Pharmacology and Toxicology:
Anticoagulants

Many people suffer from cardiovascular diseases. Stroke and myocardial infarction rank among the most frequent causes of death due to cardiovascular diseases. The causes are blocked vessels and the resulting insufficient blood supply of vital organs and tissue. Surgeries are usually the last resort and, at the same time, the start of a new, safe and hopefully healthier life. In this article, you get to know more about the mechanism of action, the medical application as well as the possible side effects of anticoagulants.

The Role of Anticoagulants in Medicine

Drugs that inhibit blood coagulation are referred to as anticoagulants. Anticoagulants are designed to prevent blood coagulation and the formation of blood clots, which are clumps that form as a result of hardening from a liquid to a solid. Blood clots occurring inside veins or arteries are known as thrombi. Thrombi are, therefore, not part of the platelet plug formed during wound healing.
The danger due to thrombi is due to their ability to migrate even into the smallest vessels, which are blocked leading to loss of nutrient supply via blood circulation to the respective organ, resulting in pulmonary embolism, myocardial infarction or stroke. In the normal population, anticoagulants are more commonly known as ‘blood thinners’. However, blood is not actually thinned; instead, anticoagulants prevent the formation of lethal thrombi by ensuring that thrombocytes do not adhere to each other.

The 2 groups of anticoagulants include:

- **Anticoagulants**, which inhibit the formation or prevent the effect of coagulation factors.
- **Antiplatelets (thrombocyte aggregation inhibitors)**, which inhibit the clotting of thrombocytes.

The type of anticoagulant used depends on the underlying disease, patient’s age, and concomitant illnesses or risk factors. Anamnesis should exclude the possible incompatibility with specific anticoagulants prior to administration. The advantages and disadvantages of anticoagulants specific to each individual should be considered.
Effects of Anticoagulants

Coumarin

Coumarin and coumarin derivatives are used to inhibit blood coagulation over long periods. Coumarins inhibit the vitamin-K dependent synthesis of the coagulation factors IX, X, VII, and II (keyword: 1972), which are produced in the liver. Therefore, vitamin K holds key to blood coagulation.

As a result, the effect of coumarin derivatives is observed only in vivo. Coumarin derivatives are administered orally and are fully effective in 2–4 days because the coagulation factors existing in the blood are degraded first.

Heparins

Heparins manifest their effects a few hours after administration and are therefore preferred after surgery, to prevent thrombosis. Heparin is a glycosaminoglycan and inhibits the formation of thrombin from prothrombin in the secondary coagulation cascade. Physiologically, heparin is stored within the basophilic granulocytes, inside the liver, and inside the mast cells.

Heparin increases the effect of antithrombin III, the strongest anticoagulant in the body, by approx. 100 times. It also plays an important role in inhibiting the coagulation factor X. As mentioned above, in addition to endogenous synthesis, the administration of heparin is dictated by other clinical scenarios. In hospitals, heparin is used in anticoagulation and administered externally. Parenteral subcutaneous administration is frequently used to prevent thrombosis, which often occurs in immobile, bedridden patients after surgeries.
The lack of clinical effectiveness is most frequently attributed to a lack of antithrombin III. **Protamine sulfate** acts as a heparin antagonist to neutralize the effect of an overdose of heparin.

## Anticoagulants

### Apixaban

Apixaban is administered orally in tablet form twice a day. It is a direct **reversible antagonist** of the coagulation factor Xa, which is responsible for converting prothrombin into thrombin. In the absence of thrombin, all subsequent steps in the coagulation cascade are inhibited, including the formation of a fibrin mesh. Therefore, the formation of red thrombus during wound closure is delayed or prevented completely.

Since 2011, apixaban has been approved for the **prevention of relapse** within the European Union in patients after hip or knee replacement surgery, stroke, pulmonary embolism, and atrial fibrillation. Other anticoagulants are also indicated for similar indications. On average, the effect of apixaban lasts for 12 hours and is metabolized eventually by the body, with **75%** of the metabolism occurring in the **biliary tree** (via liver and bile) and **25%** **renally** (via the **kidneys**). Apixaban is detoxified and then excreted. Compared to the injection of heparin, the oral administration of apixaban is preferred to the ease of use.

### Dabigatran

Dabigatran is an oral anticoagulant, which is used to inhibit thrombin formation at the cellular level. Dabigatran is administered as an inactive precursor, **Dabigatran etexilate**, which is converted in the liver and blood plasma to its active form via **hydrolysis**. In the coagulation cascade, thrombin activates fibrinogen to fibrin under the
effect of the coagulation factor XII.

Dabigatran also inhibits **platelet aggregation during primary hemostasis**. The metabolism and excretion occur in the kidneys, which clean and filter the blood, and then excrete the toxic residue in the urine. Dabigatran etexilate is therefore not indicated for patients with renal insufficiency.

**Rivaroxaban**

Rivaroxaban is also a direct antagonist of the coagulation factor Xa, which is taken orally in tablet form. Due to its interference with secondary hemostasis, the **oxazolidinone derivative** does not affect platelet aggregation. Therefore, the primary wound closure remains intact. However, the wound is still fragile and easily reopened, since the formation of the final fibrin clot is prevented by the inhibition of secondary hemostasis. Rivaroxaban is reabsorbed rapidly by the villi on the epithelia of the small intestine, and the concentrated drug in the plasma is available within a maximum period of 2–4 hours after administration.
Marcumar

Marcumar is a vitamin K antagonist, which inhibits the $\gamma$-carboxylation of glutamate and thereby prevents the synthesis and secretion of the coagulation factors X, IX, VII and II. Both primary and secondary hemostasis is restricted greatly. Marcumar is also known as phenprocoumon, and it is administered orally in the form of tablets. Marcumar is a 4-hydroxycumarin, which inhibits vitamin K epoxide reductase.

Effects of Antiplatelets

Antiplatelets, also known as thrombocyte aggregation inhibitors, are used to inhibit the aggregation of thrombocytes. Compared to anticoagulants, the effect of antiplatelets is substantially lower, and therefore are not primarily administered after surgery. They are frequently used in patients diagnosed with myocardial infarction or stroke, to prevent or reduce the risk of another adverse event. Examples of antiplatelet drugs include dipyridamole, clopidogrel and acetylsalicylic acid (ASA).

Acetylsalicylic acid (ASA, Aspirin)

Aspirin is part of almost every medicine cabinet in households worldwide. Whether it is a headache or pain in the neck, menstrual or dental pain, fever or a simple cold, aspirin has been the ‘superstar’ among painkillers, and therefore, usually the first choice for symptom relief.
The over-the-counter (OTC) availability of this painkiller in pharmacies is currently a hot topic among the general public. The discussion centers around the issue of responsible treatment of patients with this drug. The World Health Organization already listed aspirin among essential pharmaceuticals in 1977. The advantages of the active agent acetylsalicylic acid are attributed to its antiplatelet, anti-inflammatory, analgesic, and antipyretic effects. The mechanism of action along with additional information is discussed in another article on arachidonic acid derivatives.

**Side Effects**

Notwithstanding the benefit of anticoagulants, they can lead to severe challenges when used at the wrong time. Anticoagulants do not completely disable the blood coagulation; however, initiation of the coagulation cascade as well as wound closing or wound healing is delayed significantly.

Severe cuts or skin damage increases the risk of a major and lethal blood loss. Therefore, it is necessary to add vitamin K or coagulation factors to stop blood coagulation under extreme conditions. Vitamin K can be administered as droplets directly under the tongue. Histologically, the mucosa in this area consists of non-keratinized squamous epithelium, which facilitates the entry of the substance into the vascular system, resulting in a rapid effect.

Overall, the treatment with ‘blood thinners’ increases the risk of persistent bleeding from the nose and gums. A small injury to the superficial epithelium through fingernails, toothbrush or other sharp objects can result in long-lasting bleeding.

Frequent nose- or gum bleeds, larger hematomas, red urine or dark red to black stool are side effects of anticoagulant therapy. Cerebral hemorrhage is the most serious adverse effect of treatment with anticoagulant treatment, manifesting as sudden, severe headache in combination with dizziness and visual disturbances.
A record of medications taken should always be documented for reference to enable rapid triage and appropriate interventions in the hospital, and prevention of complications and interactions with other drugs.

Interactions with other medications

Medications used for other therapies in combination with anticoagulants can lead to interactions, such as gastric bleeding, which can either increase or decrease the effect of anticoagulants. Therefore, such medications should only be administered after consulting with the attending physician.

The Effect of Nutrition on Blood Coagulation

As already mentioned, vitamin K is a substance that promotes blood coagulation. Coumarin acts by removing vitamin K out of the liver or inhibiting its synthesis. Foods such as cabbage, spinach, calf’s liver, ‘regular’ quark, mushrooms, tomatoes, beans, and peas are rich in vitamin K. However, a diet rich in vitamin K can decrease the effect of medicinally administered vitamin K antagonists.
Therefore, patients who are undergoing treatment with Marcumar should not eat large amounts of cabbage or other foods mentioned above, since the preventive effect of another possible stroke is no longer present. However, it is also not recommended to completely avoid any of the above-mentioned foods. Vitamin K deficiency, which is frequently observed in infants and in individuals exposed to dietary changes or malnutrition, prolongs the bleeding time.

**Vitamin K deficiency disorders** are relatively rare since several foods contain vitamin K, which is also produced by the intestinal flora. A balanced diet is recommended. However, the chronic intake of antibiotics destroys the gut bacteria. Patients diagnosed with hepatic diseases and diseases of the gastrointestinal tract as well as cancer represent a high-risk group for vitamin K deficiency disorders.

**References**


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