Phenobarbital

CAS number: 50-06-6
MF: $C_{12}H_{12}N_2O_3$
FW: 232.2
Water solubility: 1.11 g/l.

Major uses
Phenobarbital, a barbiturate, is the central nervous system (CNS) depressant. It is used as an anticonvulsant for the treatment of epileptic seizures and as a sedative to relieve anxiety. Phenobarbital is also used for treatment of neonatal hyperbilirubinemia. Long-term use of phenobarbital may result in addiction [1].

Human toxicity
Phenobarbital intoxication may give the following symptoms: nystagmus, dysarthria, ataxia, drowsiness, respiratory depression, and coma are commonly found. Hypotension, cardiovascular collapse, and hypothermia are less frequent effects. A case study reported that a nonocclusive intestinal infarction in an adult male following overdose of phenobarbital. Multisystem hypersensitivity reactions may include mucocutaneous eruptions, fever, lymphadenopathy, eosinophilia, myopathy, hepatitis, and nephritis. These hypersensitivity reactions are often clinically indistinguishable. Symptoms can usually be registered within 1 to 2 h [1].

Early death is due to cardiac and/or respiratory arrest. Death may take place secondary to circulatory collapse, acute renal failure, aspiration pneumonitis, lung abscess, pulmonary edema, and cerebral edema. Lethal overdoses without coingestants are rare.

Toxic effects have been reported from a dose of 8 mg/kg unless the person is tolerant due to addiction. Addicts have been known to utilize 1g/day. Development of cardiac arrest has been reported in 0.5% of acute overdoses of barbiturates [1]. The mean lethal dose in adults, based on the data from several handbooks, was 7.8 g, and minimal lethal dose was 4.8 g [2].

The therapeutic blood concentration is between 10 and 40 mg/l; the toxic concentration is 40-60 mg/l [3]. The mean lethal serum concentration (data from several handbooks) is 136 mg/l, as long as the patient is not a drug addict [2].

Carcinogenicity: Group B2, probable human carcinogen (EPA, 2004).

Kinetic data
Absorption: 80% of the administered dose is absorbed [1].

Volume of distribution: 0.5-0.6 l/kg [4].

Distribution: barbiturates, including phenobarbital, are highly lipid soluble, and they are rapidly distributed into the vascular areas of brain (gray matter). Maximal uptake may occur within 30 seconds, inducing sleep within a few minutes [5].

Peak plasma level usually occurs 6 to 8 h after ingestion, but may be delayed.

Elimination half-life is up to 100 h in adults, at the overdose situation [2].

Protein binding: 5% [5]. Other barbiturates have much higher protein binding, up to 50% [5].

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

Metabolism and excretion
Phenobarbital is metabolized by liver via oxidative hydroxylation, and the inactive metabolite p-hydroxyphenobarbital is formed. It is consequently conjugated with glucuronic acid. Sixty to 75% of phenobarbital is hydroxylated [4, 5].

Excretion: From 78-87% of a single labeled dose is excreted in the urine within 16 days as unchanged drug (25-33%), N-glycosyl-phenobarbital (24-30%), and free or conjugated p-hydroxyphenobarbital (reviewed in [4]).

Toxicological mechanisms
Barbiturates slightly depress respiration at usual hypnotic doses. However, larger doses markedly decrease the rate, depth, and volume of respiration, probably through a direct action on medullary centers in the brain. Barbiturates act as nonselective depressants of the CNS [5].

The sedative-hypnotic and anticonvulsant effects of barbiturates have been suggested to be related to their ability to enhance and/or mimic the inhibitory synaptic action of gamma-aminobutyric acid (GABA). There is also suggested that barbiturates have a particular effect at the level of the thalamus where they inhibit ascending conduction in the reticular formation, thus interfering with the transmission of impulses to the cortex [5, 6].

Serum bilirubin concentration is decreased by phenobarbital, probably by induction of glucuronyl transferase, the enzyme which conjugates bilirubin [6].

Target organs: CNS, heart [2]

References

1. Poisindex, Thomson Micromedex (2005).
2. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, B., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26: 571-616.
3. Winek, C.L. (1994) Drug and chemical blood-level data. *Winek's Toxicological Annual*, Pittsburgh. Allegheny County Department Laboratories.
4. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*, 4th edn., pp. 612-614. Foster City, CA, USA: Chemical Toxicology Institute.
5. Haddad, L.M. & Winchester, J.F. (1990) Clinical Management of Poisoning and Drug Overdose, 2nd edn., Philadelphia, PA, USA: W.B. Saunders.
6. HSDB (2005).

Written by Erica Toft, Stockholm, September 2005; revised February 2007