitamin K is regenerated.

**Pharmacokinetics**
- absorption: vitamin K1 and K2 are fat soluble vitamins requires bile salts for absorption from the gastro-intestinal; vitamin K3 is water soluble it is absorbed easily.
- metabolism: in the liver;
- elimination: renal.

Indications
- deficit of vitamin K (bowel resection, malabsorption syndromes, prolonged antibiotic therapy etc).
- prevention of bleeding in premature infants;
- as an antidote to overdose of oral anticoagulants (only vitamins K1 and K2).

Adverse effects
- hemolysis (in patients with deficiency of glucose - 6 - phosphate dehydrogenase, G6PDH);
- kernicterus in neonates;
- dyspnea, retrosternal pain;
- methemoglobinemia.

Contraindications
- thrombophlebitis;
- thromboembolism.

Protamine sulfate
Mechanism of action: the physico-chemical mechanism the basic molecule of protamine sulfate determines the inactivation of heparin.

Indications
- antidote to the overdose of heparin;
- surgery using cardiopulmonary bypass.

Adverse effects
- dyspnea;
- bradycardia;
- hypotension.

Coagulation factors
Representatives of:
- factor I (human fibrinogen);
- factor VIII;
- factor IX;
- factor XIII (fibrin stabilizing).

Administration: i.v. infusion

Indications:
- hemophilia: factor VIII, factor IX, factor XIII;
- hypo-or afibrinogenemii: factor I.

Adverse effects:
- factor VIII: allergies, antibody formation, risk of transmission of viral infections (hepatitis, HIV);
- factor IX: fever, nausea, vomiting, headache, changes in blood pressure.
- stimulating factor VIII activity: Desmopressin, Danazol.

Etamsylate
Mechanism of action:
- increase in resistance by reducing capillary permeability.

Indications:
- bleeding by capillary fragility;
- menorrhagia, metrorrhagia.

Adverse effects: transient hypotension, headache, rash.

Epsilon-aminocaproic acid (EACA)

Mechanisms of action:
- inhibition of the plasminogen activator;
- anti-inflammatory effect.

Administration: parenteral route.

Indications:
- adjuvant treatment in hemophilia;
- bleeding by hyperfibrinolysis;
- prophylaxis: bleeding after dental extractions, bleeding in intracranial aneurysms;
- after prostatectomy;
- liver disease.

Adverse effects: hypotension, abdominal pain, diarrhea, arrhythmias.

2. ANTITROMBOTIC DRUGS
2.1. Anticoagulants:

Classification of anticoagulant drugs:
- indirect thrombin inhibitors
  - Parenteral anticoagulants:
    - Unfractioned heparin:
      - Heparin
      - Calciparin
    - Low molecular weight heparins:
      - Enoxaparin,
      - Dalteparin,
      - Nadroparin,
      - Tinzaparin,
      - Fondaparinux,
      - Others: Ardeparin, Reviparin, Parnaparin, Certoparin, Idraparinux
    - Heparinoids and hirudins:
      - Danaparoid,
      - Lepirudin,
      - Hyaluronidase
      - Others: Bivalirudin, Argatroban, Drotrecogin alfa, Desirudin,
  - Oral anticoagulants:
    - 4-hydroxycoumarin:
      - Warfarin,
      - Acenocoumarol,
• Others: Bisdihydroxicumarin, Ethyl biscumacetat, Tioclomarol, Cyclocumarol, Phenprocoumon;
  ▪ indan-1,3-dione:
  ▪ Phenindione,
  ▪ Others: Difenadione, Anisindione, Bromindione, Fluindionone;
  ▪ In vitro anticoagulants:
    ▪ Sodium oxalate,
    ▪ Sodium Fluoride,
    ▪ Sodium citrate,
    ▪ Sodium edetate
• direct thrombin inhibitors:
  ▪ iv
    ▪ Lepirudin (recombinant hirudin)
    ▪ Bivalirudin,
    ▪ Argatroban,
  ▪ sc
    ▪ Desirudin (recombinant hirudin)
    ▪ Melagatran,
  ▪ p.o.
    ▪ Dabigatran
    ▪ Ximelagatran

Heparin
Heparin anticoagulant activity is in international units (IU).
Heparin has anticoagulant activity both in vivo and in vitro.

Mechanisms of action
- heparin binds to antithrombin III → results a complex that inhibits factors II, IX, X, XI, XIII of coagulation;
- activation of lipoprotein lipase;
- inhibition of hyaluronidase;
- inhibition of serum complement;
- inhibition of the production of aldosterone;
- decrease activity of antithrombin III (in chronic administration).

Pharmacokinetics
- Heparin does not cross the blood-brain barrier, it does not cross the placental barrier and it does not pass into the milk.
- administration: Heparin: iv/sc, Calciparin: sc

Indications
- treatment of choice in deep vein thrombosis, pulmonary embolism, arterial embolism, myocardial infarction;
- prophylaxis: postoperative (prevention of venous thrombosis).

Adverse effects
- bleeding by overdose;
- thrombocytopenia by the anti-heparin (frequently, IgG-like);
- stimulation of platelet aggregation;
- osteoporosis, spontaneous fractures;
- transient reversible alopecia;
- rarely, allergic reactions (rhinitis, conjunctivitis, bronchospasm, urticaria, anaphylactic shock).

**During treatment** → evaluation of **aPTT** (activated partial thromboplastin time).

In **overdose** → heparin antidote is protamine sulfate.

**Contraindications**
- i.m. administration;
- hemophilia, thrombocytopenia, purpura;
- high blood pressure, intracranial hypertension;
- endocarditis;
- active tuberculosis;
- liver carcinoma, liver failure;
- gastrointestinal ulcerative lesions.

**Low molecular weight heparins**

**Mechanisms of action**
- inhibit only activated factor X clotting.

**Pharmacokinetics**
- administration: s.c. only;
- the time for action is long;
- elimination: renal excretion.

**Indications, contraindications, adverse effects** → are similar to those of Heparin.

**Advantages**
- time for action is long,
- low risk for osteoporosis,
- allergic reactions are rare.

Not require monitoring by **aPTT** monitoring.

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2.2. Antiplatelet drugs

**Classification of antiplatelet drugs:**

- **antiagregant effect depending on dose or as secondary effect:**
  - Acetylsalicylic acid,
  - Dipyridamole,
  - Flurbiprofen, Sulfinpyrasone,
  - prostaglandine derivatives
    - PGI2 derivatives: Epoprostenol
    - PGE1 derivatives: Alprostadil

- **antagonists on platelets receptors for fibrinogen:**
  - Ticlopidine,
  - Clopidogrel;

- **glycoprotein IIb/IIIa antagonists:**
- Abciximab,
- Eptifibatide,
- Tirofiban,
- Optifiban;

**5HT2 receptor antagonists:**
- Ritanserine.

**Mechanism of action**
- Acetylsalicylic acid: inhibition of thromboxane synthase (this will inhibit the release of thromboxane A2);
- antiplatelet effect occurs only at low doses (80-325 mg / day), increasing the dose is lost, hold 5-7 days after the last dose.
- Dipyridamole: inhibition of platelet accession to thrombogenic surfaces, inhibiting phosphodiesterase activity.
- platelet fibrinogen receptor blockers: block the platelet receptor for fibrinogen by inhibiting binding of ADP-dependent type.
- GP-IIb/IIIa of platelet receptor antagonists: block platelet integrin receptors and other proagregante substances.

**Pharmacodynamic effects:** decrease platelet agregability.

**Indications:** prevention of thromboembolic accidents or transient ischemic attacks in patients with increased thrombotic risk (myocardial infarction, unstable angina, stroke etc).

**Adverse effects:**
- promote bleeding.
- for Ticlopidine: blood dyscrasias (leukopenia, agranulocytosis, aplastic anemia), increase in transaminases and alkaline phosphatase, hypercholesterolemia, hypertriglyceridemia, skin reactions

**Contraindications:** in acute hemorrhagic stroke, thrombocytopenia.

**Oral anticoagulants**

**Mechanisms of action**
- inhibition of the epoxide reductase (enzyme involved in regeneration of vitamin K) → results in production of inactive coagulation factors;

The anticoagulant effect occurs after a latency period of at least 8-12 hours, but the therapeutic effect is achieved after 36 hours of charging.

**During treatment: necessary evaluation of INR (= prothrombin index).**

**Pharmacokinetics:**
- digestive absorption: very good;
- plasma protein binding of warfarin: 99%;
- cross the placenta;
- metabolism: hepatic;
- elimination: renal.

**Indications:**
- prosthetic valves;
- chronic pulmonary embolism;
- embolism in chronic atrial fibrillation;
- post-thrombotic syndromes;
- secondary prevention of stroke and atrial fibrillation;
- postoperative immobilization;
- cancers.

**Adverse effects:**
- bleeding due to overdose;
- rash;
- teratogenic effects;
- Warfarin: bronchodilation, alopecia;
- bis-dihydroxycoumarin: capillary damage, increase transaminases;
- Phenindione: liver damage; kidney damage;
- Anisindione: agranulocytosis, proteinuria.

In ** overdose → ** oral anticoagulants antidote is vitamin K1 or K2.

**Contraindications**
- pregnancy;
- breastfeeding;
- hemophilia;
- severe hypertension;
- acute hemorrhagic stroke.

**Drug Interactions**
- increase the anticoagulant effect:
  - phenylbutazone (and other NSAIDs), vitamin E → because of removing them from plasma proteins;
  - Cimetidine, Ketoconazole, Erythromycin → because inhibit their metabolism;
  - platelet agregants → because of potentiating synergism;
- reduce the effect of anticoagulant:
  - Cholestyramine: decreases absorption;
  - barbiturates, carbamazepine, rifampicin → enzyme induction.

### 2.3. Fibrinolytic drugs

**Classification of fibrinolytic drugs:**
- proteolytic enzyme produced by beta haemolytic Streptococcus: Streptokinase,
- enzyme synthesized in the human kidney: Urokinase,
- tissue-type plasminogen activators
  - Alteplase,
  - Reteplase,
  - Tenecteplase,
- complex of streptokinase plasminogen activator: Anistreplase (anisoylated plasminogen streptokinase activator complex; APSAC).

**Indications** (fibrinolytics are effective within the first 6 hours of thrombus formation):
- acute myocardial infarction;
- multiple pulmonary thromboembolism;
- peripheral vascular disease;
- syndrome of superior vena cava.

**Adverse effects:**
- bleeding:
- allergic reactions, fever;
- mobilization of thrombus lysed fragments;
- reperfusion arrhythmias;
- streptokinase has high antigenic properties.

**Contraindications:** history of allergies.

**Overdose:** In the fibrinolytic overdose epsilon-aminocaproic acid is administered.

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### 5. Fluids and electrolytes

**Classification**

1. **Oral preparations for fluid and electrolyte imbalance (oral rehydration therapy)**
   - oral potassium, oral sodium and water, oral bicarbonate

3. **Parenteral preparations for fluid and electrolyte imbalance**
   - electrolyte solutions (micromolecular solutions)
     - Single electrolyte:
       - Sodium chloride,
       - Glucose (Dextrose monohydrate),
       - Potassium chloride,
       - Sodium bicarbonate,
       - Sodium lactate,
     - Mixtures of electrolytes:
       - Sodium chloride and glucose,
       - Ringer solution (contains Ca\(^{2+}\), K\(^+\), Na\(^+\), Cl\(^-\)),
       - Ringer lactate (contains Ca\(^{2+}\), K\(^+\), Na\(^+\), Cl\(^-\), HCO\(_3\)^-)
   - plasma substitutes (macromolecular solutions):
     - Dextran (Dextran-40 and Dextran-70 are polysaccharides)
     - Polygeline (gelatin-derived polymer)
     - Etherified starch: hetastarch, hexastarch, and pentastarch
       - High-molecular-weight hetastarch (average molecular weight 450000 to 480000) and medium-molecular-weight pentastarch (average molecular weight 200000 to 250000). Other etherified starches are low-molecular-weight pentastarch and medium-molecular-weight hexastarch, with a degree of etherification between that of pentastarch and hetastarch.

**Pharmacodynamic effects**

- electrolyte solutions (micromolecular solutions)
  - provide osmotic pressure;
  - recover fluid for a short time as soon leave the vascular bed;
- plasma substitutes (macromolecular solutions)
  - ensure the colloid-osmotic and oncotic pressure;
  - are removed from the body in more than 24 hours (partially degraded, partially eliminated in urine) → restore circulating mass and BP for long interval;
- other effects for Dextran 40:
• antithrombotic action by inhibiting platelet aggregation;
• prevent erythrocyte aggregation.

**Indications**
- restoring volume expansion after excessive loss through diarrhea, vomiting, bleeding, burns etc.

**Adverse effects**
- electrolyte solutions (micromolecular solutions)
  - Sodium chloride: Hypernatraemia, hyperchloraemic;
  - in overdosage: nausea, vomiting, headache, fever, abdominal cramps, tachycardia, peripheral and pulmonary edema, convulsions, respiratory arrest.
- plasma substitutes (macromolecular solutions)
  - Dextran 70: type I immunological reactions, increased bleeding time, interfere with the determination of glucose, total protein and bilirubin.
  - Gelofusine, hydroxyethyl starch: rash (rare).

**Contraindications**: hypertension, edema.