BLOOD

INFLUENCING OF BLOOD COAGULABILITY

ANTICOAGULANTS

COMPOUNDS BINDING CALCIUM IONS

Ions of calcium Ca^{2+} are for coagulation necessary. Their „scavenging" for example by binding to citrate or EDTA prevents blood coagulation. Possibility to manage this *in vitro* only. Used for taking of blood.

HEPARINS (heparin inhibits the factors of blood coagulation)

COUMARINE DERIVATIVES (block synthesis of blood coagulation factors)

HEPARINUM CALCIUM, HEPARINUM NATRIUM (ČL 2005)
Heparin calcium salt, Heparin natrium salt

Natrium or calcium salt of sulphated glucosaminoglycane

MW 15.000-20.000

Source: lungs of beef cattle, intestinal mucose of beef cattle, pigs or sheep

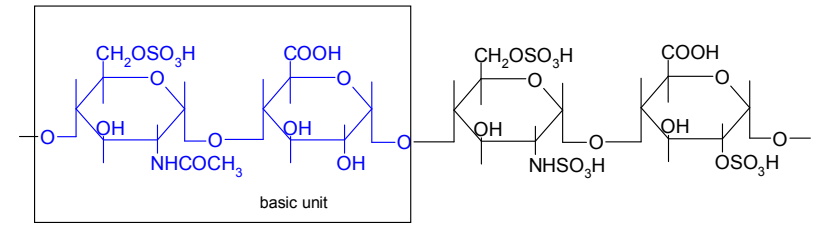
Almost white moderately hygroscopic powder, easily soluble in water

Mechanism of effect: activation of the body's own glycoprotein antithrombine III

Hydrolysis:

- D-glucosamine
- D-glucuronic acid
- L-iduronic acid (epimer of glucuronic acid)
- Sulphuric acid
- Acetic acid

STRUCTURE OF HEPARIN



sulphatated and acetyled glucosamine

glucuronic acid

HEPARIN USAGE

- Prophylaxis of thromboses
- Therapy of thromboses, it means prevention of further growth of thrombus
- Consumption coagulopathy
- Emboli
- Myocardial infarction

Parenteral application, in organism rapid decomposition (repeated administration necessary)

Side effects:
- Bleeding in high doses (antidote protamin)
- Allergic reactions
- Thrombocytopenia
- Osteoporosis, reversible hair loss (long-termed application)

LOW-MOLECULAR HEPARIN
(fragments of heparin)

Prepared by directed cleavage of native heparin
MW cca 5000

Usage:
Prophylaxis of thromboses (benefit is long-termed effect)

Side effects:
- Bleeding
- Thrombocytopenia - rare
- More difficult antagonisation with protamine

HEPARINOIDS

Polyesters of saccharides with sulphuric acid, lowing coagulability
MW cca 7000

Source: low-molecular residues after heparin production or natural polysaccharides (dextrans, xylans, cellulose, starch, pectin, chitin)

Anticoagulation effect in comparison to heparin weaker, heparinoids are more toxic

Usage:
Local in ointments for treatment of inflammatory diseases and hematomas

HIRUDIN

Source: *Hirudo medicinalis* L., bloodsucker; ambidextrous worm from sub-class of annelids. Hirudin is protein with MW 16 000, it is present in oral glands

Hirudin reacts directly with thrombin, with cooperation with antitrombin III, inactivates thrombin and prohibits the blood coagulation

Relatively difficult obtain from bloodsucker; possible usage of gene engineering

Usage: for patients with increased risk of thrombocytopenia; necessary clinical trials for real comparison of effect with heparin

Bloodsuckers in pharmacies: usage has strong impact and posseses strong psychotherapeutic potential

COUMARINS

Cattle feeded by fermented hey with rich content of common melilot suffered by increased bleeding

Link 1941 – effect triggered by dicoumarol (from coumarins)

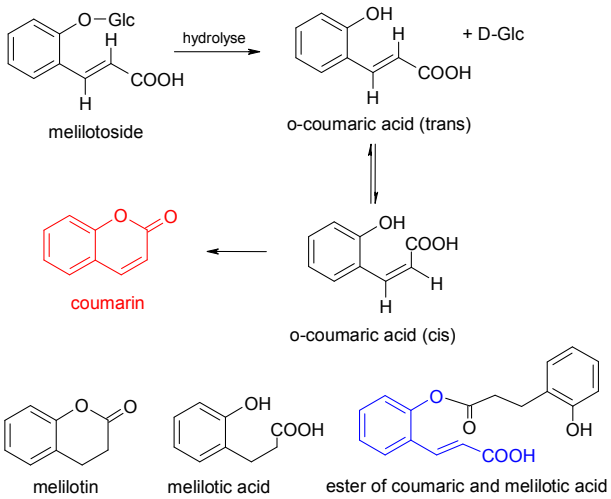
Source: Meliloti herba (ČL 2005) – common melilot herb

Melilotus officinalis (L.) LAM. – common melilot (Fabaceae)

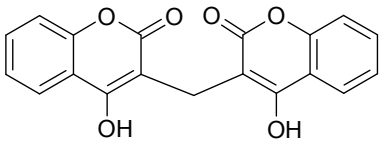
Dicoumarol introduced into practise – lead compound for synthesis → Pelentan

Mechanism of effect – competitive antagonism with vitamine K

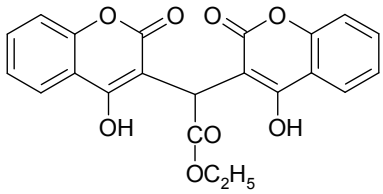
COUMARIN BIOSYNTHESIS



DICOUMAROL, PELENTAN

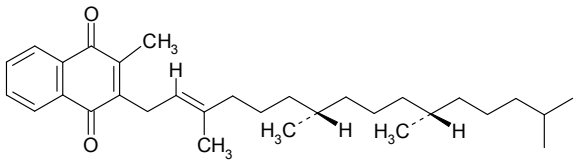


dicoumarol

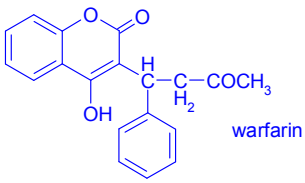


Pelentan

COUMARINS – ANTAGONISTS OF VITAMIN K



vitamin K_1, phytomenadion
2-methyl-3-phytyl-1,4-naphtoquinon



warfarin

FIBRINOLYTICS

- Disolve fresh thrombes
- Support conversion of body´s own plasminogen to plasmin, which as protease cleave fibrin to soluble cleavage products

Usage: myocardial infarction, pulmonary embolia, deep venose thromboses

The mechanism of effect shows the possibility of increased bleeding

Antidote during bleeding: inhibitors of plasmine, for example p-aminomethylbenzoic acid (PAMBA)

STREPTOKINASI SOLUTIO AD PRAEPARATIONEM (ČL 2005)
Streptokinase concentrated solution

Protein obtained from filtrate of cultured hemolytic streptococci group C; Mr 47000, it is not enzyme

Effect: It is binded to plasminogen and formed complex changes further free plasminogen molecules to plasmin, which acts as fibrinolytic

Intravenous application

Side effects: intolerance - tremor, headache, joint pain, feeling of weakness. Do not administer repeatedly – risk of allergy development

UROKINASUM ČL 2005
Urokinase

Enzyme obtained from human urine, composed of forms
- low-molecular (MW 33 000)
- high-molecular (MW 54 000), prevalent

From immunologic point of view better than streptokinases

Can be obtained from cultured human kidney tissues

Supports the conversion of plasminogen to plasmin
Physiologic importance
- dissolution of fibrin clots formed in urinary tract
- Staying of menstruation blood in liquid state

STREPTOKINASE + STREPTODORNASE
for local application

Source: hemolytic streptococci
Streptodornase (enzyme) cleaves nucleoproteins to a purine bases and pyrimidine nucleosides → liquefaction of pus

Usage:
- dissolving of fibrinose or purulent exsudates in body cavities and necrotic tissues of wounds
- Application local only, for example into pleural cavity, into lumbal space, into joint cavities, onto superficial wound

ANKROD

Fraction from poison of malaysian rattlesnake *Agkistrodon rhodostoma* , malayan pit viper

Glycoprotein MW cca 38 000

Acts as thrombin, lowers the level of fibrinogen in blood, and therefore lowers blood viscosity and blood coagulability

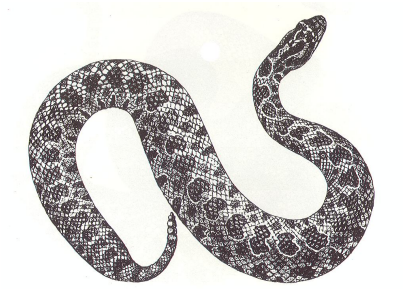
Usage: myocardial infarction, venous thromboses

BAXOTROBIN

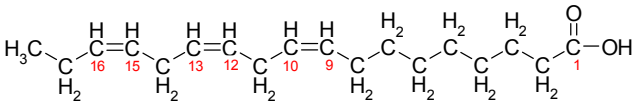
Fraction of poison of south American snake *Bothrops atrox*, common lancehead

Decreases the effect of fibrinogen on coagulation process

Ankrod and batroxobin can be interchanged during immunological problems.



LINOLENIC ACID



Nutritient, essential fatty acid (as triglycerid in many drying oils)

Occurrence: *Oleum rapae* – colza oil obtained from *Brassica oleracea var. arvensis* – turnip mustard (Brassicaceae)

Lowers increased adhesivity of thrombocytes

LOCAL FIBRINOLYTICS

Peptidhydrolases

- *Chymotrypsinum* (ČL 2005)
- *Trypsinum* (ČL 2005)

Cleavage of proteins at certain locations of chain. Reactive group of active centre of both enzymes is hydroxyl group of serin.

Chymotrypsin prefers cleavage bonds of carboxylic groups of Phe, Tyr, Trp a ester bonds

Trypsin cleavages lysyl and arginyl bonds of peptides.

DRUGS LOWERING INCREASED READINESS TO BLEEDING

Blood factors of coagulation
- thrombin
- fibrinogen

Vitamins K

Antifibrinolytics
- Protamin sulphate (during overdose of heparin)

Other drugs causing
- vasoconstriction
- astringent effect

THROMBINUM HUMANUM (ČL 2005 zkoumadla) Human thrombin

Enzyme preparation, which changes human fibrinogen on fibrin.
- Obtained from liquid human blood plasma by precipitation with suitable salts and organic solvents with controlled pH a temperature
- Protein obtained by conversion of prothrombin with thromboplastin

Usage:
- Bleeding from open wounds which is not possible to close by stitching
- To stop capillary bleeding

Application exclusively local or superficial
Never parenterally!!

PROTHROMBINUM MULTIPLEX HUMANUM (ČL 2005)
Human prothrombin complex

Lyophilized fraction of plasmatic proteins containing coagulation factor IX together with fluctuating amount of of cagulation factors II, VII and X.

Obtained by fractionation of human plasma.

FIBRINOGENUM HUMANUM ČL 2005
Human fibrinogen

Protein from human plasma, essential for proces of blood coagulation.

Obtained by ethanol fractionation of human plasma, further fractionation and lyophilisation.

Usage:

- During disorders of blood coagulation in case of missing, low content or malfunction of fibrinogen in plasma.

FIBRINI GLUTINUM (ČL 2005)
Fibrin adhesive

Composed from two components

1. Fibrinogen concentrate
2. Human thrombin

Fibrin coagulum is formed after mixing of defrozen or reconstituted components

Fibrin foam – carrier is gelatin – foamy mass strongly hygroscopic, after soaking is produced plastic pad

Usage: Bleeding from parenchymatic organs, during surgery in cavities

VITAMIN K GROUP

- Two biogenic derivatives of naphtoquinone
- Synthetic naphtoquinones

Important for syntheis of coagulation factors (prothrombin (factor II) and factors VII, IX and X.

Biogenic compounds = vitamin K_1 (in green plants), vitamin K_2 – menaquinone, (synthetised by many bacterial strains including gut microflora)

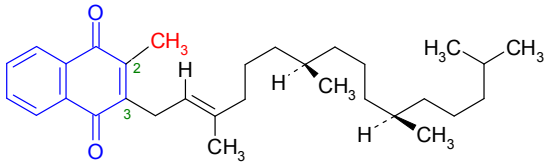
Phytomenadionum – Phytomenadione (ČL 2005)

Mixture of *trans*-phytomenadione (at least 75 %), *cis*-phytomenadione and maximally 4 % of *trans*-2,3-epoxyphytomenadione

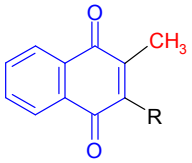
Source: *Medicago sativa* L., alfalafa (Fabaceae)

Usage: insufficiency of natural vitamin K (diseases of liver and biliar tract, hypoprothrombinemia of newborns, after destruction of intestinal microflora by broad spectral antibiotic therapy, functional disorders of gut)

PHYTOMENADIONUM – PHYTOMENADIONE (ČL 2005)



vitamin K_1



vitamin K_1 R = 4 isoprene units (phytyl-)
vitamin K_2 R = 6 isoprene units (difarnesyl-)
vitamin K_3 R = H (2-methyl-1,4-naphtoquinone)

ANTIFIBRINOLYTICS

Drugs preventing excessive fibrinolysis as a case of excessive activity of plasmin.

- Aprotininum
- Protamin

APROTININUM ČL (2005)
Aprotinine
APROTININI SOLUTIO CONCENTRATA (ČL 2005)
Aprotinin concentrated solution

- Basic polypeptid MW 6511
- Composed of 58 aminoacids
- Contains 3 disulphide bridges

Polyvalent inhibitor of proteolytic enzymes, for example chymotrypsin, kalikrein, plasmin and trypsin.
Source: beef lungs

Usage:
- Hyperfibrinolytic bleeding after/during surgery
- Chronic joint inflammation

PROTAMINI HYDROCHLORIDUM (ČL 2005)
Protamin hydrochloride
PROTAMINI SULFAS (ČL 2005)
Protamin sulphate

Mixture of hydrochlorides or sulphates of basic peptides
Source is milt or spawn of fishes (usually from families *Salmonidae* and *Clupeidae*)

Mostly often from milt of herrings (*Clupea pallasii*). Milt – pair formation oblong shape brownish color. After opening of abdominal cavity of males is taken and conserved by freezing. Isolated by extraction with acidic solutions.

Usage: antidote of heparin. In solution it is bonded to heparin with inhibiting of its anticoagulant effect.

Synonym: Klupein

LOCAL HEMOSTATICS

During bleeding from limited area of tissues or organs

Injuries, radical surgical therapy, physiologic delivery (after-delivery (postnatal) bleeding)

Substances

- Interfering with mechanism of blood coagulation (fibrin foam)
- Acting mechanically is carriers of active substances (gelatin sponge)
- Acting as astringents (tannins)

Postnatal bleeding – uterotonics, sympatolytics

TRANSFUSION LIQUIDS

Used during lowered volume and disorder of composition of circulating liquid.

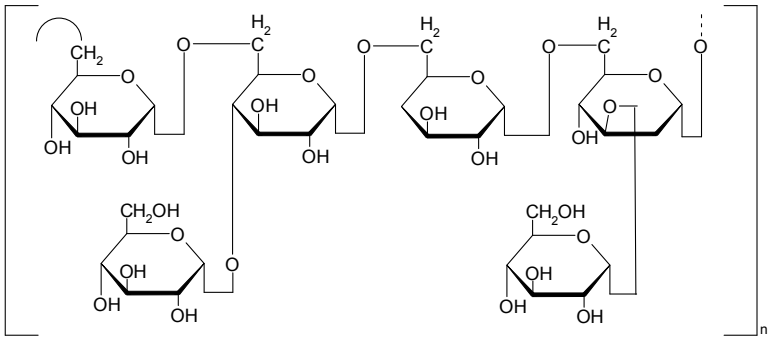
- Blood - Sanquis
- Plasma – Plasma humanum ad separationem (ČL 2005) – liquid part of human blood after separation of cellular elements. From plasma can be obtained: (fibrinogen, γ-globulin (carrier of antibody properties, increase and mediates immunity against infections) , β-globulins (preparation of thrombin), α- and β-globulins, albumin
- Albumin – Albumini humani solutio (ČL 2005)
  It possesses the biggest portion of colloid-osmotic pressure of blood plasma.

TO BODY STRANGE SUBSTITUTES OF BLOOD PLASMA
DEXTRANS

Dextrans – high molecular polysaccharides of mucilage-like consistence, MW 30 000 to 30 000 000. Basic building block is α-D-glucopyranose, connected to other glucopyranose units via glycosidic bonds prevalently at position 1→6, less 1→3 and 1→4.

Saccharose + enzymes at the surface of *Leuconostoc mesenteroides* NRRL B-15 bacteria, or relative species. Hydrolysis and condensation of glucose units. Two days cultivation, precipitation of dextran with methanol at lowered temperature, washing of material and hydrochloric acid hydrolysis at 100-105 ^{0}C, neutralization and isolation of fraction with demanded molecular weight. Mixture isomaltooligosades.

PART OF DEXTRANE MOLECULE



DEXTRANS IN PHARMACOPOEIA ČL 2005

- Dextranum 1 pro iniectione (low molecular fraction of dextran)
  Average relative molecular weight is 1 000
- Dextranum 40 pro iniectione
  Average relative molecular weight is 40 000.
- Dextranum 60 pro iniectione
  Average relative molecular weight is 60 000.
- Dextranum 70 pro iniectione
  Average relative molecular weight is 70 000.

Usage: Infusion with specific influence on capillary circulation