

Glutethimide

CAS: 77-21-4

MW: 217.3

MF: C₁₃H₁₅NO₂

LogP: 1.9

Solubility: Highly soluble in oil.

Major use

Glutethimide is a piperidinedione derivative (synthesized in 1952), related to phenobarbital (see Sodium phenobarbital in AcuBase). It is widely used as a hypnotic and sedative; it was primarily used as a night-time hypnotic [1, 2].

Human toxicity

Blurred vision, papilledema, nystagmus, unilateral fixed dilated pupil, and dilated, sluggishly reactive pupils have been reported after glutethimide overdose. Also ataxia, lethargy, cerebral edema, sudden apnea, tonic muscle spasms, hyperreflexia, intracranial hemorrhage, and absence of deep tendon reflexes, corneal reflexes, pupillary response, and gag reflex have been noted. Glutethimide intoxication may result in coma of varying depths and duration, pulmonary edema, respiratory depression, ataxia, and hypotension. Variations in coma do not correlate with plasma glutethimide concentrations [2].

Normal adult therapeutic dose is 250 to 500 mg orally at bedtime [2].

The lethal dose has been reported as 10 to 20 g. However, death has been reported with 5 g and a patient that ingested 28 g have survived. RTECS (2000) reports a LDLo (lowest published lethal dose) in a human adult of 147 mg/kg. However, as in most ingestion cases, the estimates of minimum lethal dose are unreliable [1].

Mild intoxication has been associated with glutethimide concentrations of between 0.5 and 5.6 mg%. Severe intoxications are reported between 18 mg/l and 120 mg/l, and reported fatal serum levels of glutethimide range between 2 and 88 mg/l. These correlations appear only to be valid before the glutethimide is metabolized to the inactive metabolite 4-hydroxyglutethimide [2].

Kinetic data

Absorption: Glutethimide is erratically adsorbed due to poor water solubility and intact tablets may be found for days following severe ingestion. Onset of action may occur in 30 minutes and the duration of action has been reported as 4 to 8 hours [2].

Volume of distribution: 1.7 l/kg [3].

Distribution: Glutethimide quickly concentrates in organs containing fat, such as brain and adipose tissue [2]. In addition, glutethimide (and/or its metabolites) has been detected in liver, kidneys, and bile [1].

The plasma half-life: The decline of serum concentrations of glutethimide is biphasic; the half-life for the first phase is about 4 h and the half-life for the second phase is 10-12 hours [1]. In the terminal phase, a half-life up to 22 hours has been reported [2]. In acute intoxication, the half-life may be increased [2].

Time to peak: Poor water solubility limits and delays gastrointestinal absorption, with peak levels of about 3 to 7 mg/l appearing in 1 to 6 h after a 500 mg ingestion [1].

Protein binding: 35% to 59% [1, 2].

Metabolism and excretion

Glutethimide is almost completely metabolized in the liver [1, 2]. It is hydroxylated to water-soluble derivatives [2]. Approximately 14 usual and unusual metabolites of Glutethimide have been identified, either in urine or synthesized in the laboratory. Two metabolites are known to accumulate in plasma and urine of intoxicated patients: 4-hydroxy-2-ethyl-2-phenyl-glutarimide and alpha-phenyl-gamma-butyrolactone. Glutethimide has an asymmetric carbon atom and gives two optical isomers, which are metabolized in a different fashion. The D-isomer is hydrolyzed at the glutarimide ring, loses water, and breaks down into alpha-phenyl-alpha-ethylglutaconimide, which is excreted in the urine as a nonconjugated metabolite in approximately 2% of the administered dose. A major portion of the hydrolyzed D-isomer is combined with glucuronic acid and is excreted in the urine in approximately 45% of the administered dose. The L-isomer is hydrolyzed with release of acetaldehyde from a-phenyl glutarimide. This metabolite is isolated in the urine in approximately 4 percent of the administered dose. The remaining major portion is also combined with glucuronic acid and is excreted in the urine in approximately 45 % of the administered dose. Both glucuronides are water soluble but not fat soluble and do no longer possess sedative activity.

Metabolites more toxic than glutethimide: 4-hydroxy-2-ethyl-2-phenylglutarimide [1] (see also Toxicological mechanisms).

Excretion: Less than 2% of a dose is excreted unchanged in the urine and up to 2% of a dose is excreted in the feces [1, 2]. The glucuronides are excreted by the kidney, but 70% enters the enterohepatic circulation and will then be reabsorbed from the gastrointestinal tract before final excretion by the kidneys. Approximately 30% of glucuronides are excreted directly into the urine.

Pharmacological mechanisms

Glutethimide has CNS depressant effects similar to those of the barbiturates. The mechanism of action of the drug is not known. In doses used for hypnosis, glutethimide produces cerebral depression and quiet, deep sleep. Like barbiturates, usual hypnotic doses of glutethimide significantly suppress rapid eye movement (REM) or dreaming stage of sleep. In addition to its CNS effects, glutethimide exhibits anticholinergic activity manifested by mydriasis and inhibition of salivary secretions and intestinal motility [1].

Toxicological mechanisms

Accumulation of a toxic, active metabolite 4-hydroxy-2-ethyl-2-phenylglutarimide may be the cause of the prolonged coma noted in these patients. However, there is some controversy concerning this, some authors suggest that the role of this metabolite has been overemphasized [2]. Cyclical coma, also a feature of glutethimide poisoning, seems to occur as a result of continued absorption from the gut. The anticholinergic and/or CNS depressant effects of this drug decrease bowel motility

until it has been metabolized at which time bowel motility returns, more drug is absorbed and coma once again ensues, completing the cyclical pattern [2]. Glutethimide induces liver microsomal enzymes and thus may alter the metabolism of other drugs [1].

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2005).
3. Ellenhorn, M.J. & Barceloux, D.G. (1988) *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. New York: Elsevier.

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