Metamizole

Introduction

Metamizole stands for almost 100 years of vibrant pharmaceutical history. This very often prescribed drug, whose mechanisms of action is not yet resolved, got in the cross fire of criticism in the 1970s.

Molecule structure

Chemical formula: \(C_{13}H_{16}N_{3}NaO_{4}S\)
Molecular mass: 311,36 g/mol
Melting point: 131°C
Appearance: Solid yellow crystals
Solubility: good in water, bad in organic solvents

General information

Metamizole sodium (IUPAC-name: Sodium [(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)methylamino]-methanesulfonate) is a pyrazolone derivate. It is a non-steroidal anti-inflammatory drug used as a strong painkiller and fever reducer. It is sold as pills or as liquid in combination with saccharin-sodium, citric-acid and cyclamat-sodium.

Pharmaceutical history and controversy

Metamizol was first synthesized by Hoechst in 1920, its mass production started two years later. The drug remained freely available worldwide until the 1970s, when it was discovered that it carries a small risk of causing agranulocytosis. Agranulocytosis is an acute condition involving a severe and dangerous reduction in the number of white blood cells. The mortality rate ranges from 9 to 23%. Controversy remains regarding the level of risk.

Metamizole in Sweden

A good example for the varying risk assessment is the history of metamizole in Sweden. Medical authorities banned the drug in 1974. Due to the results of the "Internationale Agranulozylose- und Aplastische Anämie Studie" (IAAAS), conducted between 1981 and 1984, metamizole was reintroduced in 1995. The study estimated an incidence of 1.1 agranulocytosis disorders per million exposed people per week of treatment. This risk is considerably lower than it was assumed before. Swedish researchers came to a different result: They registered eight cases of agranulocytosis after metamizole application in 10,892 prescriptions between 1995 and 1999, which equals a clearly higher risk than the IAAAS estimated. As a result, the Swedish health authority banned the analgesic in 1999 for the second time approval.
Situation in Germany

In Germany, metamizole has become a prescription drug against strong pain caused by tumours and colics. Since 1997, the number of prescriptions has been increasing constantly. In 2001, the drug was prescribed 5.6 million times.

Business in the Third World

Metamizole received a brief period of attention by American media in 2001, when a latino immigrant boy was admitted to a clinic in Salt Lake City, with symptoms of agranulocytosis. It was discovered that the drug, which had been banned since 1977, remained freely available on the black market and is highly popular among Mexican immigrants. The ongoing “LATIN”-study, a multicenter international case-control study, is examining the incidence of agranulocytosis in Latin America and the role of metamizole. “Ping Ping against the pain - no Ping Ping in the money bag”, claims Boehringer Ingelheim in Brazil.

In South American countries, taking painkillers containing metamizole is widespread. Boehringer Ingelheim markets a drug containing metamizole under the brand name Anador ® in Brazil.

Medical effect

As a non-opioid, metamizol does not effect the nervous system like morphine does. The drug achieves its analgesic effect by blocking pain-causing biological reactions. Prostaglandins, which are being built after a tissue damage to advance the ignition, evolve from cyclooxygenase and an peroxidase reaction. So by blocking cyclooxygenase (COX), the prostaglandins are no longer being built. Because metamizole is a non-acid-analgetica, it dispenses consistently in the body, which allocates it as an ignition-impartial-painkiller.

There are lots of prostaglandins in the body. Their effect depends on the place where they operate. They also have an effect on the blood circulation of the kidney and the elimination of sodium. The effects of the prostaglandins depend on the type of cyclooxygenase. The two most important kinds of COX are:

COX 1: synthesizes prostaglandins which are important for the blood clotting and the protection of the mucosa.

COX 2: plays a role in the synthesis of the prostaglandins that advances the ignition.

One particular prostaglandin-synthesis being blocked is the prostaglandin-E2-synthesis in the pythalamus. This results in an increased heat dissipation through an expansion of vessels and an arise of sweat production causing the body to cool down.
Synthesis

Metamizole is synthesized by the reaction of phenylhydrazone and ethyl acetoacetate. The resulting intermediate is alkylated with methylchloride and an Lewis-acid by a Friedel-Crafts-reaction. This product is an important substance that is called phenazone. Phenazone is also used as an analgesic and belongs to the group of pyrazolone. To get metamizol, phenazone is nitrosated, reduced and condensed with benzaldehyde. The next layer is the alkylation. From this intermediate, metamizol-sodium can be prepared by a Mannich-reaction with formaldehyde and sodiumhydrosulfide.

Reference

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DaMocles WS 07/08 TU Darmstadt Prof. Wolf-Dieter Fessner
A report about metamizole by René Eckert, Michael Friedrich, Felix Roth and Jörg Steffan
**NMR-spectroscopic data**

An assay of NovalginLichtenstein was analyzed by a Bruker DRX 500 NRM spectrometer. (500 Mhz)

**1H-NMR**

Estimated $\delta$ [ppm]

![Chemical structure diagram](image)

Measured $\delta$ [ppm]

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13C-NMR

Estimated δ [ppm]

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