Haloperidol

Synonym: haldol
Chemical name: 4-[4-(p-chlorophenyl)-4-hydroxypiperidol]-4'-fluorobutyrophenone
CAS: 52-86-8
MF: $C_{21}H_{23}ClFNO_2$
FW: 375.9
Solubility: insoluble in water; soluble in ethanol and DMSO.

Major uses
Haloperidol is a neuroleptic drug for the treatment of psychotic disorders (e.g. schizophrenia, mania, psychopathy etc.). It is also a widely used tranquilizer (e.g. for treatment of behavioral problems in hyperactive children) [1]. Haloperidol may be used as a drug of abuse [2].

Human toxicity
Most common major signs of acute intoxication at a massive overdose are the central nervous system (CNS) depression, somnolence, coma, respiratory depression, cardiac dysrhythmia and hypotension.

The recommended daily dose for patients with moderate symptoms is 1 to 6 mg, and for patients with severe symptoms, 6 to 15 mg. Maximum tolerated doses are between 300 and 1000 mg [2].

In adults, ingestion of 300 mg or more have experienced life-threatening symptoms. Some individuals have had fatal reactions to even therapeutic doses of haloperidol. At the same time, it happened that adults survived overdoses as large as 1000 mg [2].

Therapeutic blood plasma concentrations are in the range of 0.005-0.02 mg/l [3]. In patients who respond to haloperidol, a serum concentration of at least 0.005 mg/l is advisable to ensure a positive response. Side effects increased in incidence with plasma concentrations greater than 0.006 mg/l, at 12 to 14 h after the final administration [4]. The toxic plasma/serum level of haloperidol was reported to be 0.005-0.05 mg/l [5].

The lethal blood levels have not been definitively established; however, in one fatal case with suicidal overdose, post mortem heart blood concentration of haloperidol was 1.9 mg/l (5 μM)); in second fatal case, which was believed to be a natural cardiac death, heart blood concentration of haloperidol was 0.6 mg/l (1.6 μM) [6].

Kinetic data [4]
Absorption: haloperidol is well absorbed from the gastrointestinal tract.

Volume of distribution (Vd): 20 l/kg.

Blood protein bindning: 90-94%.

Peak serum concentration levels are attained 0.5 to 4 h after an oral dose.

Elimination: clearance occurs exclusively by hepatic metabolism.

The elimination half-life ranges from 13 to 35 h.

Metabolism and excretion
Haloperidol is mainly metabolized by the liver, where it undergoes cytochrome P450-catalyzed oxidative cleavage of hydrocarbon chain, forming inactive fluorophenyl and piperidine metabolites. An additional metabolic pathway involves reduction of the keto group on the side chain to an alcohol, forming a compound known as *reduced haloperidol*. The latter has about 25% of the antipsychotic activity of the parent drug (reviewed in [6]).

Other identified metabolites include 4-fluorobenzol-propionic acid and 4-fluoro-phenylaceturic acid [2].

Excretion: Renal excretion is negligible, with less than 1% of an administered dose excreted in the urine.

Pharmacological and toxicological mechanisms
Similar to the other neuroleptics, haloperidol is a dopamine receptor antagonist: it blocks D-2 dopamine receptors in the brain. Thus, the antipsychotic activity of this anticholinergic drug is closely associated with its ability to block the action of dopamine [1, 2].

The toxic effect of haloperidol is related to blocking of dopamine receptors in the CNS; however, the knowledge of exact mechanisms is still meager [1].

Target organs: CNS, heart, liver [1].

References
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