

Diazepam (valium)

CAS: 439-14-5

MF: C₁₆H₁₃ClN₂O

MW: 284.8

Diazepam has low solubility in water (0.05 mg/ml), but it is soluble in alcohol (1:25).

Major use

Diazepam is an antianxiety drug belonging to benzodiazepine family. It is widely used as a sedative, anticonvulsant (to help control epilepsy), anesthetics and muscle relaxant. It may also be used to treat symptoms of acute alcohol withdrawals [1].

Human toxicity

Diazepam is of low order toxicity unless ingested with other central nervous system (CNS) or respiratory depressants. At the toxic doses, diazepam exhibits neurotoxicity, such as CNS depression, lethargy, slurred speech, tachycardia, cardiac arrest, coma, and even death. However, the cases of a fatal poisoning after ingestion of diazepam are relatively rare [1].

The usual therapeutic dose is between 0.25 and 0.5 mg/kg [2]. The minimum lethal dose is 2 g/70 kg person [3].

Therapeutic diazepam blood concentration levels are 1-2 mg/l. The mean lethal plasma level is 20 mg/l [3]. The minimum lethal blood concentration, based on the data from several handbooks, is 31 mg/l [4].

Kinetic data

Absorption: diazepam is absorbed rapidly and almost completely after oral administration [4, 5, 6].

Kinetics is biphasic [4].

Volume of distribution is 1.1 l/kg [4].

Distribution: diazepam is a highly lipophilic compound which is rapidly distributed to highly perfused organs, such as brain, liver and spleen.

The mean plasma half-life is 30 h, with a range of 20-100 h. It has two distinct phases: an initial rapid distribution phase, lasting 7 to 10 hr, and a subsequent prolonged elimination phase that may last as long as 2 to 6 days.

Peak plasma concentration is reached at 15-90 min in adults. Peak blood levels after intravenous administration of diazepam are reached within 15 min as compared to 1 h after a single oral dosing [5, 6].

Plasma protein binding is 99%.

Passage of blood-brain barrier: free [4].

Elimination half-life: 96 h or longer, for the overdose situation [4].

Metabolism and excretion

Diazepam is metabolized in the liver to two psychopharmacologically active metabolites: nordiazepam (N-desmethyldiazepam) and temazepam (N-methyloxazepam). Both these metabolites are then converted to oxazepam (also psychopharmacologically active) which undergoes glucuronide conjugation prior to excretion. Nordiazepam has an even longer half-life than the parent compound [7].

Excretion occurs via renal clearance [5, 6]. Only traces of diazepam and nordiazepam are found in urine; about 33% of the dose is excreted as oxazepam glucuronide and another 20% as conjugates of nordiazepam (reviewed in [7]).

Toxicological mechanisms

The mechanism of toxicity is not enough understood. It is probably associated with down-regulation of GABA receptors, e.g. γ -aminobutyric acid receptors, which are the major inhibitory neurotransmitters in the CNS [8]. The combination with alcohol produces additive effects on the CNS, however, the mechanism is not completely understood.

Target organ: CNS.

References

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