# Thioridazine hydrochloride

Chemical name: 10-[2-(1-methyl-2-piperydyl)ethyl]-2-(methylthio)-10H-phenothiazine

CAS: 130-61-0
MF: $C_{21}H_{26}N_2S_2 \cdot HCl$
MW: 407
Solubility: insoluble in water; soluble only in organic solvents.

**Major uses**
Thioridazine hydrochloride (further thioridazine) is a representative of phenothiazine compounds, and it is an antipsychotic drug (synthesized in 1959). It relieves tension and anxiety, and acts against multiple symptoms, e.g. agitation, depression, behavior problems and sleep disturbances. Thioridazine is also effective in controlling the symptoms of schizophrenia, mania, and other psychotic diseases [1].

**Human toxicity**
Therapeutic daily doses of thioridazine are in the range of 30 to 600 mg. Chronic therapeutic dosages result in serum levels ranging 0.14 to 2.60 mg/l.

Overdosage of this drug is not an infrequent event, and in combination with other drugs or alone can lead to fatal poisoning. The minimum lethal or toxic dose is not well established in the literature. The acute fatal dose is thought to be in the range of 15 to 150 mg/kg. Acute ingestion of 1.5 to 8 g of thioridazine has resulted in arrhythmias and death [1].

The following symptoms were observed at an overdose [1]:

a) Cardiovascular: cardiac arrest and sudden death; dysrhythmias, especially ventricular tachycardia, hypotension and hypertention; hypotention is the more common serious effect;
b) Neurologic: the central nervous system (CNS) depression, coma, agitation, extrapyramidal signs and seizures;
c) Respiratory depression, pulmonary edema;
d) Gastrointestinal abnormalities;
e) Hyperthermia or hypothermia;
f) Hepatic disease.

The therapeutic blood level of thioridazine is 0.5 mg/l; the lethal blood level is 20 mg/l [2]. The average blood concentration in 8 fatal cases was 2.5 mg/l (range 0.3-8.5 mg/l) [3]. The average post-mortem blood concentration in 12 cases was estimated to be 3.5 (1.0-13.0) mg/l [4].

**Kinetic data**
*Absorption*: thioridazine is rapidly and completely absorbed from the gastrointestinal tract.

*Bioavailability*: 60%.

*Kinetics*: multiphasic [5].

*Distribution*: thioridazine is a lipophilic compound which is quickly distributed in all organs in the body.

*Volume of distribution* ($V_d$): 18 l/kg [5].

*Accumulation in vital organs*: CNS, lung, liver, kidney [5].

*Blood protein binding*: 96-99% [5].

*Peak plasma concentrations* are reached 2 to 4 h after ingestion [5].

*Plasma/serum half-life*: 21 h [1].

*Passage of blood-brain barrier*: free [3].

*Elimination half-life* is 26 h [5].

**Metabolism and excretion**

Thioridazine is extensively metabolized in the liver. Some of the resulting metabolites, e.g. mesoridazine, sulforidazine, N-desmethylthioridazine, and ring sulfoxide, possess of pharmacodynamic properties similar to those of the parent compound. The major metabolite is the side chain sulfoxide derivative, mesoridazine, which is twice as potent as thioridazine and is commercially available [1].

*Excretion*: Metabolites are conjugated with glucuronic acid to produce hydrophilic compounds that can be excreted primarily in the urine and to lesser extent in bile [6]. Only 2.5-17% of a daily dose is excreted as thioridazine or its metabolites in the 24 h urine (0.5% is excreted as thioridazine, 0.5% as mesoridazine, and about 1% as the ring sulfoxide) [7].

**Mechanisms of action**

In similarity with other phenothiazines, thioridazine blocks dopaminergic $D_2$ receptor in the brain, blocks $\alpha_1$-adrenergic receptor and depresses the release of hypothalamic and hypophyseal hormones. Moreover, thioridazine is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis [6].

**Toxicological mechanism**

Phenothiazines, including thioridazine, may so completely block dopamine $D_2$ receptor that they seriously disrupt neurotransmission via dopaminergic pathways; hypothalamic dopamine neurons; and peripheral dopaminergic areas [1].

**Target organs**: CNS, heart [5].

**References**

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