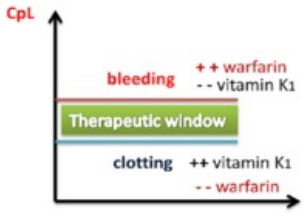
Warfarin

Warfarin is indirect oral anticoagulant. For a long time, it was more or less the only available oral drug with anticoagulation action. It was initially used as rat poison, but its potential medicinal uses were revealed by a suicide attempt that was followed by a blood coagulation disorder. Together with ethyl biscum acetate (Pelentan® – original Czechoslovak preparation, very unstable, no longer registered in the Czech Republic), warfarin belongs to the so-called ``coumarins.

Pharmaceutical form of warfarin

How does warfarin work?

Warfarin blocks vitamin K. Without vitamin K, the liver cell cannot synthesize the coagulation factors **II**, **VII**, **IX** and **X** (= vitamin K-dependent coagulation factors). Warfarin therefore *blocks the synthesis of vitamin K-dependent coagulation factors* in the liver.



How does warfarin work?

Vitamin K is a **cofactor for the carboxylation** of glutamic acid to γ-carboxyglutamic acid; γ-Carboxyglutamate is essential for the binding of Calcium by coagulation factors that use $\mathbf{Ca^{2+}}$ as a cofactor. But it also participates in the function of other proteins interacting with calcium, e.g. osteocalcin; the function of these proteins will also be affected by warfarin.

Pharmacokinetics

Favorable **pharmacokinetic properties** of warfarin include its **good absorption**, **predictable onset and end of action** and relatively long half-life. Warfarin is detectable in plasma within one hour and the maximum level in blood is reached after about 90 minutes.

There are large inter-individual differences in the pharmacokinetics of warfarin, therefore the dose must be **strictly individualized**. A polymorphism of vitamin K reductase and the CYP2C9 system is applied. **Medicines** (especially amiodarone, fluvastatin, clopidogrel, nonsteroidal antirheumatic drugs, ...) and **foods containing vitamin K** (leafy vegetables, meat from cattle fed with vitamin K) interact. Therefore, the representation of these foods in the diet should be **constant** as much as possible.

The CYP2C9 polymorphism can now be routinely determined in the laboratory.

Warfarin sensitivity

The **response** to warfarin in individual patients is **independent** of the patient's age, gender and weight. The response to warfarin may be increased or decreased. More recent research shows that hereditary predispositions also play a significant role in patients' responses to warfarin[1].

Increased response can be expected when:

- malabsorptive syndrome – in patients with deficiency of vitamin K;
- obstructive jaundice;
- liver diseases;
- therapy antibiotics suppressing saprophytic intestinal flora;
- increased metabolism – thyrotoxicosis, febrile condition (accelerated breakdown of coagulation factors);
- interaction with some drugs (see above).

We can expect a **reduced response** when:

- Congenital or acquired resistance to warfarin.

Indications for warfarin administration

The **most common indications** for the administration of warfarin are:

- prophylaxis of *phlebothrombosis*;
- prophylaxis of thrombosis and embolism in **patients with atrial fibrillation**;
- prophylaxis of thrombosis and embolism in **patients with implanted mechanical valve prostheses**.

Contraindications

The main contraindications include **bleeding conditions** and **pregnancy** (at doses above 5 mg/day, conversion to LMWH).

Administration of warfarin during pregnancy and postpartum Warfarin crosses the placenta resulting in:

- **risk of fetal embryopathy** (nasal hypoplasia and damage to the pineal glands), which is greatest between the 8th and 12th weeks. week of pregnancy;
- **neurotoxicity**, the risk of which is the same throughout pregnancy;
- **risk of bleeding**, which, together with the risk of trauma during childbirth, is greatest during this period.

The advantage of warfarin is the possibility of use during breastfeeding, as it does not pass into breast milk.

Initiation of warfarin therapy

At the beginning of treatment, there is a short-term procoagulant effect of warfarin, because the synthesis of protein C and S is somewhat reduced. Therefore, this period should be **hidden by the application of low molecular heparin**. It starts at 5 mg/day (with LMWH overlay). The dosage is then adjusted according to the results INR (Quick).

Monitoring of warfarinized patients

As already stated, the effect of warfarin fluctuates. Therefore, it is necessary to **regularly check the INR'**, which should be in the range of **2-3.5**. Measurements should be performed once every 3-5 days, in stable patients (i.e. 2x consecutively within the therapeutic range) once every 4 weeks. The current trend is home monitoring once a week.

The most common ``laboratory test *for monitoring anticoagulant therapy is the ``protrobin time*.

The test is performed by adding thromboplastin and Ca^{2+} to citrate plasma and measuring the time to the formation of the first fibrin fiber. The results can be given in percentages, the ratio of the time of the patient to the control or in the form of *INR* (International Normalized Ratio).

The INR is calculated according to the following formula:

$$INR = patient's\ prothrombin\ time^{ISI} / control's\ prothrombin\ time$$

The **ISI** (International Sensitivity Index) indicates the sensitivity of the used thromboplastin to the standard WHO thromboplastin.

INR [2]	
Clinical indication	**INR value**
Prophylaxis of postoperative DVT (general surgery)	2.0-2.5
DVT prophylaxis during operations and hip fractures	2.0-3.0
Myocardial infarction, prevention of VTE	2.0-3.0
Treatment of venous thrombosis	2.0-3.0
Treatment of pulmonary embolism	2.0-3.0
Prophylaxis of transient ischemic events	2.0-3.0
Atrial fibrillation, prophylaxis	2.0-3.0
Recurrent DVT and PE	3.0-4.5
Mechanical heart valve replacements	3.0-4.5
Recurrent systemic embolization	3.0-4.5

Complications of warfarin therapy

Bleeding is the **most common complication of therapy**. A distinction must be made between severe bleeding and mild disease. Although the grading of major and minor bleeding is still not uniform, major bleeding is usually defined as intracranial bleeding, retroperitoneal bleeding, and bleeding requiring transfusion of 2 or more units of erythrocyte mass. The most common cause of fatty hemorrhage is CNS hemorrhage. Mild bleeding manifestations are usually manifested by epistaxis, hematomas, suffusions or microscopic or macroscopic hematuria.

How should warfarin be administered?

1. It is possible to stop warfarinization - then warfarin is stopped and other risk factors for the event are considered. bleeding - age, other diseases - in case of risk of bleeding, vitamin K can be administered - 10 mg Kanavit per person.
2. It is not possible to stop warfarinization - then warfarin is temporarily stopped and the INR is checked every day; as the INR falls, he continues further warfarinization in a reduced reduction.

Links

Related Articles

- Anticoagulants
- Hemocoagulation
- Heparin
- Coagulation tests
- Haemorrhagic tendency examination

Resources

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1. The International Warfarin Pharmacogenetics Consortium. Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. The New England Journal of Medicine, 360:753-764, 2009
2. MARTÍNKOVÁ, Dahlia – MICHUDA, Stanislav – CERMANOVÁ, Jolana. *Faculty of medicine in Hradec Králobé : Coumarin anticoagulants* [online]. ©2005. [cit. 2010-06-21]. <https://www.lfhk.cuni.cz/farmakol/predn/bak/kapitoly/krev/kumarin-bak.doc/>.