

Methadone hydrochloride

CAS: 1095-90-5

MF: C₂₁H₂₇NO·HCl

FW: 345.91

Solubility: well soluble in water, isopropanol, and chloroform, and practically insoluble in ether or glycerin.

Major uses

Methadone hydrochloride (further only methadone) is a morphine like, sedative analgesic drug. Besides use against a severe pain, methadone is applied for treatment of narcotic withdrawal and dependence, and for detoxifying of opiate addicts. About 60 years it was used to treat addiction to drugs, such as heroin, morphine and some other drugs of abuse. Taken orally once a day, methadone suppresses narcotic need for 24 to 36 h. At the same time, methadone is a drug of abuse for its sedative and analgesic effects. There is a risk of physical dependence and tolerance after repeated use of methadone [1].

Methadone is also used for veterinary medication as an animal tranquilizer [2].

Human toxicity

At acute overdose, circulatory and central nervous system (CNS) depression, miosis, which is constriction of the eye's pupil, respiratory depression, lethargy, and coma may occur. Apnea (brief pauses in breathing), hypotension, bradycardia (a slower heart rate), pulmonary edema, seizures, hyperthermia, circulatory collapse, cardiac arrest and death may take place at the severe poisoning [1].

Therapeutic doses (oral, intramuscular or subcutaneous) in adults, at moderate to severe pain, are in the range of 2.5 to 10 mg/day. At detoxification treatment doses increase up to 15-40 mg/day.

The minimum lethal dose is approximately 100 mg/70 kg person [3].

Therapeutic blood concentrations of methadone at the treatment of opiate withdrawal are in the range of 0.1 to 0.4 mg/l [1].

The approximate lethal blood level of methadone is 0.5 mg/l [3]. Postmortem methadone blood concentrations ranged from 0.4 to 1.8 mg/l in 10 fatal cases [4].

Kinetic data

Absorption: Methadone is well absorbed by all routes. It is 50% as effective orally as parenterally. Its duration of action is up to 24-36 h after administration [5].

Oral bioavailability: from 41 to 99%.

Volume of distribution (Vd): 3.6 l/kg. Due to its highly lipophilic nature, methadone is rapidly distributed into all tissues in the body.

Plasma protein binding: 71 to 87%.

Peak plasma level is reached within 2 to 4 h. Methadone can be detected in plasma already after 30 min. The plasma levels of methadone correlate poorly with its pharmacological activity [5].

Peak serum concentration following a single oral dose of 15 mg was 0.075 mg/l; 0.86 mg/l for 100 mg, and 0.83 mg/l for 120 mg, all at 4 h [1].

Plasma half-life of methadone averages 25 h.

The elimination is via kidney. The elimination is biphasic: initial elimination half-life is 12 to 24 h, followed by slower elimination half-life of 55 h [6].

Passage of blood-brain barrier: limited. Methadone penetrates through the placenta [6].

Metabolism and excretion

Methadone is a synthetic narcotic drug metabolized in liver by mono- and di-N-demethylation. Main metabolites are: 2-ethylidene-1,5-dimethyl-3,3-diphenyl pyrrolidine (EDDP, 3 to 25 %), 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP), p-hydroxylated derivatives, glucuronide conjugated derivatives, methadol and normethadol. Most of these compounds are inactive metabolically [1, 7].

In the liver, methadone undergoes biotransformation by the cytochrome P450. Both cytochrome P450 isoenzymes, CYP 3A4 and CYP 2D6, are involved in this process [8].

Excretion: from 5 to 50% of ingested dose is excreted in urine as unchanged methadone over 24 h in maintenance subjects. Methadone is also excreted in feces, bile and sweat [7].

Pharmacokinetic and toxicologic mechanisms

In similarity with other opiates (e.g. morphine, codein, heroin and oxycodone) methadone depresses nerve transmission in sensory pathways of the spinal cord and brain that signal pain. Opiates bind to mu (μ) receptors, and inhibit brain centers controlling coughing, breathing, and intestinal motility. When methadone is used instead of heroin, it occupies the same receptor and is a stabilizing factor that permits addicts on heroin to change their behavior and to discontinue heroin use (addiction to heroin is often replaced by addiction to methadone, which is much less severe).

Methadone is an opioid *antagonist* of glutamate receptor N-methyl-D-aspartate (NMDA), which inhibits serotonin/norepinephrine reuptake. Blockade of NMDA receptor can decrease excitability and reduce seizure activity. NMDA receptor also has been implicated in heroin, cocaine, alcohol, and nicotine addiction [9].

The precise toxicological mechanism of methadone poisoning is still unknown. Methadone affects equilibrium of the neurotransmitters in the brain. In similarity with amphetamine and morphine, it stimulates the release of biogenic amines, such as norepinephrine and dopamine, from stores in adrenergic nerve terminals, which leads at the overdose to CNS depression and respiratory failure.

Recent studies in animal models suggested that methadone may be a substrate of P-glycoprotein. The latter limits the entry of methadone to their CNS acting sites [6].

In cultured human hepatocytes, methadone inhibits synthesis of albumin and reduces the level of intracellular glutathione [10].

Target organs: CNS, lung.

References

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