Furosemide, a Diuretikum that is primarily used for the treatment of edemas.

Authors:
Sarah Richtmann, Sven Storch, Carolin Wagner and Nathanael Weber
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**Origin**

Furosemide was first synthesized by Höchst in 1959. The patent followed in 1962 and in 1964 they started to sell it under the name “Lasix”. The substance is a less harmful high-ceiling than the, until than used, mercury compounds. High-ceiling diuretics are drugs, which support uroflow.

Furosemide does not occur naturally, but can be synthesized out of natural raw materials, which are not provided by animals.

**Structure**

The active pharmaceutical ingredient furosemide has a 4-fold substituted benzol structure. Based on the carboxygroup it is called a benzoic acid, which is additional substituted in 2-position with an ([2-Furanylmethyl]amino)-group. This is a group out of furan, which is substituted in 1-position with a methyl-group and this is bound with the benzoic acid over an amine. In 4-position the acid is substituted by chloride and by an aminosulfonyl-rest in 5-position. The aminosulfonyl-rest is a sulfon, that carries an aminogroup.

IUPAC: 5-(Aminosulfonyl)-4-chloro-2-([2-furanylmethyl]amino)benzoic acid

Empirical formular: \( C_{12}H_{11}ClN_{2}O_{5}S \)

CAS-Number: 54-31-9

The structure of furosemide gives a few qualities. The white crystalline powder has a molecular weight of 330.74 g/mol and a melting point at about 206°C. It is not soluble in water and \( CH_2Cl_2 \), hardly soluble in 96 per cent ethanol and soluble in acetone and aqueous solutions above pH 8. Itself it has a pKₐ of 3.9

**Synthesis**

There are 145 ways to synthesize furosemide.
Effect

Furosemide, or more precisely Sulfamylbenzen derivative of Anthranil acid, is a "high ceiling"-diuretic. This means that furosemide processes an almost linear concentration-operation-intercourse over a wide application rate.

Generally furosemide operates in an ascending shank in the Henle’s loop and therefore only shows a low activity in the proximale tubulus.

Therefore it operates as a reversible inhibitor on the sodium-potassium-2chloride-symporter, by attaching to the chloride ions and thus prohibiting a change of conformation which is essential for the carrier's function. This leads to a reduction of the resorption of ions in the primary urine. The salt concentration in urine rises and by osmosis more Water is stored in the primary urine, which leads to an elevated urine excretion. The effect of the carbon anhydrase does not play an important role for the impact of the loop diuretic. It is also important to mention that the impact of the furosemide, despite the high Bioavailability of about 60% at effect place is only short. It can be explained by a high connection of the plasmaprotein, this causes a low glomerulalry filtration that is also caused by the slight Biotransformation of the Molecule in the liver. It is possible that it comes to a rebound effect during the brief but strong impact period, in which the body tries to store water by regulation and afterwards the fading impact tries to stint the overly released water.

The Impact of furosemide can be split into three sections.

1. At the Henle's loop
2. On juxtaglomerular Apparatur
3. For the Aldosterone emission (RAAS)

1) As mentioned, furosemide operates in ascending shank of the loop. More precisely, it attacks the Na-K-2Cl- symporter in the luminal membrane of the tubulus’ lumen. In doing so the molecule reaches the lumen, through the active secretion in the descending thigh through a multispecifically anion transporter, which can be inhibited by Probenecid. Through this secretion furosemide has a high concentration. It is noteworthy that there is an almost selective renale effect even though the transporter is to be found in the entire body. A consequence of the inhibition of the symporter is a Natriurese, which increases from 3% to 25% and partly a Kaliurese (to 15-60%). Repeated treatment with high doses and more accordingly fluidity- and electrolyte supply with drip can lead the volume of urine to 35-45 liter within 24 hours.

2) The inhibition of the transporters which causes a high salt concentration in the tubulus at the end of the Henle's loop can lead to a widening and relaxed contraction of Vas afferens in nephritic corpuses (Glomerulus) and thus a decrease of filtration pressure, which under these circumstances almost equals the rate of the blood pressure. This means a protection before further electrolyte loss of the body. Furthermore furosemide interrupts the auto regulation of the glomerular blood circulation because the filtration pressure is dependent on the blood pressure. The second important effect at the juxtaglomerulare apparatus is the increase of the Renin emission in the cells. The elevation of the Renin emission causes an increase of the Aldosterone production and Angionstin achievement. A secondary effect is the impact on the circuit with Prostagline.

3) One distinguishes between the immediate effect and the effect after a long time, which however depends on the dose of the medication. The immediate effect indirectly results from the abolishment of tubuglomerulare feedback at the Makula densa a chemical receptor, which the NaCl-concentration monitors and regulates. The effect after time is the decrease in the operative circuit
volume which can lead to a counter regulation of the body by activating the Renin-Angiotensin-Aldosterone-system.

**Use and Importance**

Furosemide is available as tablets (20mg, 40mg and 80mg) and as injection in 2-, 4-, and 10-mL ampoules with a concentration of 10mg/mL (dissolved in water and sodium hydroxide).

The tablets are preferred in the case of chronic diseases, whereas injections are needed for emergencies, e.g. edema of the lungs. The intravenous treatment can influence the amount of excretion up to 50L per day, if enough water is applied.

A treatment with furosemide is generally used for water retentions (edemas) due to cardiac insufficiency, cirrhosis of the liver, renal impairment or burns. Furthermore, it is used to treat ascites, hypertension and hypercalcaemia. The loop diuretic increases the excretion of sodium, potassium, calcium and magnesium and the excretion of water to release the heart. Additionally, it causes a decrease of the arterial blood pressure.

The most common and most dangerous side effect is hypocalcaemia. It leads to indigestion and at worst to cardiac dysrhythmia. Therefore, furosemide is often given combined with a potassium compound. According to the huge excretion of water, the viscosity of the blood rises. This can cause thromboses or critical embolisms. In addition, the electrolyte metabolism can be disturbed by the high loss of water and salts. Even the hearing ability can be affected, due to the fact that the ear owns a similar transporter as the kidney. As there’s also an increase of the excretion of magnesium, a hypomagnesemia is possible. Symptoms are e.g. muscular cramps, biliousness or fatigue. Besides, the induction of a high loss of calcium does not allow a long-term therapy with loop diuretics as calcium is needed for the bone structure. If the treatment with furosemide provokes a deficit of sodium, the impact of the drug will be automatically limited.

**Drug interaction**

The previous themes have dealt with the origin, the effect and the use of the medicament furosemide. The following subject will amplify the effect and link it to another drug.

The exemplar examines the interplay between digoxin and furosemide. Digoxin is a steroid glycoside which can be extracted from the foxglove plant. The medicament is mostly used to treat acute and chronic heart failure by blocking the sodium-potassium-pump which pumps sodium out of the cell in exchange for potassium. This increases the force of heart contraction, but reduces the frequency of heartbeats. As a result the human body is better supplied with blood.

This positive effect can change if digoxin is combined with furosemide. A harmful side-effect of furosemide creates a heightened loss of water which could cause hypokalemia. This means that the potassium concentration in the blood is lower than normal. Furthermore this electrolyte imbalance will be increased by digoxin. It acts by inhibiting the transmembrane Na⁺/K⁺-ATPase. As a consequence of this, the following symptoms of electrolyte imbalance could evolve: dizziness, muscle cramps and weakness.
**Doping**

The pharmaceutical product furosemide is usually used in medicine to treat congestive heart failures. In contrast, many athletes abuse the drug to get an advantage in comparison to others.

As a substance that promotes the production of urine, furosemide is part of diuretics. They are included on the “World Anti-Doping Agency's Prohibited List” and for that reason they are forbidden in- and Out-of-Competition if the person has not got a medical certificate.

However diuretics are the fifth most used drugs. The effect is to increase the loss of water. This happens usually by the production of urine which can rise to a maximum of six liters per day. Therefore the drug is used to falsify the concentration of forbidden substances in urine.

Another application in sport is to lose weight in a short period of time, because many sports are divided into weight classes. This includes sports like judo, boxing and wrestling.

On the one hand furosemide is often used by human athletes. On the other hand it is used extensively to improve the activity of racehorses. In the 1970s veterinarians have proven the fact that up to 80% of horses during a tournament had blood in their pharynx, trachea or mainstem bronchi. From that day on not only humans benefit from furosemide. Although the animals have not got an advantage from losing weight, the drug helps to control the bleeding into the lungs or out the nose during a competition. This blood loss is called “exercise-induced pulmonary hemorrhage (EIPH)”.

To conclude the drug furosemide is often misused in sports like judo or horse races, to receive an advantage in relation to others. In contrast it plays an important role by acting against various medical problems, including heart or liver diseases.

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