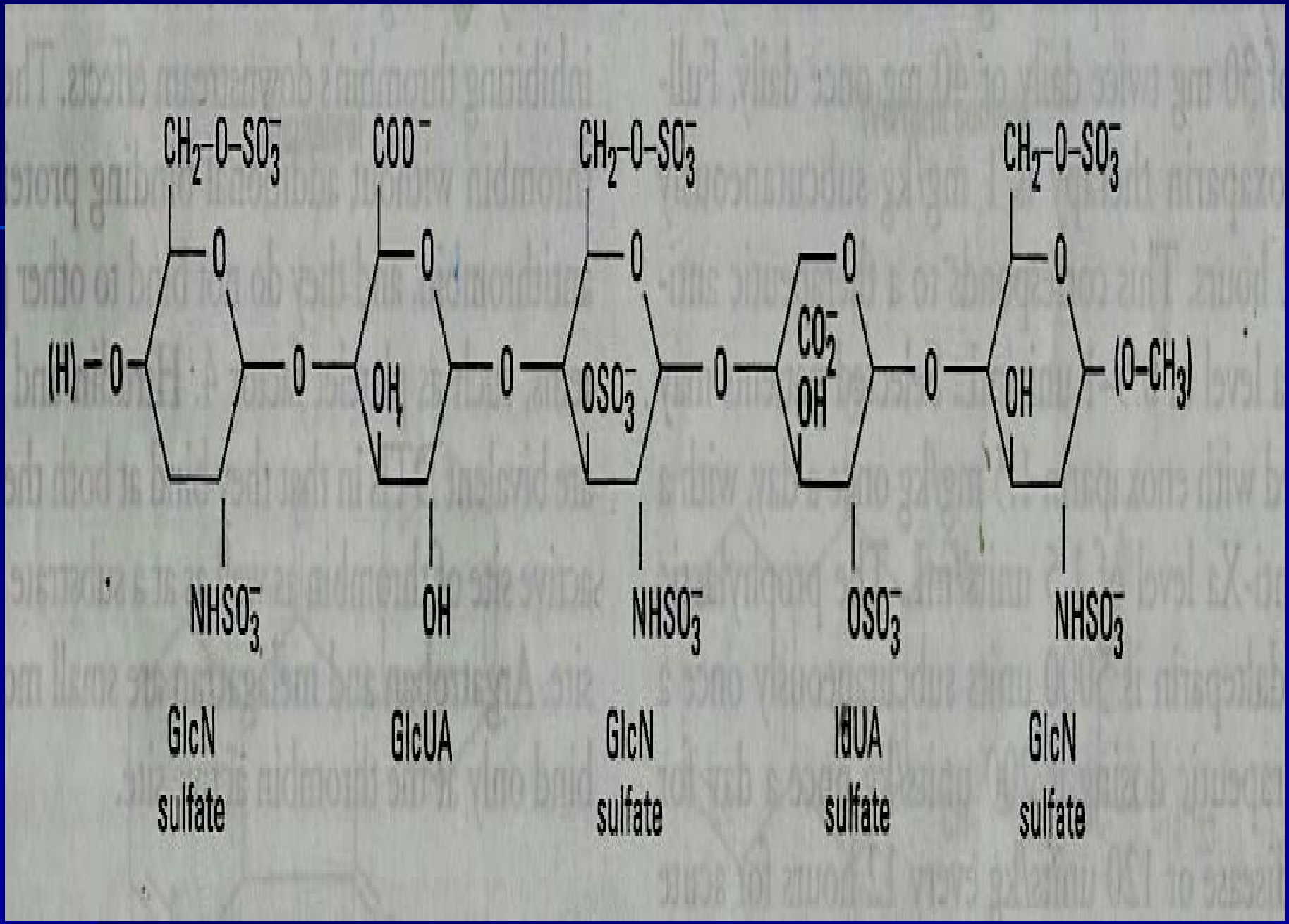
Anticoagulants

- **Oral anticoagulants**
  - warfarin
- **Parenteral anticoagulants**
  - Unfractionated high Molecular weight heparin (HMWH).
  - Low molecular weight heparin (LMWH).
  - Indirect thrombin inhibitors

Unfractionated High Molecular Weight Heparin (UHMWH)

Chemistry

- Heterogenous mixture of sulfated mucopolysaccharides.
- Highly acidic molecule.
- MW: 5000-30,000
- Extracted from porcine intestinal mucosa & bovine lung.

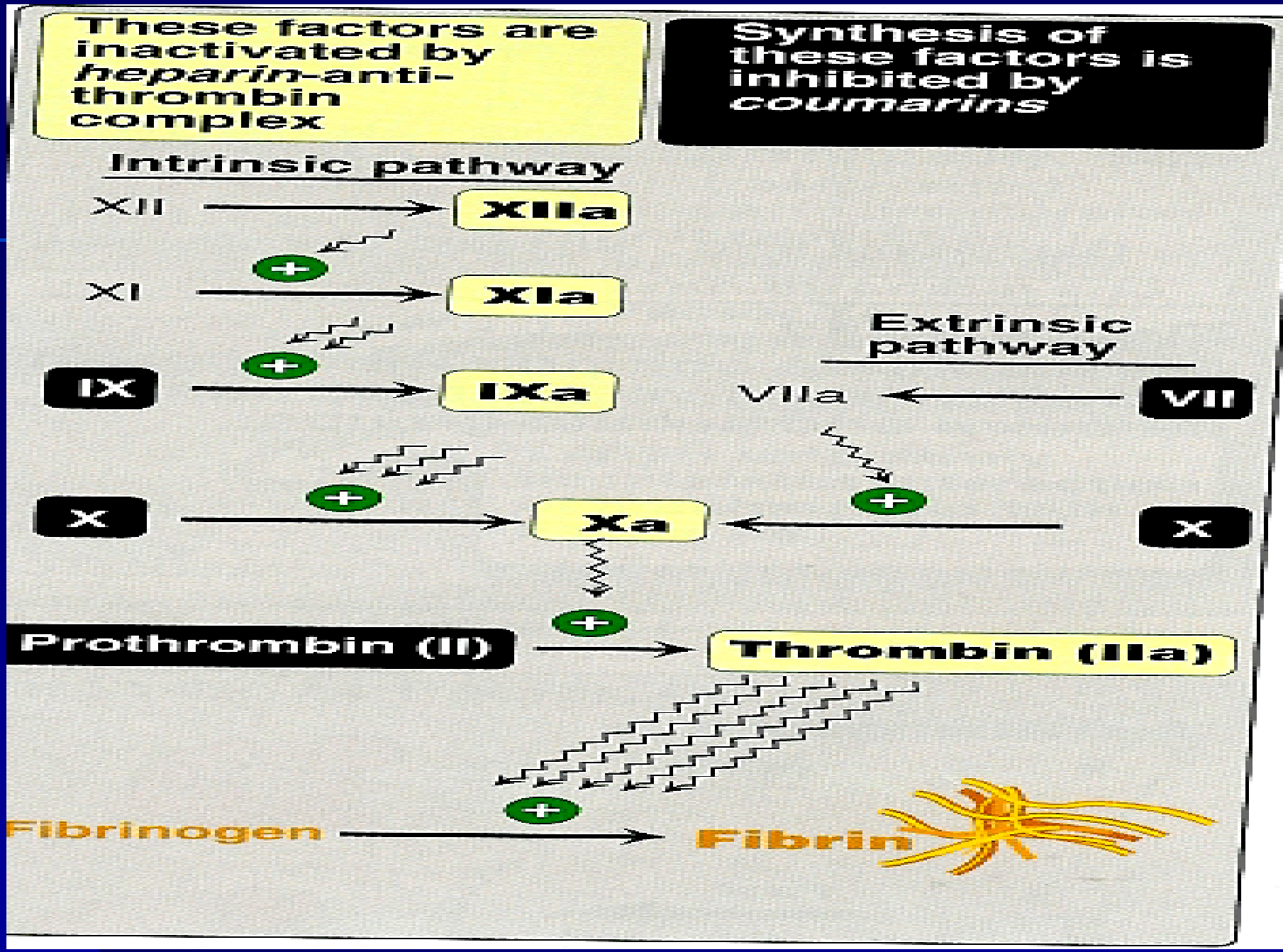

GlcN sulfate
GlcUA
GlcN sulfate
IdUA sulfate
GlcN sulfate

Mechanism of Action

- Antithrombin action.
- Acts in the blood by activating anticlotting factor, antithrombin.
- Heparin $\rightarrow\uparrow$ activity of antithrombin III by causing conformational change (**accelerated effect**).
- **Anti thrombin III** is natural plasma protease inhibitor that inhibits serine proteases activated clotting factors (IIa, IXa, Xa, XIIa) $\rightarrow$ inhibition of thrombin (IIa) and prevent conversion of fibrinogen to fibrin.

Pharmacokinetics

1. Given only parenerally (S.C. or I.V) Not I.M (hematoma).
2. Immediate anticoagulant effect (T ½ = 60 - 90 min.).
3. Metabolized in the liver (80 %) - 20 % excreted unchanged in urine (Not by microsomes).
4. Does not cross placenta & not excreted in milk.


These factors are inactivated by *heparin*-anti-thrombin complex
Synthesis of these factors is inhibited by *coumarins*
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
Extrinsic pathway
VIIa
VII
X
Xa
X
Prothrombin (II)
Thrombin (IIa)
Fibrinogen
Fibrin

Pharmacological Actions

1. Heparin has anticoagulant activity in vivo & in vitro
2. Increase activity of lipoprotein lipase from tissues → ↓ lipemia after fatty meals (clearing factor).

Uses of Heparin

Acute venous thromboembolic disorder.

1. **Pulmonary embolism.**
2. **Deep vein thrombosis.**
3. **Post - operative venous thrombosis.**
4. **Stroke.**
5. **Myocardial infarction.**
6. **Hemodialysis.**

Forms of heparin

Lithium salts (in vitro) for blood samples.

Calcium or sodium salts (in vivo).

Doses are specified in units/mg.

Doses

- Low dose prophylaxis (S.C.): 5000 U/12h
- High dose treatment (I.V. , bolus & infusion pump): 80-100 U/kg bolus then 15-22 U/kg/h.

Control of Heparin Therapy

Plasma heparin concentration:

- Protamine titration (0.2-0.4 unit/ml).
- Anti-Xa units (0.3-0.7 unit/ml).

Estimation of heparin effect:

- Activated partial thromboplastin time(aPTT) 1.5 - 2.5 times that of the normal value (30 sec.).
- Whole blood clotting time (WBCT) : 2 - 3 times the normal (5 - 7 min.).

Side Effects

1. Bleeding.
2. Thrombocytopenia (platelet count).
3. Hypersensitivity reactions : antigenic character.
4. Reversible alopecia & osteoporosis (long term).

Heparin antidote

Protamine sulphate,

- Basic peptide, given I.V. slowly 1 mg / 100 U heparin.
- Excess protamine should be avoided since it has anticoagulant effect.

Contraindications

1. Bleeding tendency, Hemophilia, thrombocytopenia.
2. Severe hypertension.
3. Intra cranial hemorrhage.
4. Ulcerative lesions of gastrointestinal tract.
5. Threatened abortion.
6. Advanced hepatic or renal disease.
7. Hypersensitivity to heparin.
8. Patients who have had surgery of the brain, eye or spinal cord.

Low Molecular Weight Heparin

Enoxaparin.

Dalteparin.

Tinzaparin

Danaproid.

Mechanism of Action

increases activity of antithrombin III thus inhibits the activity of factor Xa and to a lesser degree (IIa).

Advantages

1. Rapid onset.
2. Favorable pharmacokinetic characters.
3. Longer biological half life.
4. Increased bioavailability.
5. Less frequent dosing (once or twice/daily).
6. Less incidence of bleeding and thrombocytopenia.

Therapeutic Uses

- Patient insensitive to heparin (with low antithrombin III level).
- Anticoagulant therapy in high risk patients.
- Patients with heparin dependence thrombocytopenia.

Control of the Doses

Estimation of plasma factor Xa (0.5-1 U/ml).

Doses:

Enoxaparin: 30 mg BID or 40 mg once/d

Dalteparin: SC injection 5000 U once / day.

Differences	HMWH	LMWH
	↑ activity of a antithrombin III against active factor II, IX, X, XI, and XII.	activity of antithrombin III against Xa less IIa
Bleeding tendency	High	Low
thrombocytopenia	High	Low
T ½	Short	Long (double)
Bioavailability	Low	High
Control of dose	APTT, WBC.	Plasma factor Xa
Administration	3 - 4 dose / day (I.V. or S.C)	1 - 2 dose / day S.C. only
Efficacy	Equal	Equal
MW	5000 - 30.000	2000 - 9000

Direct Thrombin Inhibitors anticoagulants

Lepirudin (Refludan)

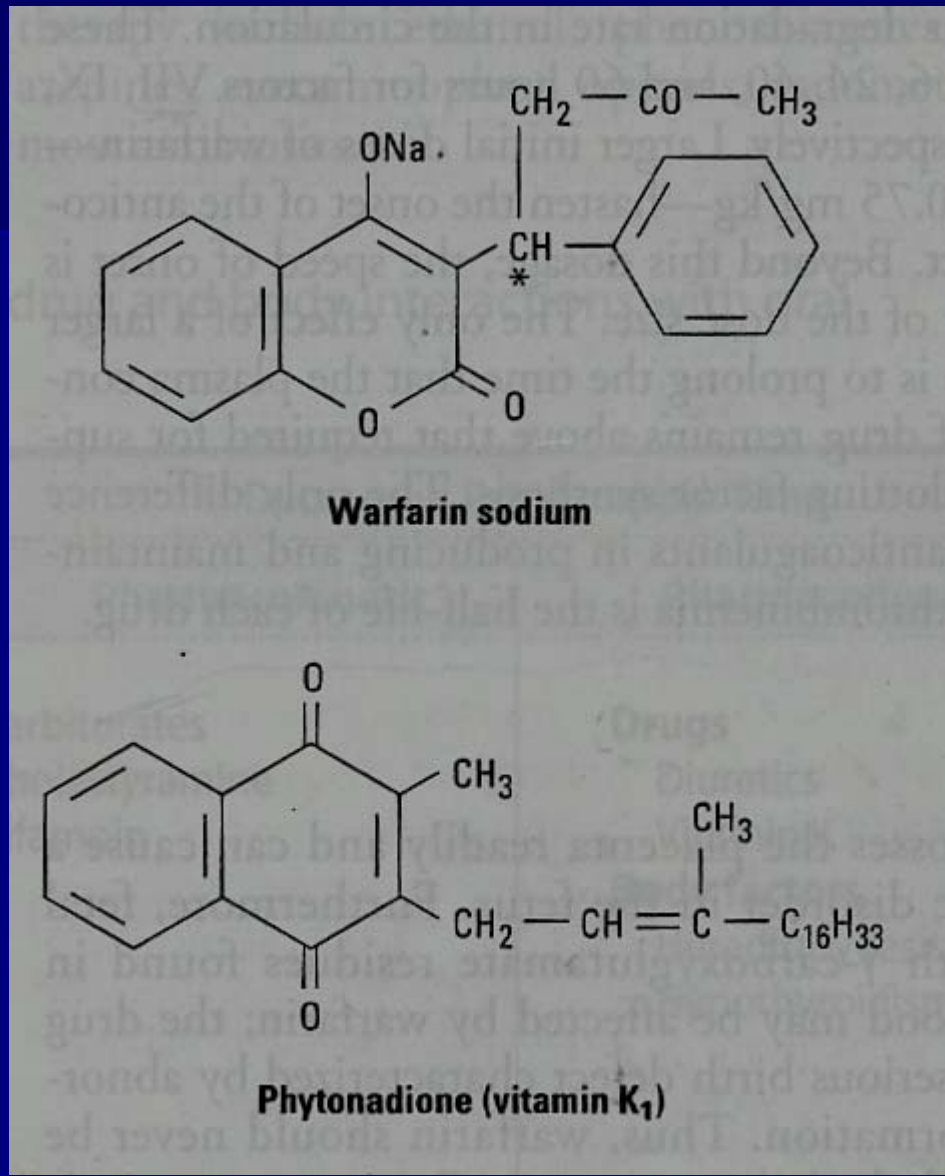
Bivalirudin (Angiomax)

- act by direct binding to the active site of thrombin.
- Prepared by DNA technology .
- independent on antithrombin III.
- Little effect on platelets or bleeding time.

- Given parenterally (I.V.).
- Has short duration of action (1 hr).
- It is monitored by aPTT
- Used for patients with thrombosis related to heparin-induced thrombocytopenia.
- Is accumulated in renal insufficiency.
- No antagonists are available.

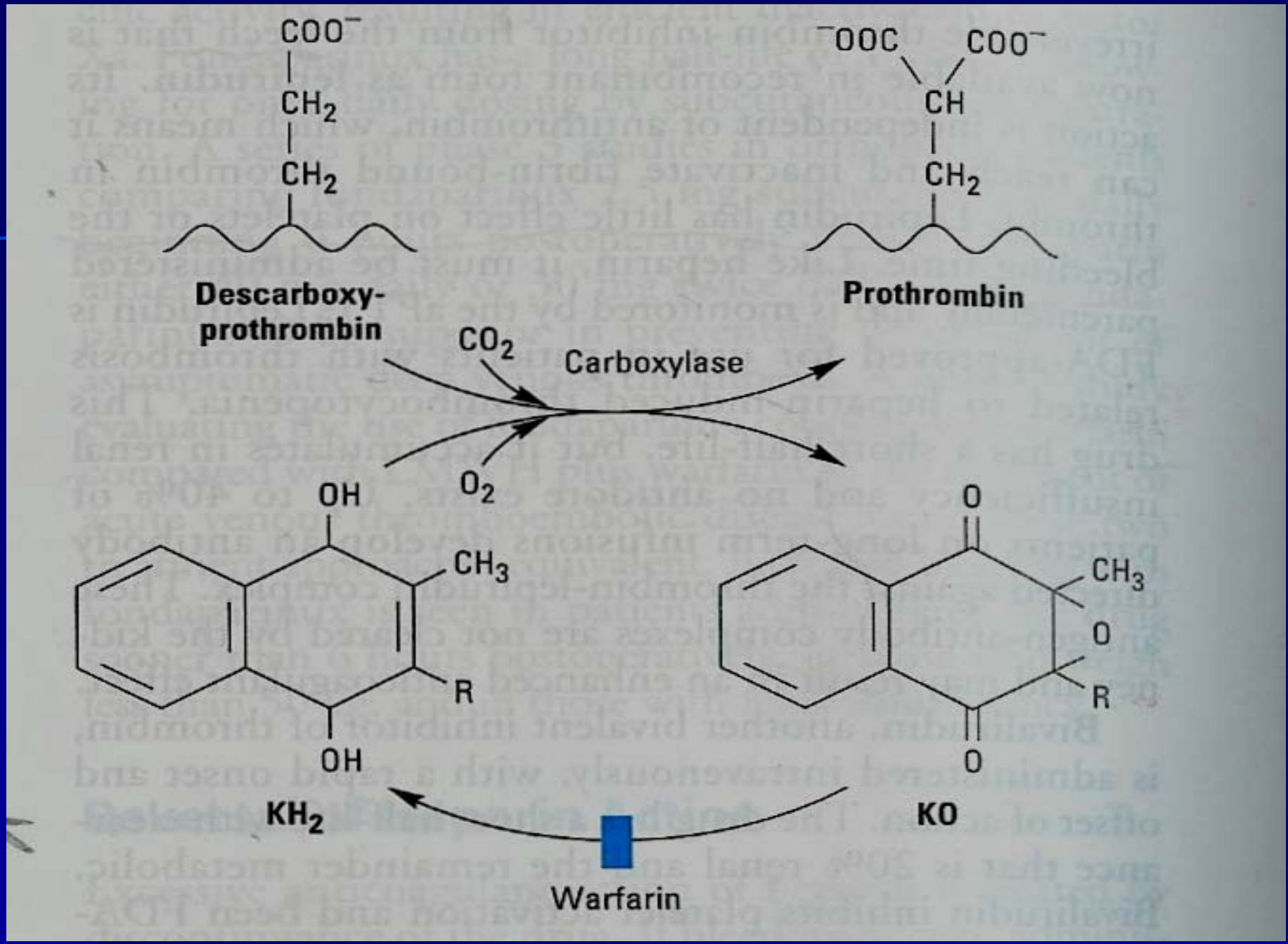
Oral anticoagulant

Warfarin – Dicumarol



Mechanism of action

- Act by inhibiting the activation of several clotting factors (II, VII, IX, X) by blocking γ-carboxylation of glutamate residues in clotting factors that require reduced vitamin K as a cofactor for their synthesis by liver.
- It is vitamin k antagonist (Vit k epoxide reductase inhibitor).


COO⁻
CH2
CH2
Descarboxy-
prothrombin
⁻OOC
COO⁻
CH
CH2
Prothrombin
CO2
O2
Carboxylase
OH
CH3
R
OH
KH2
O
CH3
O
R
O
KO
Warfarin

Kinetics

- Taken orally.
- Highly bound to plasma protein (low Vd).
- Long plasma half life (36 h).
- Cross placenta (# pregnancy).
- Metabolized in the liver by Cyt P450
- Excreted in urine and stool.
- Delayed onset of action (8-12 h).
- Large initial dose hasten the onset of effect (0.75 mg/k).

Pharmacological effects

- Acts in vivo only.

Side effects

1. Hemorrhage : treated by vitamin K 1
2. Soft tissue necrosis
3. Drug interactions
4. Teratogenic hemorrhagic disorder-abnormal bone formation in the fetus.

Drug interactions

1. **Broad spectrum antibiotics** cephalosporins
2. **Inducers** decrease warfarin action

Phenobarbitone, rifampicin, phenytoin

3. **Inhibitors** increase warfarin action

Cimetidine, erythromycin

4. Aspirin & Phenylbutazone.
5. **Diseases: augment warfarin action**

- Hyperthyroidism (clotting factors metabolism).
- Liver disease.

Contraindications

Pregnancy

Hypoprothrombinemia (Liver disease).

Control of warfarin Therapy

Prothrombin time (PT)

Time required for plasma clotting with calcium and thromboplastin (10-12 seconds) 2-4 times

International normalized ratio (INR)

Ratio between patients PT and standard PT (2.5-3.5).

Used for Maintenance of anticoagulant activity.

Reversal of action

- Vitamin k1 (phytonadione).
- Recombinant factor VIIa (rFVIIa).
- Fresh frozen plasma.
- Prothrombin complex concentrates (PCC).