Propranolol hydrochloride

Synonym: Inderal

CAS: 318-98-9
MF: $C_{16}H_{21}NO_2 \cdot HCl$
MW: 295.8
pKa: 9.5
Solubility: 5 g/100 ml water, dissolve with heat [1].

Major uses

Propranolol hydrochloride (further propranolol) is a beta (β)-adrenergic blocking agent (synthesized in 1964). It is currently used in medicine for the treatment of hypertension, arrhythmias, angina pectoris, myocardial infarction, open-angle glaucoma, migraine etc. [2, 3].

Human toxicity

The overdoses of propranolol can be toxic and even fatal. Several symptoms have been described: a) Neurological: fatigue, sleepiness, weakness, headache, visual disturbance, hallucinations etc.; b) Cardiovascular: bradycardia, hypotention, ventricular dysrhythmias, heart failure and cardiac arrest; c) Gastrointestinal: nausea and vomiting [4].

Therapeutic daily oral dose of propranolol hydrochloride is from 30 to 320 mg, depending on a disease. Therapeutic blood plasma concentrations range between 60 and 0.1 mg/l. Acute, life-threatening intoxications with propranolol were occurred after the doses of 1 to 2.5 g, or higher; the fatal cases occurred at the doses exceeding 2-3 g [4].

The average lethal blood plasma concentration of 2.2 mg/l was estimated in four clinical cases [5]. The mean clinically measured acute lethal serum concentration, based on data from four different handbooks, was 6.4 mg/ml [6]. Post-mortem blood propranolol levels varied between 2 and 167 mg/l [4].

Kinetic data

Absorption: Propranolol is completely absorbed following oral administration [6].

Bioavailability: 30% [3].

Kinetics at the overdose situation is possibly biphasic; first phase is about 3.9 h, second – 16 h or more [6].

Volume of distribution: 3-5 l/kg [2]; 2.8 l/kg [3].

Time to peak concentration: 1-2 h [6].

Blood-protein binding: 80-95% [6].

The blood plasma half-life (at the chronicle treatment): 4-6 h [4].

Passage of blood-brain barrier: free [6]. Propranolol has a highest degree of lipid solubility, compared with other β-blockers, which enables it to penetrate the BBB and to accumulate in the brain.

Elimination half-life: 2 to 3 h, prolonged up to 14 h at overdose [4].

Metabolism and excretion
Propranolol is completely metabolized. It is efficiently extracted during the first pass through the liver, where it is biotransformed, with production of several active metabolites. One of them is 4-hydroxypropranolol, which has β-blocking activity comparable to that of propranolol, and is present in plasma after oral administration of the drug, but has a shorter half-life than a parental drug. Other metabolites are norpropranolol and α-naphthoxy-2,3-propyleneglycol. Their biological activity is very low compared to that of a parental drug [2, 3, 4].

Excretion: about 84-92% of an oral dose is excreted in the 48 h urine, with 20% as naphthoxylactic acid, up to 25% as propranolol glucuronide and only about 0.5% of unchanged drug [2, 4].

Mechanisms of action
Propranolol inhibits the action of catecholamines, especially of epinephrine, on both β_1- and β_2-adrenergic receptors, and decreases its level in the CNS and in blood. This leads to a lowering of blood pressure and to suppressing of cardiac arrhythmias [3].

Toxicological mechanisms
Toxic effect of propranolol at the overdosing is possibly associated with its fast accumulation in the brain, leading to the CNS collapse [3].

Target organs: CNS, liver, kidney [6].

References
1. Sigma, *Biochemicals & Reagents* (2004-2005).
2. Baselt, R.C. & Cravey, R.H. (1995) Disposition of Toxic Drugs and Chemicals in Man, 4th edn., pp. 661-665. Chemical Toxicology Institute, Foster City, CA, USA.
3. Haddad, L.M., Winchester JF (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 1315-1326. W.B. Saunders Company.
4. Poisindex, Thomson Micromedex (2005).
5. Hallander, S., Ekwall, B. (1997) *MEIC Monography: Propranolol*. http://www.cctoxconsulting.a.se/23_propranolol.pdf
6. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, Ba., 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.

Written by Ada Kolman, December 2005; revised March 2007
ada.kolman@telia.com