Tolbutamide

APPLICATION

Tolbutamide is used as a medication against type 2 diabetes, if diet alone is not effective. It’s a first-generation sulfonylurea and its main application is to block potassium channels within cells to stimulate insulin production by the pancreas. The medication’s name is Orinase. [1][3]

STRUCTURE

IUPAC Name: \(N\)-[(Butylamino)carbonyl]-4-methylbenzenesulfonamide [1]

Formula: \(C_{12}H_{18}N_2O_3S\)

Relative molecular mass: 270,34

SULFONYLUREAS

General structure of a sulfonylurea:

Carbutamide:

Carbutamide is a first-generation sulfonylurea, which tolbutamide originated from. It has a strong bacteriostatic effect, caused by the amine group. The functional group was then substituted with a methyl group and tolbutamide was synthesized. [5]
**Glibenclamid:**

Glibenclamid is a second-generation sulfonylurea. Their main use is that they have less drug interaction with other blood level controlling substances, which ultimately leads to less hypoglycaemia as a side effect. [6]

**BIOLOGICAL PROPERTIES**

Tolbutamide is a solid crystallin white substance. Due to the SO₂-group it’s a weak acid. It’s not soluble in water (10ppm). The Substance has a melting point of 128,5°C. There are no hazard or precautionary statements however, it is possible to consume a lethal dose of tolbutamide. The poisonous amount for a rat was found to be at 2490mg/kg. [4]

**SYNTHESIS**

4-Methylbenzenesulfonamide + OCN–n-Bu → Tolbutamide

**HISTORY**

When the only treatment for diabetes was to inject insulin, there has been an urgent need for proper medication. This ultimately lead to Upjohn Company developing Orinase, with its active substance being Tolbutamid. By this it not only expanded the total market but it also changed the mindset about how diabetes was conceived by the public. It went from a non-curable degeneration to a model of “surveillance and early detection”.

In European universities the sulfonylureas were first researched for their antibiotic effect. The scientists observed serious side effects, such as blackouts and comas. The insulin researcher at the same university heard of these side effects and recognized them as common results of hypoglycaemia. The resulting class of drugs for lowering blood sugar came to be known as the sulfonylureas. During World War II the owner of these drugs changed from France to Germany and ultimately the research was continued by Western Germany pharmaceutical companies in 1952.
In 1956, the two earliest forms of sulfonylureas were brought on the market, namely Nadisan and Rastinon. American pharmaceutical companies in the post-war period seeking to establish business with the German companies, that were weakened by the war. They made a deal which ultimately lead to the production of Orinase in the USA. [1]

**Usage**

The usual recommendation given by a doctor to patients is that tolbutamide is taken by mouth once daily in the morning. It sometimes can be divided into smaller portions specially if the patient experiences stomach upset when taking the medication. The dosage is closely tied to medical condition and response to treatment of the patient.

It is a common method to start off with a low dosage and start increasing it over time to see if the patient affected by any symptoms. Also, be aware that especially first-generation drugs have interactions with other drugs. [3]

**Effect**

Tolbutamide binds to the SUR1 – receptor, which is a sub potassium-channel. This ultimately leads to a depolarization of the membrane. Now Ca²⁺-ions flow into the β-cell. These ions initiate the merger of vesicles with the membrane. Inside those vesicles sits the insulin waiting to be released from the cell. After the merger it is released into the patient’s metabolism, which leads to lowered blood sugar levels. [1][3]

The control of high blood sugar levels helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper medication against diabetes also may lessen the risk of a heart attack or stroke. [3]

**Side Effects**

1. Hypoglycaemia (various symptoms caused by low blood sugar levels, e.g. loss of consciousness)
2. Weight gain
3. Rare cases of liver damage
4. Drug interactions (especially first-generation drugs): Increased hypoglycaemia with cimetidine, insulin, salicylates, and sulphonamides [3]
SOURCES

[1] https://de.wikipedia.org/wiki/Tolbutamid (15.06.18)
[2] https://commons.wikimedia.org/wiki/File:Tolbutamide_synthesis.png (15.06.18)
[3] https://www.webmd.com/drugs/2/drug-3948/tolbutamide-oral/details (15.06.18)
[4] https://roempp.thieme.de/roempp4.0/do/data/RD-20-02031 (15.06.18)