Drugs affecting blood clotting

Notes for Pharmacology II practicals
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This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.
Drugs affecting clotting

- Anticoagulants
- Thrombolytics
- Antiplatelet drugs
- Drugs improving deformability of ery

+ Antifibrinolytics
+ Hemostatics
+ Blood products
Contact activation (intrinsic) pathway

Damaged surface

XII → XIIa → XI → IX → IXa VIIIa → VIII → VIIa → VII → Tissue factor → Trauma

Prothrombin (II) → Xa → Thrombin (IIa)

Fibrinogen (I) → Fibrin (Ia) → Cross-linked fibrin clot

Active Protein C

Protein S + Protein C + thrombomodulin

Tissue factor (extrinsic) pathway

Trauma

TFPI

Antithrombin

Common pathway
Anticoagulants

- do not work against old thrombuses
- influencing ATIII or synthesis of coag. factors
- monitoring of therapy is necessary
- **Indications:**
  - Deep venous thrombosis
  - Lung embolisation
  - Arterial embolisation
  - Prevention of arterial emboli in patients with heart valve failure, atrial fibrilation and acute myocardial infarction

**Direct**
- heparin and its derivates

**Indirect**
- peroral antikoagulants
Direct anticoagulants

HEPARIN

- parenterally (i.v., s.c. or topical) anticoagulants, used also in vitro to coat inside surface of test tubes, dialysis machines etc.
- produced by mastocytes and basophiles and released mostly in liver (hepar), lungs and gut
- commercial preparations are extracted from beef lung or pig intestine
Direct anticoagulants

HEPARIN and its derivatives

How does it work?

• antikoagulation activity of heparin depends on presence of ATIII, which is irreversible inhibitor of thrombin activity as well as some other coagulation factors (e.g. factor Xa)

• heparin cca 1000x accelerates and helps interactions of ATIII (exposing its active site for quick interaction with proteases)
Direct anticoagulants
HEPARIN

- in vitro elongation of APTT - activated parcial thromboplastin time – 25-39s, → therapy control
- decreasing adhesivity and count of thrombocytes (↓ PGF-I)
- efficient in vitro and in vivo in contrast with peroral anticoagulants
- elimination – kidneys - GF
Indication:
• Deep vein thrombosis (DVT) and pulmonary embolism (PE): treatment and prophylaxis
• Acute coronary syndromes
• Percutaneous coronary intervention (PCI)
• Thromboembolic disorders
• Arterial embolization: treatment and prophylaxis (atrial fibrillation)
• Vascular and cardiac surgery
• Extracorporeal circulation (hemodialysis, hemofiltration, and cardiopulmonary bypass during cardiac surgery)
• Arterial and venous catheters, pulmonary artery catheters (heparin flushes)
• Diagnostic and therapeutic interventional radiologic procedures
Direct anticoagulants

HEPARIN

KI: bleeding
condition after big surgery
malign hypertension
trombocytopenia
abortus imminens

Protamine sulfate = specific antagonist
- basic protein with affinity to negative charged heparin → complex
- overdose treatment 1mg/100u of heparin

AE: bleeding – GIT, urinary system and adrenal glands
• trombocytopenia
• hypersensitivity
Direct anticoagulants
Low-molecular-weight heparins

- heparin fragments
  - nadroparin (Fraxiparin), enoxaparin (Clexane), dalteparin (Fragmin), bemiparin (Zibor), parnaparin (Fluxum), reviparin, certoparin…
  - mol. weight cca 2 - 9 kDa (heparin 15 - 20)
  - s.c. application
  - lower risk of adverse effects, less frequent dosing
  - patients are able to give injections themselves at home
Direct anticoagulants
Low-molecular-weight heparins

- increase ATIII activity against IIa and Xa (early phase of coagulation)

- halflife is doubled when compared to heparin (cca 200 mins), much better bioavailability

- they do not prolong APTT, however monitoring is not required, because they are eliminated by 1st. order kinetics

- eliminated by liver, monitoring of thrombocytes
**Direct anticoagulants**

**Sulodexide**

**sulodexide (Vessel due)**

- glykosaminoglycan, mixture of heparin (80 %) + dermatan
- mild fibrinolytic effect
- anti Xa activity
- lipolytic effect – therapy monitoring
- protective and reparatory effects on endothel
Direct anticoagulants

Heparinoids

• polysulphur esters of saccharids e.g. heparansulfate, dermatansulphate or mixture danaparoid
• obtained from animal intestinal mucous membrane
• they are mostly used locally on skin (thrombophlebitis, injuries)
• we can use them to substitute heparin in HIT

Direct anticoagulants

Sulphonated pentasacharid

• fondaparinux (Arixtra), indraparinux
  - (named for Asterix a Obelix) indirectly anti-Xa, deep venous thrombosis, pulmonal embolisation
Direct anticoagulants
Thrombin inhibitors

antithrombin III - congenital deficiency

hirudin
• polypeptide present in leech saliva (Hirudo medicinalis)
• reacts directly with thrombin without ATIII

lepirudin, desirudin, bivalirudin – parenteral administration

ximelagatran → melagatran (pro-drug), dabigatran (RMP Pradaxa)
• peroral anticoagulant without necessity of monitoring
• direct thrombin inhibition
• ximelagatran withdrewd form market – hepatopathy

argatroban
Direct anticoagulants

Xa inhibitors

Xabans

- direct Xa inhibition (both pathways)
- oral administration
- no effect on platelets or thrombin
- no need for monitoring
- KI – liver diseases

rivaroxaban (RMP Xarelto)
apixaban (RMP Eliquis)
Betrixaban
Indirect anticoagulants
Indirect anticoagulants

- structural similarity with vitamin K
- kompetitive antagonists of vitamin K
  - vit K is essential for posttranslational carboxylation in clotting factors II (prothrombin), VII, IX, X, protein C and protein S
  - inducing synthesis of structurally incomplete coag. factors

- only in vivo
- delayed effect
Indirect anticoagulants

- binding to plasma protein (up to 99%)
- metabolised in liver (CYP450), excretion – bile, urine
- monitoring by measuring the INR – (international normalised ratio)
  healthy preson INR 0.8-1.2
  with warfarin INR 2-3

- AE: - haemorrhage in skin, GIT, kidneys, brain
  - rarely necrose of small intestine or skin or soft parts of the body

- KI: - gastrointestinal ulceration
  - trombocytopenia
  - malign hypertension
  - pregnancy (teratogenic, bleeding), breast-feeding
Indirect anticoagulants

- I: prevention of trombembolic diseases
  deep venous trombosis
  lung embolism
- anticoagulant effect can be suppressed by
  administering dose of vit K 20-40mg iv

  warfarin
  • p.o. or i.v. aplikation
  • D: starting doses 5-15mg
    long-term doses 5-7 mg

  dicumarol
  ethylbiscumacetate
  phenprocoumon
Indirect anticoagulants

- High variability in dosing
  - according to some published papers 0.5 – 50 mg/day!

- genetic influences
  - CYP 2C9 activity (need to reduce doses down to 60%) – in Caucasian population 10 – 20% of people

- mutation of C1 subunit epoxid-reductase (enzyme directly influenced by warfarin) – need to reduce dosing - in Caucasian population 14 - 37% of people

- the therapy must be often customized according to diet, co-morbidities
- there are tables to help physicians
**Indirect anticoagulants**

**Warfarin** – many interactions – mostly ↑ risk of bleeding (sometimes induction of biotransformation – St. John’s wort, phenobarbital, rifampicin)

- alcohol !!!, allopurinol, anabolic steroids, several ATB and chemotherapeutics, disulfiram, thyroid hormones...

- Cardiology drugs – ASA, heparin, chinidin, amiodaron…
Fibrinolytics (thrombolytics) are plazminogen activators (PA).

Ideal thrombolytic drug should be administered i.v. and should cause selective thrombolysis in the thrombus without converting plasminogen into plasmin.

Fibrinolytics

I. generation

II. generation
I. generation

Non-selective → systemic activation of plasmin

- streptokinase
- urokinase

II. generation

Binding to fibrin → fibrinolysis targeted on the thrombus

- t-PA
- anistreplase
- saruplase
**Fibrinolytics (thrombolytics)**

**Clinical use:**
- Severe lung embolisation
- Deep venous thrombosis
- Arterial occlusion
- Acute myocardial infarction therapy

**Unwanted effects:**
- Bleeding
Fibrinolytics (thrombolytics)

Contraindications

Absolute

Active bleeding from intracranial or chest trauma

Bleeding from tumor or from vascular abnormality

Relative

Hypertension

Other risks of bleeding
Fibrinolytics (thrombolytics) non-selective streptokinase

- nonenzymatic protein isolated from β-hemolytic streptococcus
- indirectly causes activation of plasminogen
- parenteral administration → lysis of ACUTE thrombi
- it is cheap, but antigenous,— prev. bolus hydrocortisoni 100 mg i.v., do not give again in 1 year after the previous usage
- I: - very good drug for recanalisation after IM infusion + AcSal
Fibrinolytics (thrombolytics) nonselective
urokinase

- origin is human urine, metabolic product of u-PA
- direct plasminogen activator
- not antigenous
- weaker than streptokinase, ↓ AE
Fibrinolytics (thrombolytics) selective t-PA (alteplase)

- high affinity to fibrin
- concentrations used in therapy are 1000x higher than physiologic, short t1/2 = risk of reoclusion

- alteplase RMP Actilyse – recombinant, single-chain t-PA
- reteplase RMP Rapilysin – similar but has a longer elimination half-life allowing bolus administration, simpler structure = only peptid domain of tPA
- tenecteplase (TMK-tPA), RMP Metalyse – even better pharmacokinetic characteristics, better effect
Fibrinolytics (thrombolytics) selective

anistreplase ASPAC

- = acetylated streptokinase – plasminogen activator complex
- inactive form, binding to fibrin → deacetylation → activation
- activated anistreplase is quickly eliminated from circulation by α2- antiplasmin → ↓ AE
- very good effect in AMI
- antigenous

Fibrinolytics (thrombolytics) selective

Saruplase (rscu–PA)

- similar to urokinase, but high affinity to fibrin
- possible combination of saruplase with t-PA for reperfusion of coronary arteries
Antifibrinolytics

- inhibit plasmin from binding to fibrin
- additive drugs used when substituting loss of coagulation factors to stop bleeding during/after surgery (e.g. tonsilectomy, prostatectomy)
- menorrhagia
- dental surgery in hemophilic patients (extraction)
- AE: nausea, KI: DIC

- ε-aminokapronic acid (EACA) ↓ activation of plasminogen, p.o., i.v.
- tranexamic acid
- p-aminomethylbenzoic acid (PAMBA)

- aprotinin – inhibits proteolytic enzymes (trypsin, chymotrypsin and plasmin) – for fibrinolytic drugs overdose, pancreatitis, patient at risk of major blood loss during heart or liver surgery
Antiplatelet drugs (Antiagregants)

- inhibition of aggregation, specific profylaxion of arterial thrombose, secundar prevention of AMI

- antiplatelet therapy after AMI needs to be started as soon as possible (for the best results not later than 1 hour after first symptoms)

- usually used in combination with heparin to ensure proper perfusion and infarction size reduction

- there are other drugs with antiplatelet activity, but these are not used in this indication: hydrochlorochin, klofibrate, indometacin, fenylbutazon, some of prostaglandins and neurotropics
Antiplatelet drugs (Antiagregants)

How do they work?

1. Inhibition of thromboxan A2 syntese - inhibition of COX
   ASA, indobufen, sulfinpyrazon

2. Inhibition of thromboxan A2 syntese via increasing cAMP level in thrombocyte
   • inhibition of fosfodiesterase – pentoxifyllin, cilostazol
   • stimulation of adenylatcyklase – dipyridamole, prostacyklin and analogues

3. Inhibition of fibrinogen cross-bridging among thrombocytes
   • inhibition of ADP P2Y_{12} receptor in thrombocyte membrane - ticloidin, clopidogrel, prasugrel, ticagrelor
   • inhibition of fibrinogen receptor in thrombocyte membrane (IIb/IIIa) – tirofiban, lamifiban, monoclonal antibodies – abciximab
Indications:

- ischemic cerebrovascular diseases
- ischemic heart disease
  - periferal arteries diseases
- to reduce thrombogenous effect of synthetic materials
Antiplatelet drugs
acetylsalicylic acid

- deacetylates and irreversibly inhibits COX

- COX:
  - in thrombocytes $\rightarrow$ TXA2 (aggregation)
  - in endothelial cells $\rightarrow$ PGI2 (antiaggregation and vasodilation)

  We want to block TXA2

- Thrombocytes unlike endothelial cells are not able to syntetise COX = selective inhibition of COX in thrombocytes (persistence 7-10 days)

- Effect depends on dose (high doses block also endothelial COX)
• Low doses of AcSal can reduce risk of AMI and sudden death in patients with angina pectoris down to 50%

• Also other NSAID (ibuprofen, naproxen) have antiagregant effect, but this effect is not irreversible

• **AMI – first-aid treatment immediately administer 500 mg ASA**
Antiplatelet drugs
acetylsalicylic acid

- D: usually 50-100mg per day
- There is no laboratory test to monitor the effectiveness of therapy – only clinical symptoms
- No antidote available, in case of need it is possible to administer hemostyptics, antifibrinolytics or thrombocytes
Indication:
- AIM, instable AP
- Prevention of AIM (also combined with warfarin)
- Ischemic brain stroke
- After PTCA, by-pass

Disadvantages:
- AE – about 20% of patients
- Resistance to ASA 10-20% of patients
Other NSAIDs with antiaggregant properties – but reversible

**Sulfinpyrazon**
- NSAID, competitive inhibitor of COX
- inhibiting adhesion of thrombocytes and releasing of several substances
- prolonging persistence of platelets in circulation

- **Indobufen** – short effect, expensive
- **Picotamide**
**Antiplatelet drugs – pentoxifyllin, cilostazol**

- **phosphodiesterase inhibitors**
  - pentoxifyllin
  - improves **deformability of erythrocytes**
  - decreases levels of fibrinogen and blood viscosity, thus improving microcirculation, antiinflammatory eff.

- **cilostazol**
  - treatment of **claudications, PAD**
  - positive effects on lipid metabolism and antiproiferative effect on smooth muscle

**Antiplatelet drugs – dipyridamol**

- **coronary vasodilatant, activation of adenylatecyclase**

- decreasing adhesivity of platelets to damaged endotel

↑ cAMP in platelets → ↓ TXA2

- used in combination with aspirin, warfarin
Antiplatelet drugs – tienopyridines

- **block ADP** (activates receptors on surface of thrombocytes → this is where fibrinogen binds)

- onset is slow (several days) and lasts 7-10 days
- NU: hemorrhage, diarrhea and leucopenia

1. ticlopidin (RMP Ticlid)
2. clopidogrel
   - better effect, less AE
   - convenient combination with ASA after PCI with stent implantation RMP Plavix, Clopidogrel…
   - Fix combination with ASA RMP Duoplavin, Duocover
3. prasugrel – 3. generation RMP Efient
4. ticagrelor – new drug, reversible action
GP IIb/IIIa Rc antagonists

- They are supposed to block all pathways of platelet activation since they all converge on activation of GP IIb/IIIa receptor
  1. Eptifibatide – small peptide, i.v. adm., short effect
  2. Tirofiban, lamifiban – similar structure to ligands for GP IIb/IIIa receptor, i.v. adm. effect lasts 2-4 hours
  3. Abciximab – monoclonal antibody fragment directed against the receptor, only for high-risk patients, immunogenous

Oral active inhibitors – sibrafiban, roxifiban, lefradafiban… – did not pass clinical trials
Antagonists IIb/IIIa Rc

In clinical practise we have currently available these intravenous drugs: *abciximab* (ReoPro), *tirofiban* (Aggrastat) a *eptifibatid* (Integrilin)

Disadvantage is high price

In our conditions we consider IIb/IIIa blockers indicated in:
- PCI with thrombus in coronar arthey confirmed by angiography
- high-risk patient (with positive troponin, diabetics)
- in intervention on degeneratively changed aortocoronar bypass
Hemostatics

• Used to control and stop bleeding in injured patients or after surgery or in diseases causing excessive bleeding.

• gelatine
• gelatine sponge
• colagen
• etamsylate
• vasopresine derivates

• frozen blood plasma, human fibrinogen, thrombin, coagulation factors (Novo VII)
Etamsylate (RMP Dicynon):
- antihemorrhagic and angioprotective effect
- no influence on coagulation factors or fibrinolysis
- stimulates trombopoiesis
- increase PGI2 synthesis

Vasopresine derivates:
- terlipresin, ornipresin, lypresin
  - strong vasoconstriction, decrease of blood flow in splanchnic area (decrease in portal pressure)

Note. desmopresin is used in treatment of diabetes insipidus (longer t1/2 than vasopresin) and nykturia in children and adults