Chlormethiazole

Chemical name: 5-(2-chloroethyl)-4-methylthiazole
Synonym: Hemineurin
CAS: 533-45-9
MF: C_4H_8NSCl
MW: 161.7
Solubility: it has solubility in water of 1%; miscible with most organic solvents [1].

Major use
Chlormethiazole is used as a sedative/hypnotic drug, and as an anticonvulsant (for the treatment of epilepsy). It is also used in the treatment of alcoholism (to suppress symptoms of alcohol withdrawal) and drug addiction [2].

Chlormethiazole is widely abused especially by alcoholics and dependence may occur; it should only be used for inpatient care.

Human toxicity
Chlormethiazole may be toxic and even fatal at an overdose. A combination of the high doses of chlormethiazole with alcohol can be fatal.

Acute lethal toxicity is mainly due to CNS depression, sometimes including signs of cardiac failure, i.e. pulmonary edema [3].

Main symptoms of poisoning are a deep coma, with absent muscle tone or deep tendon reflexes, respiratory depression, hypotension, tachycardia, hypothermia, and an increase in salivation.

The therapeutic hypnotic doses of chlormethiazole are in the range of 192-384 mg. Some alcoholists may take more than 25 g daily [2]. Blood plasma levels from peroral sedative therapy are between 0.4 and 1.3 mg/l [3].

Blood plasma levels from nine adult patients in coma who ingested the overdose of chlormethiazole ranged from 8 to 66 mg/l. In another series, patients admitted in coma had plasma levels of 7 to 36 mg/l. All these patients survived. Deaths were associated with plasma levels up to 60 mg/l without incidence of ethanol, and up to 18 mg/l with ethanol level present. Blood levels roughly correlate with dose ingested and clinical course, but are useful for confirmation of diagnosis (reviewed in [2].

Kinetic data
Absorption: rapidly absorbed from the gastrointestinal tract [2].

Bioavailability: is low and variable (5-60%) and may increase at higher doses. The elderly patients have higher blood concentrations than healthy adults, indicating an increased bioavailability (about 10 times) in elderly patients [1].

Toxicokinetics is linear [3].

Volume of distribution: 5 l/kg [2].

Distribution:even distribution in all organs [3].

Accumulation in the brain in fatal cases [3].

Plasma half-life: 4-15 h at overdose [3].

Time to peak blood concentration: 1-2 h.

Plasma protein binding: about 65% [1].

Passage of blood-brain barrier: free [3].

Elimination half-life: 3 to 6 h [2].

Metabolism and excretion

Chlormethiazole is a thiazole derivative, related to the thiazole part of the vitamin B1 (thiamine) molecule. It is extensively and almost completely metabolized by the first-pass effect in the liver.

Two main metabolites are 5-acetyl-4-methylthiazole and 5-(1-hydroxyethyl)-4-methylthiazole, with half-lives about 5.5 and 18 h, respectively. The pharmacologic activity of the metabolites is not known (reviewed in [2]).

Excretion: less than 5% of chlormethiazole is excreted unchanged in the urine; the metabolites (see above) are excreted in the urine and feces [1].

Mechanisms of action

The action of chlormethiazole likes a barbiturate, which are a sedative, hypnotic, muscle relaxant and anticonvulsant. Chlormethiazole acts on receptors in the brain known as GABA (Gamma-AminoButyric Acid) which is a major inhibitory neurotransmitter in the human body. Chlormethiazole increases the activity of GABA, thereby reducing the functioning of certain areas of the brain. This results in sleepiness, a decrease in anxiety and relaxation of muscles.

The animal experiments suggest that chlormethiazole does not interact with GABA or benzodiazepine binding sites and does not change the brain levels of GABA or glutamate [1].

Chlormethiazole also inhibits an enzyme called alcohol dehydrogenase that is responsible for breaking down alcohol in the body, which helps to relieve the sudden effects of alcohol withdrawal in alcoholics.

Toxicological mechanisms

Unknown.

In vitro studies suggest that chlormethiazole acts on some types of Ca^{2+}- dependent chloride ion channels [1].

CNS depression may be through inhibition of GABA synapses?

Target organs: CNS, heart.

References

1. Drug Database, via Internet
https://www.eknowhow.com/ekh_drugdatabase/html/default.asp
2. Ellenhorn, M., Schonwald, S., Ordog, G., Wasserberger, J. (1997) *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed., pp. 695-697. Williams & Wilkins.

3. Ekwall, B., Ekwall, Ba., Clemedson, C. (2001) *Chlormethiazole. The MEIC Monograph.* http://www.cctoxconsulting.a.se

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