Malaria

Malaria is one of most present tropical diseases, which is widespread in equatorial regions. The cause is a protozoic parasite which is transferred by the females of the anopheles mosquito. There are five different forms of malaria, not all of them are deadly but serious. The most dangerous form is malaria tropica which is treat with Proguanil. The symptoms are highly periodically fever and chills as well as seizures. Malaria led to 300 - 500 Mio. infections and causes up to 1.8 million deaths each year.

Proguanil

Proguanil is an agent against the malaria plasmodium and therefore used as an antimalarial drug for therapy and preventive. It was developed by Imperial chemical Industries in the 1940th. Proguanil is effective against two of five forms of malaria and in addition to it the treatment failure of pure Proguanil lies between 30 and 90 %. Due to this fact Proguanil is often used in combination with other antimalarial agents such as Chloroquin and Atovaquon. The activity increases and the frequency of failure are lower than 2%.

Structure

Proguanil belongs to the group of drugs called biguanides(red marked). The IUPAC name is 1(4-chlorophenyl)-2-(N- propan-2-ylcarbamimidoyl) guanidine.\(^1\)

Synthesis

The process for the preparation of Proguanil hydrochloride is based on the reaction of p-chlorophenylcyanoguanidine and isopropylamine in presence of copper sulfate pentahydrat. The reaction is carried out at a temperature between 50-65°C for 2-10h in solvent THF and water. During the reaction a copper complex of Proguanil gets developed. Absence of p-chlorophenylcyanoguanidin is confirmed by checking the reaction mixture by thin layer chromatography. After completion of the reaction the organic solvent is distilled at 70-75°C.
Hydrochloric acid is added to the reaction mass. The Proguanil copper complex gets broken by adding chelating agent such as sodium sulphide or ethylene diamine tetracetic acid disodium salt in presence of ammonia. The last step is to isolate the proguanil hydrochloride by filtration.

To get a better purity, Proguanil hydrochloride has to be purified by dissolving in water at 85-95°C, adding activated charcoal and stirring for 15 min. The hot mass has to be filtered. After that the filtrate gets stirred at temperature 10-15°C to crystallize the product. The product is dissolved in methanol, gets filtered and ethyl acetate was added. Stirred again and cooled down to 10-15°C. The crystallized product gets filtered, washed with cold ethyl acetate and dried.

Advantages of this process are it is ecofriendly, economically and industrially viable because of the high purity (more than 99%) and yield (75-90%) of the product.

Mechanism

In the First step p-Chloroaniline reacts with the calcium salt of dicyanamide. p-Chloroaniline is prepared by nitration of chlorobenzene and the following reduction of the nitro group.

Dicyanamide is prepared from calcium carbide in the following reaction:

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The reaction of p-Chloroaniline and the calcium salt of dicyanamide proceeds according to the following mechanism:

The intermediate p-Chlorophenylcyano-guanidine is built which reacts in a second step with isopropylamine.\[^{[5]}\]

Effects

Proguanil is absorbed in the alimentary tract and transported by blood into the liver. There it gets metabolised into Cycloguanil which is the actual active substance against the plasmodia (Pro-Drug System). 20-30% of the Proguanil gets metabolised into Cycloguanil.\[^{[6]}\]

Cycloguanil avoids the growth of the plasmodia (bacteria that causes malaria) by blocking the active centre of the dihydrofolate reductase. That means the plasmodia can not produce the for the DNA essential nucleic acids Thymine and Purine.
After ingesting the drug the effect assists between 2-18 hours dependend on bodytype and gender but 20% of the african and asian as well as 3% of the Caucasian population, can not convert Proguanil into Cycloguanil due to a missing enzyme. Proguanil even can be used by pregnant women without harming the fetus.

**Side effects**

There are less known side effects. Some of them are hairloss, rash and in some cases hemic diseases (extremely less).

**Sources**