Mepacrine

Mepacrine is a medicament, which was used in the past as an antimalarial. Mepacrine is nowadays rarely used due to many side effects.

Properties

**Appearance**: bright yellow powder

**Molecular weight**: 399.95 g/mol

**Water solubility**: 2.8 g/ 100 ml

**Melting point**: 248-250°C

**LD₅₀ (Maus, i.v.)**: 50
Origin

Already in 1912, the antiprotozoal usage of acridine derivatives has been discovered by Paul Ehrlich. Based on these results, Walther Kikuth tested 12000 substances for malaria effectiveness in 1930. Mepacrine turned out to be a highly promising substance.

The term “mepcarine” derives from the terms “methyl”, “paldism”, and “acridine”, formerly better known as “Atebrine” or “Quinacrine”. The first synthesis, conducted by Bayer, opened new military capabilities. It was now possible to synthesize a malaria effective medicine while being independent from import products.

Mepacrine was first used in large quantities at the World War II on the Allied side. Therefore the main synthesis took place in the USA.

Synthesis

1. Because of the two chlorine atoms the benzene ring becomes electron-poor and the amine group is able to do a nucleophilic attack on the ring.

2. The POCl₃ chlorinates the carboxyl group; as a result the carboxyl group is able to attack the other benzene ring.

3. The POCl₃ chlorinates the carbonyl group.

4. The amine group does a nucleophilic attack at the chlorine atom and the result is then Mepacrine.

Image 3: Synthesis of Mepacrine.
Fluorescence

In general, fluorescent is the emission of light after an excitation of a substance. Therefore an electron gets excited to a higher energy level, and when returning to the initial state, it emits light whose energy is the difference of the two energy levels of the electron.

Mepacrine is a fluorescent substance which also has the property to bind to the DNA. This is exploited in the fluorescence microscopy. To see a substance in the fluorescence microscopy it needs to be either fluorescent or it can be colorized with a fluorescent dye. Since DNS itself does not fluoresce you can color it with Mepacrine to make cells or similar selectively visible.  

Effect of Mepacrine

General

Mepacrine acts antiparastic and get used for the treatment of Giardiasis and tapeworms,

Giardiasis is an infectious disease of the small intestine.

The real mechanism of action is unclear, but it is assumed, that the pathogen gets destroyed by the intercalation between Mepacrine and the DNA of the pathogen.

Giardiasis:

The giardiasis is the only disease, which is further treated with Mepacrine. It is an infectious disease of the small intestine and is caused by the so-called Giardia.

This giardia or also known as small intestinal parasites may get into the human body through contaminated water or fecal contaminated food.

They cause stomach pain, diarrhea & vomiting and headache.

A giardiasis often heal after a few days by itself, if a chronic infection should be present, antibiotics or a high doses of Mepacrine will be used.

In addition to that, you have to drink a lot of water, because of the extreme fluid loss.
Biological effects:

The biological effect of Mepacrine is unknown, but it is assumed that Mepacrine intercalates with the DNA of the pathogen and gets destroyed.

This happens where Mepacrine is either in or between the DNA and effects an inhibition of the DNA & RNA polymerases.

As a consequence of that, there will be no further replication of DNA and no more transcription of DNA, in consequence of that the pathogen get destroyed.

A second method is that the Mepacrine causes by insertion into the DNA a point mutation and thereby defective proteins will be created, which have a mutagenic effect on the pathogen. 10-14

Side effects

Unwanted effects usually do not occur after ingestion.

Central nervous system:
Fatigue, headache, nausea, vomiting, dizziness, profuse sweating, fever, insomnia, possibly psychosis (particularly among Asians, very young and very old people).

Kidney:
Urine gets a deep yellow color.

Skin:
Itching, stainwise discoloration of the oral mucosa, eczema, skin lesions particularly on hands and feet, yellow skin.

Musculoskeletal:
At high doses occurs joint or muscle pain. 4

Even after long exposure liver, kidney and brain are not affected (blood-brain barrier will not be overcome). 4

Toxicity:
Mepacrine can encourage other diseases even in preventive taking.

Toxic to children under one year old and children in the womb.

No taking along with alcohol consumption, as Mepacrine preferably accumulates in the liver and occupies the degrading enzymes for alcohol.

Suicide attempts with up to 6 g mepacrine increased adverse effects, but leaves no permanent damage.
Elimination

Elimination half-life in malaria patients: 14 days.

Biological elimination half-life: 5 days.

Elimination:

Mainly through deep yellow urine, partially sweat. Excretion takes place with great individual differences.⁴

Further applications

Treatment of tapeworms:
Mepacrine has been used successfully in treatment against numerous tapeworm species. In this case mepacrine affects the brain of the tapeworm, therefore they separate themselves from the intestinal walls and are excreted the normal way.
Mepacrine is effective against fish tapeworms, cat and dog tapeworms, rat tapeworms, dwarf tapeworms and beef and pork tapeworms.⁶
Sterilization of women:
The method is discussed controversially, despite some clinical studies in the United States. The initial failure rate was below 3.1%.
The sterilization is carried out by two-time insertion of Mepacrine pellets through the cervix into the uterus. First insertion takes place 6-12 days after the start of the menstrual cycle, the second follows a month later.7

By the sclerotic effect (reduction of blood vessels) in about 6 weeks scar tissue is formed, which closes the connection between the uterus and the ovaries.
Recent studies suggest that sterilization by Mepacrine is far safer than surgical sterilisation. Solely India prohibited the import of Mepacrine since 1998, due to suspicions of carcinogenicity and increased likelihood of ectopic pregnancy.7

Sources

Links:

Images:
[1] https://de.wikipedia.org/wiki/Mepacrin, 21.06.15