

5,5-Diphenylhydantoin

Synonym: Phenytoin

Chemical name: 5,5-diphenyl-2,4-imidazolidinedione

CAS: MF: C₁₅H₁₂N₂O₂

MW: 252.26

pKa=8.3 (phenytoin is a weak organic acid)

Solubility: phenytoin is practically insoluble in water, slightly soluble in chloroform and ether, and highly soluble in alkali. Solubility in alcohol: 1 g dissolves in 60 ml alcohol.

Phenytoin sodium is freely soluble in water [1].

Major uses

5,5-diphenylhydantoin, further **phenytoin** (first synthesized 1908), is used mainly in the treatment of epilepsy. Additionally, it is used to control arrhythmias, to treat migraine headache, and to treat facial nerve pain. It is also used for controlling seizures. Phenytoin is structurally related to the barbiturates (e.g. phenobarbital) but it has low hypnotic activity.

Human toxicity

Common toxic effects generally include the central nervous system (CNS) depression: nystagmus (disturbance in the eye movement), ataxia, mental status changing, hallucinations, lethargy, cerebellar atrophy, and in severe cases coma may also occur.

Deaths are relatively rare even with massive acute oral overdosage (100 to 160 mg/kg) and have been reported with the relatively serious hypersensitivity reactions seen with chronic use. There are few published reports on fatal poisoning when people committed suicide by taking an overdose of the drug.

Cardiotoxicity has not been reported with oral overdose; however, dysrhythmia and hypotension are associated with rapid intravenous infusion of phenytoin and appear to be due to the diluent, propylene glycol.

Therapeutic oral doses are 300 to 400 mg/day (up to 600 mg/day if it is necessary). Therapeutic blood concentrations are 10 to 20 mg/l (40 to 80 µM). Toxic effects are rare at plasma levels less than 20 mg/l, but are common in patients with plasma levels greater than 30 mg/l (119 µM) [1]. The mean clinically measured acute lethal concentration of phenytoin, based on data from several handbooks, was 91 mg/l [2].

Carcinogenicity: Phenytoin is possibly carcinogenic to humans; group 2B (IARC, 2004) [3].

Kinetic data

Absorption of ingested phenytoin is slow, variable, and incomplete. It is poorly absorbed in the stomach, but relatively well absorbed from the small intestine [1].

Kinetics is zero-order and first-order (see below *Elimination*) [2].

Volume of distribution: 0.5 to 0.8 l/kg [1]; 0.6 l/kg at the overdose [2].

Passage of blood-brain barrier: free [2].

Plasma half-life: at the therapeutic doses about 12 h; at a massive overdose 24 h- 230 h [1, 2].

Time to peak serum levels is approximately 3 to 12 h after ingestion (therapeutic doses) [1]. Time to peak may be prolonged to 30-120 h at an overdose situation [2].

Plasma protein binding: 60% or greater. It is bound mostly to albumin [5]. The individual differences in protein binding are common and vary from 62 to 92% (reviewed in [4]).

Elimination: phenytoin has a unique pharmacokinetic pattern. At therapeutic serum levels, phenytoin elimination follows first-order (exponential) kinetics. There is a linear relationship between the daily dose and the steady state (dynamic equilibrium).

In overdose settings, saturation of the hepatic hydroxylation system occurs, and zero-order kinetics predominates. As phenytoin accumulates, serum phenytoin levels and half-life increase with disproportionate rapidity [4].

Metabolism and excretion

Ninety five percent of the drug is metabolized in the liver by the microsomal enzyme system, through para-hydroxylation to 5-(4-hydroxyphenyl)-5-phenylhydantoin (also under name p-hydroxyphenytoin). The latter is the main metabolite of phenytoin, and typically accounts for 67-88% of the dose in the urine [1]. Minor metabolites include 5-(3-hydroxyphenyl)-5-phenylhydantoin, hydantoic acid, α -aminodiphenylacetic acid, catechol, 3-*O*-methylecatechol, and 3,4-dihydro-3,4-dihydroxyphenytoin [5, 6].

Metabolites of phenytoin are not therapeutically active [1].

Excretion: the metabolites are conjugated with glucuronide and excreted in the bile and, subsequently, in the urine. Approximately 44 to 62% of phenytoin administered to man appeared in the urine in the hydroxylated form. Only a minor fraction (less than 4%) of a dose is excreted unchanged in the urine [1, 5].

Mechanisms of action

One proposed mechanism of phenytoin's anticonvulsant activity is folate depletion. Folic acids and their derivatives appear to have convulsant properties. Phenytoin decreases cerebrospinal fluid and red blood cell folate level [6].

The increased cerebellar activity has been postulated to play a role in phenytoin's anticonvulsant effect by activation of inhibitory pathways to the cerebral cortex.

Phenytoin has been shown to increase brain concentrations of the neurotransmitter γ -aminobutyric acid (GABA) which functions as a stimulatory neurotransmitter in the cerebellum and as an inhibitory neurotransmitter in the cerebral cortex (reviewed in [4]).

Phenobarbital, carbamazepine, diazepam, ethanol, folic acid, and calcium may cause a decrease in serum phenytoin level. These drugs decrease absorption, increase biotransformation through enzyme induction, or increase excretion. The result is a decrease in phenytoin serum half-life [6].

Toxicological mechanisms

The mechanisms are not well known. Hypothetical mechanisms: 1) Phenytoin binds to specific receptors in neuronal cell membrane; 2) Phenytoin inhibits voltage-dependent sodium channels [2].

Increased toxicity of phenytoin by mechanisms not yet established can be caused by other drugs (e.g. amiodarone and imipramine) [4].

Target organs: CNS (cerebellum), heart [2].

References

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