Chlorpromazine hydrochloride

Chemical name: 2-Chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride
Synonym: Thorazine
CAS: 69-09-0
MF: $C_{17}H_{19}ClN_2S \cdot HCl$
MW: 355.3
Solubility: soluble in water, in 100% ethanol, methanol and chloroform.

Major use
Chlorpromazine hydrochloride (CPH) belongs to antipsychotic drugs, also called neuroleptics; and it is mainly used for the treatment of neurological disorders. CPH has sedative, hypotensive and antiemetic properties.

CPH, which is an aliphatic phenothiazine, was first synthesized in 1952. It was extensively studied and used as a model for a big class of neuroleptic agents. Haloperidol, thioridazine, clozapine, promethazine, and many other drugs belong to the same class [1, 2].

Human toxicity
Fatalities with the therapeutic use or abuse of neuroleptic drugs are uncommon, and toxicity is less severe than that of the chemically related tricyclic antidepressants [1].

The therapeutic single oral dose of CPH is in the range of 25-100 mg for acute disturbances or in chronic daily amounts of up to 2400 mg for the maintenance of mental patients [2].

A single oral 25 mg dose produced an average peak plasma CPH concentration in 4 subjects of 0.001 mg/l at 2.8 h. Following a single oral administration of 150 mg CPH, an average peak plasma concentration of 0.018 mg/l (range, 0.010-0.026) was achieved in 3 h and declined to 0.013 mg/l by 6 h (reviewed in [2]).

Major adverse effect of CPH is the central nervous system (CNS) depression to the point of somnolence and coma with ingestion of overdose. Among other effects are: hypotention, seizures, ECG changes and dysrhythmias, as well as agitation and restlessness. Cardiac arrest, respiratory depression and pulmonary edema may occur with CPH overdose.

Adults have survived ingestion of 9.75 g of CPH. Two adults became comatose after 0.8 and 17 g of CHP. The acute fatal dose for CPH was reported to be from 15 to 150 mg/kg (reviewed in [3]).

CPH blood plasma levels above 0.75 mg/ml were found to produce tremors and convulsions in most patients. In one fatal case (ingestion of unknown amount of CPH) blood concentration of the drug was 6.6 mg/ml. In a series of 8 fatal cases concentrations averaged 17 mg/l (range, 3 -35) (reviewed in [2]).

Kinetic data
Absorption: the oral absorption is diverse and unpredictable depending on the metabolism either within the gastrointestinal lumen or during absorption through the bowel wall [2].

Bioavailability: approximately 32% (range 10 to 69%). The best bioavailability is achieved through parenteral administration [1].

Kinetics: possibly biphasic? Data are not available.

Distribution: CPH appears to be concentrated in brain against the plasma gradient, and brain levels have been estimated to be 5 times greater than plasma concentrations (reviewed in [4]). In the fatal cases, high amounts of CPH were also found in liver and kidney [2].

Volume of distribution: 20 l/kg [1]; 10-35 l/kg [2].

Mean plasma half-life: 18 h (range, 6 to 119 h) [1].

Time to peak blood concentration: peak CPH plasma levels are normally seen within 2 to 3 h of a single oral dose, with a rapid fall-off in plasma concentration during the following 3 to 6 h (reviewed by [1]).

Plasma protein binding: CPH is extensively bound to tissues (particularly in the brain) and plasma protein (mostly albumin) [1].

Passage of blood brain barrier: free (my own conclusion based on high brain concentrations at fatal cases, AK).

Metabolism and excretion

The metabolism of CPH is exceedingly complex: 168 possible metabolites have been postulated and at least 20 of these have been isolated. The most common pathways of biotransformation are: conversion to the sulfoxide, with probable loss of activity; demethylation to nor- and di-norchlorpromazine, which are one-fourth and one-eight as active as the parent compound, respectively; phenolic hydroxylation at the 7 position to produce an active metabolite, with subsequent glucuronide conjugation; N-oxide formation; and combination of nearly all of these mechanisms [2].

Excretion: about 23% of a single oral dose is excreted in the urine, primarily as metabolites. Also fecal excretion is believed to play an important role in the elimination of this drug [2].

Mechanisms of action

The antipsychotic activity of CPH and other neuroleptic drugs is closely associated with their capacity to block D2 dopamine receptors in the brain. Dopamine functions as a neurotransmitter, activating dopamine receptor. Neuroleptic drugs can block also other neurotransmitter receptors, such as histamine (H_1 and H_2), alpha-adrenergic ($alpha_1$ and $alpha_2$), muscarinic*, and serotonin receptors [1].

Toxicological mechanisms

The therapeutic as well as toxic effects of CPH (and other neuroleptic drugs) stem from their dopamine receptor antagonism within the CNS. Blockade of dopaminergic neurons by these drugs causes a loss of the normal dopaminergic inhibitory effect on cholinergic neurons with the consequent development of hypokinetic side effects (e.g. parkinsonism) (reviewed in [1]).

CPH may so completely block dopamine D2 receptors that it seriously disrupts neurotransmission in the nigrostrial**, mesolimbic***, and mesocortical***

dopaminergic pathways, hypothalamic dopamine neurons, and peripheral dopaminergic areas [reviewed in [3]).

Cardiovascular toxicity of CPH may result in death, although infrequent, and is usually manifested by either electrophysiological changes (electrocardiographic, ECG, changes) or hypotension [1].

Target organs: CNS, heart [2, 4].

References

1. Haddad, L.M. & Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 780-793. W.B. Saunders Company.
2. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*. 4th ed., pp. 158-162. Chemical Toxicology Institute, Foster City, California.
3. Poisindex, Thomson Micromedex (2006).
4. *Casarett and Doull's Toxicology* (The Basic Science of Poisons), (1986) Klaassen, C.D., Amdur, M.O., Doull, J., eds., p. 881. Macmillan Publishing Company.

* Type of receptor, in the parasympathetic nervous system, that releases acetylcholine as its neurotransmitter.
** Pathway that connects 2 parts of the brain which are important for movement: the substantia nigra and the corpus striatum.
*** One of the four major pathways where the neurotransmitter dopamine is found.

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