Diphenhydramine

CAS: 58-73-1
MW: 255.35
MF: $C_{17}H_{21}NO$
logP: 3.27
Solubility: in water 1 in 1 and in ethanol 1 in 2.

Major use
Diphenhydramine is a histamine H-1 antagonist of the ethanolamine class with anti-emetic, anti-cholinergic, antimotion-sickness, CNS antitussive, CNS excitation and depression, and local anesthetic properties [1, 2].

Human toxicity
Somnolence, anticholinergic effects (mydriasis, flushing, fever, dry mouth, decreased bowel sounds), tachycardia, nausea and vomiting are common after overdose. Agitation, confusion and hallucinations may develop with moderate poisoning. Severe effects may include delirium, psychosis, seizures, coma, and ventricular dysrhythmias, including torsades de pointes (cardiac arrhythmia, which may cause blackouts or even sudden death), but are generally only reported in adults after ingestions of 1 g or more of diphenhydramine. Liver and kidney injuries are rare [2]. Death following diphenhydramine poisoning is rare [3].

Oral therapeutic dose for adults are 25 to 100 mg every 4 to 8 h, not to exceed 400 mg/24 h [2].

Severe toxicity (i.e., delirium, seizures, and coma) generally develops only after ingestion of 1 g or more in adults. A 35-year-old female developed hypotension, lethargy, seizures, and prolonged QRS and QTc intervals following a deliberate ingestion of 16 grams of diphenhydramine in a suicide attempt. Ingestion of 25 mg/kg diphenhydramine was fatal in an adult. In a similar case, a healthy 26-year-old male ingested 25 g of diphenhydramine and developed lethargy, coma, seizures, and prolonged QRS and QTc interval. Torsades de pointes occurred approximately 6.5 hours after ingestion and laboratory evidence of metabolic acidosis and hypokalemia were also observed, but he made a complete recovery [2].

A single 50 mg oral dose produced average blood plasma concentrations of 0.083 mg/l at 3 h, 0.049 mg/l at 6 h, and 0.009 mg/l by 24 h; and a 100 mg oral dose produced average plasma levels of 0.112 mg/l at 2 hours and 0.014 mg/l by 24 hours [2]. A review of 136 cases of diphenhydramine overdose revealed a wide range of plasma levels (0.1 to 4.7 mg/l) which did not correlate with symptoms or signs. Expected effects at given blood concentrations: a) Antihistaminic effect: > 0.025 mg/l; b) Drowsiness: 0.03 to 0.04 mg/l; c) Mental impairment: >0. 06 mg/l [2].

A fatal case had a diphenhydramine plasma level of 5 mg/l and liver tissue level of about 34 mg/g. The diphenhydramine blood concentration, in a 48-year-old female following a fatal ingestion of diphenhydramine in an unknown amount, was 8.8 mg/l (approximately 100 times greater than the average peak plasma concentration following a single therapeutic dose) [2]. The average diphenhydramine blood concentration in 11 fatalities due to acute ingestion was 16 mg/l (range 8-31 mg/l) [3].

Kinetic data
Absorption: >90% [4].

Bioavailability: Systemic bioavailability in a study varied from 26 to 60% [4].

Volume of distribution: Reported to be 3 to 7 l/kg [2] or 3.28 l/kg [4].

The plasma half-life: Range 2.4-8h, mean 3.3 h [2, 4].

Time to peak: A 50 mg dose produced an average peak plasma level of 0.066 mg/l at 2.3 hours post-ingestion [2].

Protein binding: 85-99% [2, 4].

Passage of blood brain barrier: free [4].

Metabolism and excretion
Diphenhydramine is extensively metabolized, mainly in the liver. The tertiary amine group is sequentially N-demethylate to give monodesmethyldiphenhydramine and didesmethyldiphenhydramine, respectively. The resultant primary amine is oxidatively deaminated to yield the carboxylic acid, diphenylmethoxy acetic acid, which may then be conjugated with glutamine or glycine [4].

Excretion: The major route of excretion is via the kidneys, with up to 65% of the dose eliminated as metabolites in the urine in 96 h [2, 4]. Metabolites in the urine include glutamine and glucuronide-conjugated and unconjugated diphenylmethoxyacetic acid [2, 3]. Approximately 1% of the drug is excreted unchanged in the urine [2].

Pharmacological mechanisms
Diphenhydramine is a histamine H-1 antagonist of the ethanolamine class. It has the properties and uses of the antihistamines which do not inhibit histamine release, antibody production, or antigen-antibody reaction but rather antagonize histamine effects on receptor sites. The central antimuscarinic effects of diphenhydramine blunt the excitatory action of the cholinergic system on the nigrostriatal pathways. H1 antagonists inhibit both the vasoconstrictor effect of histamine and the more rapid vasodilator effects mediated by H1 receptors on endothelial cells. Residual vasodilation reflects involvement of H2 receptors on smooth muscles [2].

Toxicological mechanism
Diphenhydramine can act as a blocker of the potassium channels which are responsible for the rapid component of the cardiac repolarizing current, resulting in prolongation of the QT interval [4].

Target organs: CNS, heart [2].

References

1. HSDB, TOXNET (2006).
2. Poisindex, Thomson Micromedex (2006).

3. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*, 4th edn., pp. 264-267. Chemical Toxicology Institute, Foster City, California, USA.
4. *Therapeutic drugs*, vol. 1, ed. C. Dollery, 1992, Churchill Livingstone.

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