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Perphenazine

Updated: July 1, 2020.

OVERVIEW

Introduction

Perphenazine is a phenothiazine and antipsychotic agent, now rarely used in clinical practice. Perphenazine can cause mild and transient serum enzyme elevations and is a rare cause of clinically apparent acute and chronic cholestatic liver injury.

Background

Perphenazine (per fen' a zeen) is a piperazine phenothiazine derivative which acts by postsynaptic inhibition of dopamine receptors. Perphenazine has other peripheral and central nervous system effects, producing both alpha adrenergic stimulation and blocking histamine- and serotonin-mediated effects. Perphenazine is indicated for the therapy of acute and psychosis and is also used for management of nausea and vomiting. Perphenazine was approved for use in the United States in 1957 and was formerly a commonly prescribed antipsychotic, but in recent years, has been replaced in large part by the atypical antipsychotics, which have fewer extrapyramidal side effects. Perphenazine is available in generic forms as tablets of 2, 4, 8 and 16 mg and previously under the brand name of Trilafon. Oral solutions are also available. Typical doses used to treat schizophrenia are 4 to 16 mg two to three times daily, attempting to reduce the dose as soon as possible to a minimum. Common side effects include drowsiness, dizziness, headache, blurred vision, dry mouth, constipation, tremor, restlessness, muscle spasms and weight gain. Uncommon but potentially severe adverse events include increased risk of death in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension and hypersensitivity reactions.

Hepatotoxicity

Transient liver test abnormalities occur in a proportion of patients on long term therapy with perphenazine and other phenothiazines, but the elevations are usually mild, asymptomatic and reverse even with continuation of medication. Chlorpromazine, the prototype phenothiazine, is a well known cause clinically apparent acute liver injury which occurs in approximately 1% of treated patients. It is unclear whether perphenazine causes a similar syndrome, but if so, it is rare and far less common than with chlorpromazine. Case series of drug induced liver injury have occasionally listed perphenazine as a cause, but the clinical characteristics of the injury have not been described. Typical phenothiazine induced liver injury usually presents within 1 to 4 weeks of starting therapy, with a cholestatic or mixed pattern of serum enzyme elevations. Immunoallergic manifestations (fever and eosinophilia) are common but usually not prominent, and autoantibodies are rare. Phenothiazine induced jaundice can be severe and prolonged and result in vanishing bile duct syndrome, but is rarely fatal.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which perphenazine causes serum aminotransferase elevations is not known. The clinically apparent, cholestatic liver injury that occurs with many phenothiazines is likely to be due to hypersensitivity, being often accompanied by fever and eosinophilia and occurring with a shorted latency upon rechallenge. Perphenazine is extensively metabolized by the liver via sulfoxidation and oxidation, and some instances of serum aminotransferase elevations as well as more clinically 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 perphenazine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. The acute cholestatic hepatitis caused by phenothiazines is typically self-limited and benign, but should lead to prompt discontinuation. A proportion of cases are followed by prolonged jaundice and cholestasis, and many instances of vanishing bile duct syndrome have been attributed to chlorpromazine and prochlorperazine. Many patients with chronic cholestasis eventually improve, but they often have persistent enzyme elevations and biliary cirrhosis. Rechallenge usually causes a prompt recurrence of the liver injury and should be avoided. Patients with perphenazine induced liver injury may have cross sensitivity to other phenothiazines, but should tolerate the atypical antipsychotics without increased risk of liver injury.

Drug Class: Antipsychotic Agents

Other Drugs in the Subclass, Phenothiazines: Chlorpromazine, Fluphenazine, Prochlorperazine, Thioridazine, Trifluoperazine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Perphenazine – Generic, Trilafon®

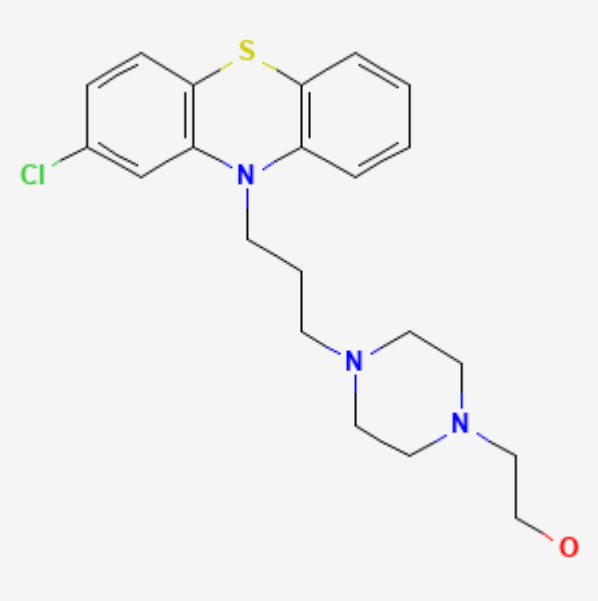
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Perphenazine	58-39-9	C21-H26-Cl-N3-O-S	

ANNOTATED BIBLIOGRAPHY

References updated: 01 July 2020

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 phenothiazines published in 1999; several hundred cases of chlorpromazine jaundice 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 liver injury, except for prochlorperazine).

Larry D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 447-62.

(Review of phenothiazine hepatotoxicity 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; prodrome of fever and abdominal pain is common; prolonged course in 7%; similar injury can be seen with other phenothiazines but much less commonly).

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

(Textbook of pharmacology and therapeutics).

Cook GC, Sherlock S. Jaundice and its relation to therapeutic agents. Lancet. 1965;1:175–9. PubMed PMID: 14238042.

(Summary of cases of drug induced liver disease seen at Royal Free Hospital from 1959-65; 11 cases of acute liver failure including 3 due to iproniazid, 2 phenelzine, 2 phenoxypropazine, 1 prochlorperazine and 3 halogenated

anesthetics; 20 cases of cholestatic hepatitis including 18 due to chlorpromazine, 1 perphenazine and 1 nitrofurantoin).

McQueen EG. Toxic effects of phenothiazine tranquillizers. N Z Med J. 1963;62:460–2. PubMed PMID: 14073060.

(Review of the phenothiazines and their side effects; "Jaundice has occurred in about 1% of patients taking chlorpromazine and also, although less frequently, in patients taking one of the more recently developed analogues").

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

(A 32 year old woman and a 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).

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 phenothiazine induced hepatotoxicity from the files of the Armed Forces Institute of Pathology; 33 due to chlorpromazine, 3 prochlorperazine; mean onset 15 days, eosinophilia in 73%, mean bilirubin 12.4 mg/dL, Alk P ~8 fold elevated, ALT 146 U/L; 6 [17%] had prolonged course for 10-16 months).

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, 54 were attributed to chlorpromazine [9%, ranking 2nd behind halothane], latency averaging 14 days [range 11-46]; 5 deaths; no other phenothiazine mentioned).

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 and 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").

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years experience. N Z 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 were not mentioned).

Gaertner I, Altendorf K, Batra A, Gaertner HJ. Relevance of liver enzyme elevations with four different neuroleptics: a retrospective review of 7,263 treatment courses. J Clin Psychopharmacol. 2001;21:215–22. PubMed PMID: 11270919.

(Retrospective review of 233 psychiatric inpatients between 1980-92; any increase in ALT in 78% of patients on clozapine, 50% haloperidol and 15% perphenazine; 3-fold increase in ALT in 15% with clozapine, 2.4% with haloperidol and 1.4% perphenazine; no elevation in alkaline phosphatase with perphenazine).

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: frequency of 261 per 100,000 person year exposures; no other phenothiazine mentioned).

Kane JM, Meltzer HY, Carson WH Jr, McQuade RD, Marcus RN, Sanchez R; Aripiprazole Study Group. Aripiprazole for treatment-resistant schizophrenia: results of a multicenter, randomized, double-blind, comparison study versus perphenazine. J Clin Psychiatry. 2007;68:213–23. PubMed PMID: 17335319.

(Controlled trial of aripiprazole vs perphenazine in 416 adults with treatment resistant schizophrenia; the "incidence of potentially clinically significant laboratory abnormalities during the study was low" and there was no mention of ALT elevations or hepatotoxicity).

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 due to phenothiazines).

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 for quetiapine, nefazodone, fluoxetine and venlafaxine, but none for 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).

Drugs for psychiatric disorders. Treat Guidel Med Lett. 2013;11(130):53–64. PubMed PMID: 23715100.

(Concise review and recommendations on use of antidepressants and antipsychotic medications including perphenazine; no discussion of hepatotoxicity).

Marwick KF, Taylor M, Walker SW. Antipsychotics and abnormal liver function tests: systematic review. Clin Neuropharmacol. 2012;35:244–53. PubMed PMID: 22986798.

(Systematic review of the literature found rates of any serum enzyme elevation during antipsychotic therapy to range from 5-78% and "clinically significant' elevations in 0-15%; does not list perphenazine).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, only one of which was attributed to chlorpromazine, the only antipsychotic medication listed).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 5 cases [0.6%] were attributed to antipsychotic agents, including 3 due to quetiapine and 2 to olanzapine, but none to perphenazine or other phenothiazines]).

Drugs for psychotic disorders. Med Lett Drugs Ther. 2016;58(1510):160–4. PubMed PMID: 27960194.

(Concise review of medications available in the US for therapy of psychotic disorders; mentions that the phenothiazines commonly cause sedation, postural hypotension and weight gain and often have extrapyramidal effects, but does not mention ALT elevations or hepatotoxicity).

Schreiner NM, Windham S, Barker A. Atypical neuroleptic malignant syndrome: diagnosis and proposal for an expanded treatment algorithm: a case report. A A Case Rep. 2017;9:339–43. PubMed PMID: 28767476.

(48 year old man with bipolar disorder and NASH underwent liver transplantation and developed confusion, dyskinesia, rigidity, hyperthermia and tachycardia/tachypnea postoperatively having been given lithium, lamotrigine, promethazine and ziprasidone, responding to therapy of neuroleptic malignant syndrome with benzodiazepines and propofol).

Baeza I, de la Serna E, Calvo-Escalona R, Merchán-Naranjo J, Rodríguez-Latorre P, Martínez-Cantarero MC, Andrés P, et al. One-year prospective study of liver function tests in children and adolescents on second-generation antipsychotics: is there a link with metabolic syndrome? J Child Adolesc Psychopharmacol. 2018;28:463–73. PubMed PMID: 29975563.

(Among 216 children and adolescents starting atypical antipsychotics, mean weight gain at 6 months was 6.5 kg and mean ALT levels increased by 8.6 U/L, while among 37 taking olanzapine mean weight gain was 10.3 kg and ALT increase 2.6 U/L, increases in ALT associated with development of the metabolic syndrome, mean ALT increasing by 27.8 U/L at 6 months).