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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Wilson Disease Agents. [Updated 2020 Jul 25].
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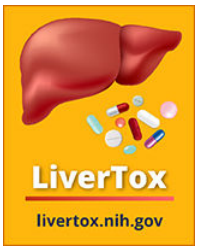

Wilson Disease Agents

Updated: July 25, 2020.

OVERVIEW

Wilson disease is an inherited abnormality of copper metabolism that leads to excess copper accumulation and injury to liver, brain and other organs. The metabolic defect in Wilson disease is caused by mutations in ATPase7B, a hepatic enzyme responsible for transmembrane transport and excretion of copper into the bile. The metabolic defect leads to accumulation of free copper in liver and blood and secondarily in other organs, particularly brain and kidney. The disease usually presents in childhood or adolescence with neurologic syndromes, signs of advanced liver disease and hemolytic anemia. If untreated it is invariably fatal, death being from progressive neurologic disease or acute or chronic liver failure. Therapy of Wilson disease is usually based upon copper chelation, but limitation of copper in the diet and approaches to inhibiting copper absorption can also be important.

Copper chelating agents available in the United States include penicillamine, trientine and dimercaprol. These agents lower blood and tissue copper levels and, when given chronically, prevent copper accumulation and injury in Wilson disease. Penicillamine is considered the first line therapy of Wilson disease, but is often limited by its unique side effects that can be severe and may be dose limiting. Trientine is a second line agent and is less effective than penicillamine in chelating copper, but it has fewer serious side effects and is generally well tolerated. Both of these agents are given orally. Dimercaprol (also known as British anti-Lewisite or BAL) was the initial copper chelating agent developed for Wilson disease, but it requires parenteral administration and has frequent serious adverse effects. Dimercaprol is currently rarely used for Wilson disease and generally only in conjunction with oral copper chelating agents, for a short period of time, and in patients with severe symptomatic disease. Zinc is also useful in managing Wilson disease and acts by inhibition of copper absorption, rather than chelation of excess copper in tissue or the circulation. Zinc has been used as a first line therapy, but is currently recommended largely as maintenance therapy once chelation of excess copper has been accomplished.

Among the drugs used for Wilson disease, only penicillamine has been linked to cases of clinically apparent liver injury. Penicillamine has been linked to cases of acute, immunoallergic hepatitis which is likely due to hypersensitivity.

Information on the mechanism of action, clinical use and potential hepatotoxicity of the agents used to treat Wilson disease are given in the individual drug records for each of the following:

- Dimercaprol
- Penicillamine
- Trientine
- Zinc

ANNOTATED BIBLIOGRAPHY

References updated: 25 July 2020

Byrns MC, Penning TM. Treatment of metal exposure. Environmental toxicology: carcinogens and heavy metals. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1311-5.

(Textbook of pharmacology and therapeutics).

Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. Am J Med. 1956;21:487–95. PubMed PMID: 13362281.

(Initial studies on efficacy of oral penicillamine [β,β-dimethyl cysteine, a monothiol] in inducing cupruresis in Wilson disease and lack of effect of cysteine and methionine; no toxic reactions were observed).

Sternlieb I, Scheinberg IH. Prevention of Wilson's disease in asymptomatic patients. N Engl J Med. 1968;278:352–9. PubMed PMID: 5635646.

(Among 42 asymptomatic persons who were diagnosed with Wilson disease and treated with penicillamine for up to 8 years, none developed symptomatic disease).

Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet. 1982;1(8273):643–7. PubMed PMID: 6121964.

(Among 20 patients with Wilson disease who were intolerant of penicillamine therapy, all responded to trientine therapy, although complications of penicillamine [lupus syndrome, elastosis perforans] did not always improve; no evidence of toxicity including hepatotoxicity).

Hoogenraad TU, Van den Hamer CJ. 3 years of continuous oral zinc therapy in 4 patients with Wilson's disease. Acta Neurol Scand. 1983;67:356–64. PubMed PMID: 6613522.

(4 patients [17 to 46 year old men] with Wilson disease previously treated with penicillamine were treated with oral zinc for at least 3 years and all showed clinical improvement and no adverse events, including no changes in liver tests during zinc therapy).

Brewer GJ, Hill GM, Prasad AS, Cossck ZT, Rabbani P. Oral zinc therapy for Wilson's disease. Ann Intern Med. 1983;99:314–9. PubMed PMID: 6614680.

(5 patients [25 to 34 years old, 3 men, 2 women] with stable Wilson disease after penicillamine therapy underwent careful copper balance studies while on zinc therapy alone, demonstrating a negative copper balance largely due to increased fecal loss).

Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med. 1998;132:264–78. PubMed PMID: 9794697.

(Description of patterns of change in urinary, hepatic and serum copper and zinc levels and liver tests in 141 patients with Wilson disease treated with zinc; adverse reactions were "minimal", the most common being initial abdominal discomfort).

Vilensky JA, Redman K. British anti-Lewisite (dimercaprol): an amazing history. Ann Emerg Med. 2003;41:378–83. PubMed PMID: 12605205.

(History of development and use of dimercaprol, initially synthesized at Oxford during WWII as a means of reversing Lewisite arsenical gas poisoning [thus British anti-Lewisite (BAL)] and now still used for emergency therapy of heavy metal poisoning: arsenic, gold, copper and mercury).

Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet. 2007;369(9559):397–408. PubMed PMID: 17276780.

(Review of the clinical features, pathogenesis, genetics, diagnosis and treatment).

Roberts EA, Schilsky ML. AASLD. Diagnosis and treatment of Wilson disease: an update. Hepatology. 2008;47:2089–111. PubMed PMID: 18506894.

(Thorough review of the cause, natural history, diagnosis and treatment of Wilson disease with specific recommendations for use of penicillamine, trientine and zinc).

Walshe JM. The conquest of Wilson's disease. Brain. 2009;132(Pt 8):2289–95. PubMed PMID: 19596747.

(History of the initial description of Wilson disease, its link to copper accumulation, and therapies several of which were developed by the author).

Weiss KH, Stremmel W. Evolving perspectives in Wilson disease diagnosis: treatment and monitoring. Curr Gastroenterol Rep. 2012;14:1–7. PubMed PMID: 22083169.

(Review of the diagnosis and management of Wilson disease, including the role of genetic testing and the choice of medical therapies).

Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, Merle U, et al. EUROWILSON Consortium. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. Clin Gastroenterol Hepatol. 2013;11:1028–35.e1. PubMed PMID: 23542331.

(Among 467 patients with Wilson followed in a retrospective, multicenter study for an average of 13 years, penicillamine and trientine appeared to be equally effective in reversing the liver disease, and while penicillamine had lower rates of neurological worsening [2% vs 11%], it had higher rates of discontinuations due to adverse reactions [29% vs 7%]; there were no deaths from adverse reactions and no mention of hepatotoxicity).

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, none of which was attributed to an agent used to treat Wilson disease).

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, one case was attributed to penicillamine [cholestatic hepatitis in a woman with scleroderma], but none were attributed to drugs being used for Wilson disease).

Pfeiffenberger J, Beinhardt S, Gotthardt DN, Haag N, Freissmuth C, Reuner U, Gauss A, et al. Pregnancy in Wilson's disease: management and outcome. Hepatology. 2018;67:1261–9. PubMed PMID: 28859232.

(Among 282 pregnancies in 136 patients with Wilson disease analyzed in a retrospective, multicenter study, spontaneous abortion was less common among patients being treated with penicillamine [17%] or zinc [10%] than untreated patients [41%], which was proportionally greater than with trientine [28%] and similar to that in patients who discontinued therapy during pregnancy [36%]; worsening of liver disease arose in some patients on treatment but was self-limiting and resolved after delivery; birth defects were found in 7 of 209 [3%] newborns and did not vary with chelator use or appear to be drug related, suggesting that chelation therapy should be continued during pregnancy).

Roberts EA. Update on the diagnosis and management of Wilson disease. Curr Gastroenterol Rep. 2018;20:56. PubMed PMID: 30397835.

(Review of recent advances in the understanding of the pathogenesis, clinical features, diagnosis, and treatment of Wilson disease).