



## Thioridazine

Updated: December 11, 2013.

### OVERVIEW

#### Introduction

Thioridazine is a phenothiazine and antipsychotic agent that is no longer in common use. Thioridazine has been linked to rare instances of clinically apparent acute cholestatic liver injury.

#### Background

Thioridazine is a piperazine phenothiazine derivative which acts by postsynaptic inhibition of dopamine receptors. Thioridazine has other peripheral and central nervous system effects, producing both alpha adrenergic stimulation and blocking histamine- and serotonin-mediated effects. Thioridazine is indicated for the therapy of acute and chronic psychosis. Thioridazine was approved for use in the United States in 1978 and was formerly a commonly prescribed antipsychotic medication, but in recent years has been replaced in large part by the atypical antipsychotics, which have fewer extrapyramidal side effects. Use of thioridazine is also restricted because of its propensity to cause prolongation of the QTc interval and increased risk of sudden death.

Thioridazine is available as tablets of 10, 25, 50 and 100 mg in generic forms and previously under the brand name Mellaril. The usual recommended dose in adults is 50 to 100 mg three times daily, increasing based upon effect and tolerance to a maximum of 800 mg daily. Common side effects include drowsiness, dizziness, headache, blurred vision, dry mouth, constipation, tremor, restlessness, muscle spasms and weight gain.

#### Hepatotoxicity

Liver test abnormalities have been reported to occur in a high proportion of patients on long term phenothiazine therapy, but elevations are uncommonly above 3 times the upper limit of normal. The aminotransferase abnormalities are usually mild, asymptomatic and transient, reversing even with continuation of medication. Rare instances of clinically apparent acute liver injury have been reported due to thioridazine, with some resemblance to cases of chlorpromazine jaundice. The onset of jaundice occurred within a few weeks to several months of therapy and the pattern of serum enzyme elevations was typically cholestatic, although hepatocellular patterns have also been reported. Immunoallergic manifestations (fever, rash and eosinophilia) were not prominent and autoantibodies were not detected. Some cases were associated with agranulocytosis which is a rare but known complication of the phenothiazines.

#### Mechanism of Injury

The mechanism by which the phenothiazines cause serum aminotransferase elevations is not known. Thioridazine is extensively metabolized by the liver via sulfoxidation and oxidation, and some instances of

serum aminotransferase elevations as well as more clinical apparent liver injury may be caused by production of a toxic intermediate of its metabolism.

## Outcome and Management

The serum aminotransferase elevations that occur on thioridazine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. The acute clinically apparent liver injury caused by thioridazine is typically self-limited and benign. Instances of chronic cholestasis and vanishing bile duct syndrome have not been reported with thioridazine, but many cases have been attributed to other phenothiazines. Rechallenge with thioridazine usually causes a prompt recurrence of the liver injury and should be avoided. Patients with thioridazine induced liver injury may have cross sensitivity to other phenothiazines, but generally tolerate the atypical antipsychotics.

Drug Class: [Antipsychotic Agents](#)

Other Drugs in the Subclass, Phenothiazines: [Chlorpromazine](#), [Fluphenazine](#), [Perphenazine](#), [Prochlorperazine](#), [Trifluoperazine](#)

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Thioridazine – Generic, Mellaril®

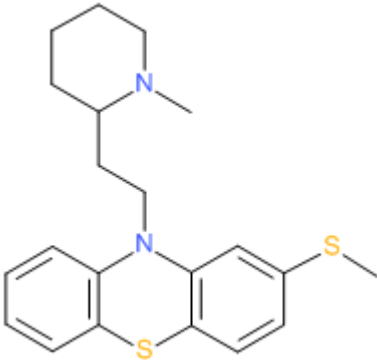
### DRUG CLASS

Antipsychotic Agents

### COMPLETE LABELING

Product labeling at [DailyMed](#), National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Thioridazine	<a href="#">50-52-2</a>	C <sub>21</sub> -H <sub>26</sub> -N <sub>2</sub> -S <sub>2</sub>	

## ANNOTATED BIBLIOGRAPHY

References updated: 11 December 2013

Zimmerman HJ. Neuroleptic drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 483-91.

*(Expert review of hepatotoxicity of neuroleptic drugs including chlorpromazine published in 1999; several hundred cases of jaundice due to chlorpromazine have been reported, usually cholestatic, arising after 1-5 weeks, often with fever and eosinophilia, sometimes causing vanishing bile duct syndrome; other phenothiazines have only rarely been linked to a similar form of liver injury, except for prochlorperazine).*

Larrey D, Ripault M-P. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 443-62. *(Review of hepatotoxicity of*

*phenothiazines mentions that hundreds of cases of chlorpromazine jaundice have been published, frequency ~0.5-1%; onset in 2-5 weeks, usually acute cholestatic hepatitis with jaundice and pruritus; a prodrome of fever and abdominal pain is common; prolonged course in 7% but often benign; other phenothiazines have been linked to liver injury similar to that of chlorpromazine, "but with a lower frequency").*

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56.

*(Textbook of pharmacology and therapeutics).*

Brunold H. [Experiences with a new phenothiazine derivative. Mellaril, Sandoz]. Ther Umsch 1959; 16: 90-2. PubMed PMID: 13647410.

*(Among 89 patients treated with thioridazine with escalating doses to 800 mg/day, one patient developed jaundice which was not otherwise characterized).*

Block SL. Jaundice following thioridazine administration. Am J Psychol 1962; 119: 77. PubMed PMID: 13870055.

*(79 year old woman with dementia developed elevated liver enzymes but without symptoms 9 months after starting thioridazine, resolving rapidly with stopping; jaundice was not mentioned in text of the report).*

Winkelmayer R. Subicterus following the administration of thioridazine and chlordiazepoxide. Del Med J 1966; 38: 334-6. PubMed PMID: 5978248.

*(35 year old man developed jaundice 24 days after starting thioridazine with slight elevation in "icteric index", but normal serum bilirubin and aminotransferase levels, a pattern that recurred on chlordiazepoxide but not upon restarting thioridazine).*

Reinhart MJ, Benson RM, Kwass SK, Storey WF. Suggestive evidence of hepatotoxicity concomitant with thioridazine hydrochloride use. JAMA 1966; 197: 767-9. PubMed PMID: 5953369.

*(3 cases of thioridazine hepatotoxicity; case 1, 53 year old man with rise in ALT [600 U/L], Alk P [~10 fold] and bilirubin [5.2 mg/dL] within days of switching from chlorpromazine to thioridazine and rapid recovery with stopping; case 2, 32 year old woman switched from chlorpromazine to thioridazine because of ALT elevations and 4 months later developed fatigue [bilirubin normal, ALT 320 U/L, Alk P normal], resolving upon stopping; case 3, 17 year old boy had minor ALT elevations [<60 U/L] without Alk P or bilirubin abnormalities on thioridazine).*

Walker CO, Combes B. Biliary cirrhosis induced by chlorpromazine. Gastroenterology 1966; 51: 631-40. PubMed PMID: 5926937.

*(32 year old woman and 31 year old man developed persistent jaundice [>4 years], cholestasis and liver fibrosis 3 and 4 weeks after starting chlorpromazine; acute cholestatic hepatitis evolving into chronic form with biopsies showing cirrhosis and complications of portal hypertension, most likely due to vanishing bile duct syndrome).*

- Barancik M, Brandborg LL, Albion MJ. Thioridazine-induced cholestasis. *JAMA* 1967; 200: 69-70. PubMed PMID: 6071857.
- (34 year old man with chronic alcoholism developed jaundice 5 months after being switched from chlorpromazine to thioridazine [bilirubin 6.7 mg/dL, ALT 59 U/L, Alk P 7 Bessey-Lowry U/L], resolving rapidly upon stopping; biopsy showed intrahepatic cholestasis and not alcoholic hepatitis).*
- Kane FJ Jr, Moore LP. Hepatotoxicity occurring with thioridazine therapy. *South Med J* 1971; 64: 573. PubMed PMID: 5573073.
- (13 year old boy developed transient rash after 22 days of thioridazine [bilirubin 2.2 mg/dL, 1.1 direct], which then decreased to normal weeks after stopping; ALT and Alk P levels were not obtained at time of rash, but were normal in follow up).*
- Ishak KG, Irey NS. Hepatic injury associated with the phenothiazines. Clinicopathologic and follow-up study of 36 patients. *Arch Pathol* 1972; 93: 283-304. PubMed PMID: 5017281.
- (Review of 36 liver biopsies of patients with phenothiazine induced liver injury from Armed Forces Institute of Pathology, 33 due to chlorpromazine and 3 to prochlorperazine hepatotoxicity; mean time to onset 15 days, eosinophilia in 73%, mean peak bilirubin 12.4 mg/dL, Alk P ~8 fold elevated, ALT 146 U/L; 6 [17%] had prolonged course for 10 to 16 months).*
- Weiden PL, Buckner CD. Thioridazine toxicity. Agranulocytosis and hepatitis with encephalopathy. *JAMA* 1973; 224: 518-20. PubMed PMID: 4739612.
- (54 year old man developed cellulitis and jaundice 7 weeks after starting thioridazine [bilirubin 7.0 mg/dL, AST 68 U/L, Alk P ~5 times ULN], with neutropenia and agranulocytosis on bone marrow biopsy; slow but complete recovery of bone marrow and liver).*
- Kristensen O. [Icterus induced by thioridazine(Melleril). Report of 1 case]. *Tidsskr Nor Laegeforen* 1975; 95: 1910-1. Norwegian. PubMed PMID: 1188902.
- (58 year old with a history of chlorpromazine hepatotoxicity developed jaundice 15 months after starting thioridazine and imiprazine [bilirubin 3.5 mg/dL, ALT 115 U/L, Alk P 1.5 times ULN], resolving upon stopping both drugs and worsening after short rechallenge with thioridazine).*
- Døssing M, Andreasen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. *Scand J Gastroenterol* 1982; 17: 205-11. PubMed PMID: 6982502.
- (Among 572 cases of drug induced liver disease seen between 1968-78 in Denmark, 51 were attributed to chlorpromazine [9%, ranking 2nd behind halothane], latency averaged 14 days [range 11-46]; 5 deaths; no mention of other phenothiazines).*
- Kaplowitz N, Aw TY, Simon FR, Stolz A. Drug-induced hepatotoxicity. *Ann Intern Med* 1986; 104: 826-39. PubMed PMID: 3518564.
- (Review of drug induced hepatotoxicity including phenothiazine jaundice).*
- Munyon WH, Salo R, Briones DF. Cytotoxic effects of neuroleptic drugs. *Psychopharmacology (Berl)* 1987; 91: 182-8. PubMed PMID: 2883697.
- (In vitro assay for cytotoxicity of 8 neuroleptic drugs found that chlorpromazine was more toxic than haloperidol or loxapine, but similar to other phenothiazines).*
- Regal RE, Bili JE, Glazer HM. Phenothiazine-induced cholestatic jaundice. *Clinical Pharmacy* 1987; 6: 787-94. PubMed PMID: 2905941.
- (Review of phenothiazine induced liver injury; cross sensitivity is rare "but does exist").*

Urberg M. Thioridazine-induced non-icteric hepatotoxicity. Report of a case. *J Fam Pract* 1990; 30: 342-3. PubMed PMID: 2307948.

*(34 year old man with 100 lb weight gain after 2 years of thioridazine therapy was thought to have “tense ascites” and “hepatic failure”, but liver tests were normal except for ALT of 46 U/L; ascites was not present 1 week later when ultrasound showed “loss of the normal internal echo architecture of the liver”).*

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years experience. *NZ Med J* 1996; 109: 315-9. PubMed PMID: 8816722.

*(Over 21 year period in New Zealand, there were 943 official reports of liver injury involving 205 drugs; chlorpromazine was in the top 20 drugs implicated accounting for 2.7% of cases; prochlorperazine was cause of 4 cases, but other phenothiazines not mentioned).*

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. *Aliment Pharmacol Ther* 2007; 25: 1401-9. PubMed PMID: 17539979.

*(Among 126 cases of drug induced liver injury seen in Spain between 1993-2000, 3 were due to chlorpromazine with relative risk of 613; and frequency of 261 per 100,000 person year exposures; no other phenothiazine discussed).*

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.

*(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to phenothiazines).*

Flanagan RJ. Fatal toxicity of drugs used in psychiatry. *Hum Psychopharmacol* 2008; 23 Suppl 1: 43-51. PubMed PMID: 18098225.

*(Deaths from fatal poisonings decreased in England and Wales between 1993-2004, antipsychotic overdose fatalities were higher for phenothiazines than atypicals; deaths/million prescriptions being 29 for chlorpromazine, 15.5 thioridazine, 3.9 trifluoperazine, 13.3 olanzapine, 21 clozapine and 31.3 quetiapine; deaths were due to respiratory depression, not acute liver failure).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 4 due to psychotropic agents; one each due to quetiapine, nefazodone, fluoxetine and venlafaxine, but none due to phenothiazines).*

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. *J Pediatr Gastroenterol Nutr* 2011; 53: 182-9. PubMed PMID: 21788760.

*(Among 30 children with suspected drug induced liver injury, half [n=15] were due to antimicrobials [minocycline 4, INH 3, azithromycin 3] and the rest largely due to CNS agents and anticonvulsants; one case was attributed to perphenazine).*