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Tolcapone

Updated: July 20, 2017.

OVERVIEW

Introduction

Tolcapone is a catechol-O-methyltransferase inhibitor used in the therapy of Parkinson disease as adjunctive therapy in combination with levodopa and carbidopa. Tolcapone has been associated with serum enzyme elevations during treatment and with several instances of clinically apparent acute liver injury, which can be severe and even fatal.

Background

Tolcapone (tol' ka pone) is a specific inhibitor of cathechol-O-methyltransferase (COMT), which is a major enzyme in the pathway of levodopa metabolism. As a result, tolcapone slows the metabolism of levodopa and results in an increase in its bioavailability and duration of action. Tolcapone inhibits COMT activity both peripherally and in the central nervous system. Tolcapone was approved for use in the United States in 1998 for the therapy of symptomatic Parkinson disease as an adjunct to levodopa/carbidopa therapy in patients with motor complications. it was subsequently withdrawn after several instances of acute liver failure were attributed to its use. Subsequent tolcapone was reintroduced, but with requirements for monitoring of serum enzymes. Tolcapone is currently available in tablets of 100 and 200 mg under the brand name of Tasmar. Tolcapone is typically initiated in doses of 100 mg three times daily, with adjustment upwards based upon tolerance and clinical effects to a maximum of 600 mg daily. Common side effects include somnolence, dizziness, confusion, dyskinesia, vivid dreams, hallucinations, depression, fatigue, headache, diarrhea and gastrointestinal upset, symptoms that are typical of dopaminergic stimulation and enhanced effects of levodopa.

Hepatotoxicity

Tolcapone has been reported to cause serum aminotransferase elevations above 3 times the upper limit of normal in 1% to 5% of patients. While these abnormalities are usually asymptomatic and self-limiting, some persist if therapy is continued and resolved only with stopping tolcapone. More importantly, tolcapone has been implicated in several cases of severe, clinically apparent acute liver injury and at least three cases of death from acute liver failure. The onset of injury was insidious, arising 1 to 5 months after starting treatment. The pattern of serum enzyme elevations was hepatocellular and the clinical phenotype was acute viral hepatitis-like. Immunoallergic manifestations were not present, but some patients had autoantibodies of unclear significance. Because of these reports, regular monitoring of serum aminotransferase levels has been mandated (every 2 to 4 weeks for the first 6 months of treatment and as clinically indicated thereafter) during tolcapone therapy, and treatment should be promptly discontinued if ALT or AST levels rise above twice the upper limit of the normal range or if signs or symptoms of liver injury are present.

Likelihood score: C (probable cause of clinically apparent liver injury).

Mechanism of Injury

Tolcapone is metabolized extensively in the liver and undergoes glucuronidation prior to excretion. The hepatotoxicity of tolcapone is likely due to production of a toxic intermediate that overwhelms the usual protective mechanisms of excretion. Increased likelihood of hepatic injury due to tolcapone has been linked to variants of the gene that is responsible for glucuronidation, UDP-glucuronosyl transferase.

Outcome and Management

Liver injury caused by tolcapone ranges from mild, transient and asymptomatic serum enzyme elevations to clinically apparent hepatitis and acute liver failure. Tolcapone therapy has not been associated with chronic hepatitis or vanishing bile duct syndrome. Therapy of acute liver failure due to medications is largely supportive, but infusions of n-acetyl cysteine may be beneficial if given early. In at least one case report of acute liver failure due to tolcapone, autoimmune features led to the use of corticosteroids which appeared to be beneficial. Because of the propensity for tolcapone to cause acute liver failure, routine testing for serum aminotransferase levels should be done every 2 to 4 weeks for 6 months after initiation of therapy and as clinically indicated thereafter. Tolcapone should be discontinued if ALT or AST levels rise above twice the upper limit of the normal range or if any signs and symptoms suggestive of liver injury appear. There does not appear to be cross sensitivity to hepatic injury between tolcapone and entacapone, a COMT inhibitor with a similar chemical structure.

Drug Class: Antiparkinson Agents

Other Drugs in the Subclass, COMT Inhibitors: Entacapone

CASE REPORT

Case 1. Acute liver failure attributed to tolcapone.

[Modified from: Spahr L, Rubbia-Brandt L, Burkhard PR, Assal F, Hadengue A. Tolcapone-related fulminant hepatitis: electron microscopy shows mitochondrial alterations. Dig Dis Sci 2000; 45: 1881-4. PubMed Citation]

A 74 year old woman with Parkinson disease developed jaundice 8 weeks after being switched from amantadine to tolcapone (100 mg twice daily), because of motor fluctuations during long term levodopa therapy. She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. She had suffered from Parkinson disease for more than 15 years and was maintained on levodopa and benserazide (25 mg three times daily: a decarboxylase inhibitor similar to carbidopa). Other medications included etilefrine (30 mg daily: an oral adrenergic sympathomimetic amine) for orthostatic hypotension, amiloride (2.5 mg) combined with hydrochlorothiazine (25 mg) twice weekly for edema, and oxazepam (15 mg) at bedtime for sleep, all of these medications having been taken chronically. She had normal liver test results on several occasions in the past while taking these medications. On presentation with jaundice, she was confused and was considered to have stage 2 hepatic encephalopathy. Her resting tremor, akinesia and rigidity were unchanged from before. Laboratory test results showed bilirubin elevations (total 21.5 mg/dL) and marked increases in serum aminotransferase levels (ALT 2904 U/L, AST 2541 U/L), with minimal abnormality in alkaline phosphatase levels (177 U/L) (Table). The prothrombin time was prolonged (21 seconds; INR 1.7) and ammonia levels were elevated (102 μmol/L). Tests for hepatitis A, B and C were negative and abdominal ultrasound showed no evidence of biliary obstruction or tumor. A transjugular liver biopsy showed large areas of parenchymal collapse that was predominantly centrolobular (zone 3) and accompanied by dense infiltration with chronic inflammatory cells (including eosinophils). There was marked cholestasis, but normal numbers of uninjured bile ducts. There was no fibrosis. The hepatic venous pressure gradient was 7.5 mm Hg (normal <6). Tolcapone was

discontinued on admission, but she continued to deteriorate with steadily rising bilirubin levels and worsening consciousness, and she died 13 days later.

Key Points

Medication:	Tolcapone (200 mg daily)
Pattern:	Hepatocellular (R=~80)
Severity:	5+ (death within 2 weeks from acute liver failure)
Latency:	2 months
Recovery:	None
Other medications:	Levodopa, benserazide, etilefride, amiloride/hydrochlorothiazide, oxazepam

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
-1 year		21			1 year before starting
2 months	0	2904	117	21.4	Admission
	1 day	2810		24.8	Liver biopsy
	2 days	2625		29.8	Worsening coma
	3 days	2710		39.2	
	4 days	2150		35.4	
	5 days	2275		42.4	
	6 days	1905		35.6	
	7 days	1930		40.9	
	8 days	1783			
2.5 months	2 weeks	Patient died of hepatic failure			
Normal Values		**<36**	**<125**	**<1.2**	

* Some values estimated from Figure 2.

Comment

This was the first case report in the literature of acute liver failure attributed to tolcapone. The case was published initially as a letter to the editor (Assal: 1998), then as a full case report with details of hepatic histology (Spahr: 2000), and then summarized with 3 other cases of acute liver failure in support of guidelines for monitoring patients on tolcapone (Olanow: 2000). The timing of onset, severe hepatocellular injury and exclusion of other causes of acute liver disease supported the diagnosis of tolcapone induced acute liver injury. Subsequently, routine monitoring for serum enzyme levels during tolcapone therapy was not only recommended, but mandated by the US Food and Drug Administration and no further cases of acute liver failure have been published. However, the concern over hepatotoxicity and the requirement for monitoring has led to a limited use of this medication. Because it appears to be more effective than other COMT inhibitors and can have a beneficial effect in advanced Parkinson disease, it has been reintroduced with strict guidelines for monitoring.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tolcapone – Generic, Tasmar®

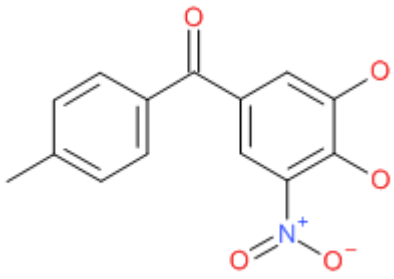
DRUG CLASS

Antiparkinson Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tolcapone	134308-13-7	C14-H11-N-O5	

REFERENCES

References updated: 20 July 2017

Zimmerman HJ. Antiparkinsonism drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 715-7.

(Expert review of hepatotoxicity published in 1999; among anticholinergic agents, "only trihexyphenidyl has been incriminated in hepatic injury"; other antiparkinsonism drugs discussed include levodopa, lergotrile [no longer available], pergolide and bromocriptine, but not tolcapone).

Larrey 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 Inc, 2013, pp. 443-62.

(Review of hepatotoxicity of agents acting on the central nervous system).

Standaert DG, Roberson ED. Treatment of central nervous system degenerative disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 609-28.

(Textbook of pharmacology and therapeutics).

Waters CH, Kurth M, Bailey P, Shulman LM, LeWitt P, Dorflinger E, Deptula D, S. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. Tolcapone Stable Study Group. Neurology 1998 May; 50 (5 Suppl 5): S39-45. *(Among 298 patients with stable Parkinson* PubMed PMID: 9591521.

disease treated with levodopa and either tolcapone [n=196] or placebo [n=102], ALT abnormalities occurred in 3-5% of tolcapone treated patients between month 1 and 6 of therapy, 4 were withdrawn and recovered; abnormalities resolved in another 4 despite continuing on therapy).

Hauser RA, Molho E, Shale H, Pedder S, Dorflinger EE. A pilot evaluation of the tolerability, safety, and efficacy of tolcapone alone and in combination with oral selegiline in untreated Parkinson's disease patients. Tolcapone De Novo Study Group. Mov Disord 1998; 13: 643-7. PubMed PMID: 9686768.

(Among 83 patients with Parkinson disease treated with tolcapone with or without selegiline for 8 weeks, ALT elevations occurred in 1 patient [2%] on tolcapone alone).

Tolcapone for Parkinson's disease. Med Let Drugs Ther 1998; 40: 60-1. PubMed PMID: 9629124.

(Concise summary of clinical efficacy and safety of tolcapone shortly after its approval in the US; common side effects were diarrhea, increase in levodopa related [dopaminergic] side effects and serum ALT elevations).

Assal F, Spahr L, Hadengue A, Rubbia-Brandt L, Burkhard PR. Tolcapone and fulminant hepatitis. Lancet 1998; 352: 958. PubMed PMID: 9752821.

(74 year old woman with Parkinson disease developed jaundice 9 weeks after starting tolcapone [bilirubin 17.1 mg/dL, ALT 2904 U/L, Alk P 177 U/L, protime 21 sec], progressing to hepatic failure and death 2 weeks later).

Rivest J, Barclay CL, Suchowersky O. COMT inhibitors in Parkinson's disease. Can J Neurol Sci 1999; 26 Suppl 2: S34-8. PubMed PMID: 10451758.

(Review of efficacy and safety of tolcapone and entacapone in Parkinson disease; ALT elevations above 3 times the ULN occurred in 2-5% of tolcapone, but in no entacapone recipients; reports of 3 cases of acute liver failure due to tolcapone led to its withdrawal in several countries).

Kaakkola S. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. Drugs 2000; 59: 1233-50. PubMed PMID: 10882160.

(Review of the mechanism of action, pharmacology, efficacy and side effects of tolcapone and entacapone; both enhance dopaminergic effects of levodopa and diarrhea is a frequent dose modifying side effect; hepatotoxicity occurs with tolcapone, but has not been reported with entacapone).

Lambert D, Waters CH. Comparative tolerability of the newer generation antiparkinsonian agents. Drugs Aging 2000; 16: 55-65. PubMed PMID: 10733264.

(Review of mechanism of action, tolerability and safety of selegiline, pramipexole, ropinirole, tolcapone and entacapone in Parkinson disease).

Olanow CW. Tolcapone and hepatotoxic effects. Tasmar Advisory Panel Arch Neurol 2000; 57: 263-7. PubMed PMID: 10681087.

(Consensus recommendations for monitoring patients on tolcapone after 4 reports of acute liver failure; among 1535 patients treated in phase III studies, ALT or AST elevations [>3 times ULN] occurred in 1.3-3.7% of patients, returning to normal when discontinued and one woman developed jaundice and died; postmarketing reports included 4 patients, ages 66-74, with onset of symptoms and jaundice after 2-4 months, [bilirubin 6.9-26.1 mg/dL, ALT 1245-5020 U/L, Alk P 66-347 U/L], 3 died within 1-2 weeks of presentation).

Spahr L, Rubbia-Brandt L, Burkhard PR, Assal F, Hadengue A. Tolcapone-related fulminant hepatitis: electron microscopy shows mitochondrial alterations. Dig Dis Sci 2000; 45: 1881-4. PubMed PMID: 11052337.

(Histologic analysis of patient with acute liver failure due to tolcapone [Assal 1988], showed multilobular collapse, inflammatory infiltrates including eosinophils, cholestasis, and focal microvescular steatosis; electron microscopy suggested mitochondrial injury: Case 1).

Watkins P. COMT inhibitors and liver toxicity. Neurology 2000; 55 (11 Suppl 4): S51-2; discussion S53-6. PubMed PMID: 11147510.

(Review of hepatotoxicity of tolcapone and entacapone suggesting that liver injury is not a class effect and that there have been no reports of jaundice attributed to entacapone).

Entacapone for Parkinson's disease. Med Let Drugs Ther 2000; 42: 7-8. PubMed PMID: 10696231.

(Concise summary of clinical efficacy and safety of entacapone shortly after its approval in the US; common side effects were diarrhea, increase in levodopa related side effects, but no reported hepatotoxicity as occurs with tolcapone).

Blum MW, Siegel AM, Meier R, Hess K. Neuroleptic malignant-like syndrome and acute hepatitis during tolcapone and clozapine medication. Eur Neurol 2001; 46: 158-60. PubMed PMID: 11598337.

(70 year old woman developed stupor, rigidity and hyperthermia with increases in CPK [3132 U/L] and ALT [988 U/L], but not bilirubin or alkaline phosphatase while on the combination of tolcapone and clozapine, resolving rapidly on stopping therapy; compatible with neuroleptic malignant-like syndrome).

Myllylä VV, Kultalahti ER, Haapaniemi H, Leinonen M; FILOMEN Study Group. Twelve-month safety of entacapone in patients with Parkinson's disease. Eur J Neurol 2001; 8: 53-60. PubMed PMID: 11509081.

(Among 326 patients with Parkinson disease treated with entacapone or placebo, ALT elevations occurred in 6.9% on drug vs 4.6% on placebo and were above 3 times ULN in 0.9% vs 0.0%; no patient developed clinically apparent liver injury that could be attributed to entacapone).

Acuña G, Foernzler D, Leong D, Rabbia M, Smit R, Dorflinger E, Gasser R, et al. Pharmacogenetic analysis of adverse drug effect reveals genetic variant for susceptibility to liver toxicity. Pharmacogenomics J 2002; 2: 327-34. PubMed PMID: 12439739.

(DNA genotyping of 30 single nucleotide polymorphisms in 135 patients who had liver enzyme elevations during tolcapone therapy and controls found variants within the UDP-glucuronsyl transferase gene that were associated with liver injury).

Fisher A, Croft-Baker J, Davis M, Purcell P, McLean AJ. Entacapone-induced hepatotoxicity and hepatic dysfunction. Mov Disord 2002; 17: 1362-5. PubMed PMID: 12465084.

(Three cases of clinically apparent liver injury attributed to entacapone use; 74 year old woman developed nausea and fatigue 2 weeks after adding entacapone to a regimen of levodopa/benserazide for Parkinson disease [bilirubin 2.4 mg/dL, ALT 104 U/L, Alk P 238 U/L], with rapid improvement on stopping; 2 other cases were reported to Australian Drug Reaction Database with only partial documentation, arising 5 and 6 weeks after starting entacapone, with cholestatic liver enzyme elevations and mild jaundice).

Benabou R, Waters C. Hepatotoxic profile of catechol-O-methyltransferase inhibitors in Parkinson's disease. Expert Opin Drug Saf 2003; 2: 263-7. PubMed PMID: 12904105.

(Review of hepatotoxicity of tolcapone and entacapone).

Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. Drug Saf 2003; 26: 743-7. PubMed PMID: 12908845.

(Review of hepatotoxicity of tolcapone and possible mechanisms).

Brooks DJ. Safety and tolerability of COMT inhibitors. Neurology 2004; 62 (1 Suppl 1): S39-46. PubMed PMID: 14718679.

(Review of safety and side effects of entacapone; in phase III trials ALT elevations >3 times ULN occurred in 0.3-0.5% of patients taking entacapone and 0.4% on placebo, and there were no cases of jaundice or clinically apparent liver injury among ~1600 entacapone treated patients).

Deane KH, Spieker S, Clarke CE. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev 2004; (4): CD004554. PubMed PMID: 15495119.

(Systematic review of efficacy of tolcapone and entacapone; ALT elevations reported in variable proportions of patients on tolcapone).

Levodopa + carbidopa + entacapone. Entacapone: a second look: new preparations. Parkinson's disease: a modest effect. Prescrire Int 2005; 14: 51-4. PubMed PMID: 15875340.

(Review of risks and benefits of a fixed dose combination of levodopa, carbidopa and entacapone mentions that entacapone may cause cholestatic hepatitis and that is has not been shown to be more effective than bromocriptine).

Borges N. Tolcapone in Parkinson's disease: liver toxicity and clinical efficacy. Expert Opin Drug Saf 2005; 4: 69-73. PubMed PMID: 15709899.

(Review of hepatotoxicity of tolcapone and its possible mechanisms).

Korri H, Awada A. [Serious tolcapone-induced hepatitis 17 months after commencing treatment]. Rev Neurol (Paris) 2005; 161: 1113-5. French. PubMed PMID: 16288178.

(61 year old man with Parkinson disease developed jaundice and fever 17 months after starting tolcapone [bilirubin 3.1 mg/dL, ALT 399 U/L, Alk P 115 U/L], resolving upon stopping).

Martignoni E, Cosentino M, Ferrari M, Porta G, Mattarucchi E, Marino F, Lecchini S, et al. Two patients with COMT inhibitor-induced hepatic dysfunction and UGT1A9 genetic polymorphism. Neurology 2005; 65: 1820-2. PubMed PMID: 16344532.

*(Two patients who had ALT elevations [78 and 284 U/L] during tolcapone therapy, one of whom had similar elevations during entacapone treatment; both had the A(T)$_9$AT sequence [1A9*1] in the promoter of the UGT1A9 gene).*

Tolcapone: new drug. In Parkinson's disease: unacceptable risk of severe hepatitis. Prescrire Int 2006; 15: 54-7. PubMed PMID: 16604736.

(Review of tolcapone as adjunctive therapy in Parkinson disease suggests that the hepatotoxicity risk makes it an unacceptable option).

Leegwater-Kim J, Waters C. Tolcapone in the management of Parkinson's disease. Expert Opin Pharmacother 2006; 7: 2263-70. PubMed PMID: 17059382.

(Review on use of tolcapone in Parkinson disease suggesting that with proper monitoring, the potential for hepatotoxicity is "negligibly small").

Stocchi F, De Pandis MF. Utility of tolcapone in fluctuating Parkinson's disease. Clin Interv Aging 2006; 1: 317-25. PubMed PMID: 18046910.

(Review of role of tolcapone in treatment of Parkinson disease, indicating its efficacy in patients with fluctuating symptoms and its safety with proper monitoring of serum enzymes).

Entacapone to Tolcapone Switch Study Investigators. Entacapone to tolcapone switch: Multicenter double-blind, randomized, active-controlled trial in advanced Parkinson's disease. Mov Disord 2007; 22: 14-9. PubMed PMID: 17089403.

(Randomized controlled trial of replacing entacapone with tolcapone in patients with Parkinson disease and motor fluctuations on long term levodopa therapy; ALT elevations occurred in 3% on entacapone and 9% on tolcapone, but were mild and self-limiting).

Leegwater-Kim J, Waters C. Role of tolcapone in the treatment of Parkinson's disease. Expert Rev Neurother 2007; 7: 1649-57. PubMed PMID: 18052761.

(Review of the pharmacology, metabolism, clinical efficacy and safety of tolcapone, indicating that the risk of hepatotoxicity "is very small if proper hepatic monitoring guidelines are followed").

Lees AJ, Ratziu V, Tolosa E, Oertel WH. Safety and tolerability of adjunctive tolcapone treatment in patients with early Parkinson's disease. J Neurol Neurosurg Psychiatry 2007; 78: 944-8. PubMed PMID: 17098835.

(Controlled trial of tolcapone vs placebo combined with levodopa and carbidopa in 677 patients with early Parkinson disease; ALT or AST elevations occurred in 20% of placebo- vs 27% of tolcapone treated patients and were >3 times ULN in 1.2% [placebo] vs 1.8% [tolcapone], almost all during first 6 months; 1% of tolcapone treated patients stopped because of ALT elevations, but none developed jaundice or clinically apparent liver injury).

Lew MF, Kricorian G. Results from a 2-year centralized tolcapone liver enzyme monitoring program. Clin Neuropharmacol 2007; 30: 281-6. PubMed PMID: 17909306.

(Centralized testing for ALT and AST in 1725 patients with Parkinson disease treated with tolcapone for up to 2 years; 69 [3.9%] had at least one elevation, but <1% had an elevation above 2 times the ULN and most returned to normal despite continuing therapy).

Entacapone: hepatitis (continued). The risk of liver damage is being confirmed. It is better not to expose parkinsonian patients to this drug. Prescrire Int 2008; 17: 113-4. PubMed PMID: 18630358.

(Commentary mentions that the European Medicines Agency has reported 29 cases of hepatic disorders linked to entacapone).

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 injury in the US collected between 2004 and 2008, none were due to drugs used for Parkinson disease).

Canesi M, Zecchinelli AL, Pezzoli G, Antonini A. Clinical experience of tolcapone in advanced Parkinson's disease. Neurol Sci 2008; 29 Suppl 5: S380-2. PubMed PMID: 19381768.

(Among 66 patients with advanced Parkinson disease treated with tolcapone, 2 [3%] were withdrawn from therapy because of ALT elevations).

Brooks DJ, Leinonen M, Kuoppamäki M, Nissinen H. Five-year efficacy and safety of levodopa/DDCI and entacapone in patients with Parkinson's disease. J Neural Transm 2008; 115: 843-9. PubMed PMID: 18259682.

(Retrospective, pooled analysis of 5 controlled trials with 5 year extension phases that included 806 patients with Parkinson disease treated with entacapone added to levodopa/carbodopa; there were "few clinically significant changes in liver function tests" and none of the 478 serious adverse events that were reported were due to hepatotoxicity).

Ebersbach G, Storch A. Tolcapone in elderly patients with Parkinson's disease: a prospective open-label multicenter non-interventional trial. Arch Gerontol Geriatr 2009; 49: e40-4. PubMed PMID: 18835049.

(Among 237 patients with advanced Parkinson disease treated with tolcapone, diarrhea was the most common side effect [3.4%], ALT or AST elevations occurred in 18%, but were mostly mild and "not clinically significant").

McBurney RN, Hines WM, Von Tungeln LS, Schnackenberg LK, Beger RD, Moland CL, Han T, et al. The liver toxicity biomarker study: phase I design and preliminary results. Toxicol Pathol 2009; 37: 52-64. PubMed PMID: 19171931.

(Design and early results of a comprehensive study of rats given 28 days of entacapone or tolcapone as examples of two related agents, one of which causes liver injury in man and one which does not, assessing liver enzymes, histology, gene transcription, proteomics, metabolomics and possible biomarkers to identify predictors of idiosyncratic liver injury in humans).

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 but none were attributed to agents used for Parkinson disease).

Fischer JJ, Michaelis S, Schrey AK, Graebner OG, Glinski M, Dreger M, Kroll F, et al. Capture compound mass spectrometry sheds light on the molecular mechanisms of liver toxicity of two Parkinson drugs. Toxicol Sci 2010; 113: 243-53. PubMed PMID: 19783845.

(In vitro study of binding of tolcapone and entacapone to other proteins; unlike entacapone, tolcapone interacted with a number of non-COMT intracellular proteins which are involved in the respiratory chain actions, fatty acid beta-oxidation and bile acid synthesis, perhaps accounting for its potential for hepatotoxicity).

Haasio K. Toxicology and safety of COMT inhibitors. Int Rev Neurobiol 2010; 95: 163-89. PubMed PMID: 21095462.

(Extensive review of the mechanism of hepatic injury from tolcapone; "at the moment there is no explanation to the hepatotoxicity appeared in clinical use").

Marsala SZ, Gioulis M, Ceravolo R, Tinazzi M. A systematic review of catechol-0-methyltransferase inhibitors: efficacy and safety in clinical practice. Clin Neuropharmacol 2012; 35: 185-90. PubMed PMID: 22805229.

(Systematic review of literature on safety and efficacy of tolcapone and entacapone recommends use of tolcapone only if entacapone treatment fails and liver tests are normal).

McBurney RN, Hines WM, VonTungeln LS, Schnackenberg LK, Beger RD, Moland CL, Han T, et al. The liver toxicity biomarker study phase I: markers for the effects of tolcapone or entacapone. Toxicol Pathol 2012; 40: 951-64. PubMed PMID: 22573522.

(Comparison of the molecular effects of tolcapone vs entacapone on rat liver and plasma biomarkers found that changes from the two drugs only partially overlapped and different effects were present at 3 and 28 days, suggesting that some of these "off-target" and specific effects of tolcapone may account for its occasional hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25,1425. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 were attributed to an agent used to treat Parkinson disease).

Drugs for Parkinson's disease. Treat Guidel Med Lett 2013; 11 (135): 101-6. PubMed PMID: 24165688.

(Concise review of recommendations for therapy of Parkinson disease with description of mechanisms of action, efficacy and adverse events).

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.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to an agent to treat Parkinson disease).

Eggert K, Oertel WH, Lees AJ; German Competence Network on Parkinson's disease. Safety and efficacy of tolcapone in the long-term use in Parkinson disease: an observational study. Clin Neuropharmacol 2014; 37: 1-5. PubMed PMID: 24434524.

(Among 391 patients with Parkinson disease treated with tolcapone in an observation study conducted at 48 neurologic centers and followed for one year, 34 [8.7%] developed liver enzyme elevation, usually within the first 3 months, which were above twice ULN in only 5 [1.3%] and resolved spontaneously in most; no patient developed clinically apparent liver injury).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, none were attributed to an agent used to treat Parkinson disease).

Longo DM, Yang Y, Watkins PB, Howell BA, Siler SQ. Elucidating differences in the hepatotoxic potential of tolcapone and entacapone with DILIsym(®), a mechanistic model of drug-induced liver injury. CPT Pharmacometrics Syst Pharmacol 2016; 5 (1): 31-9. PubMed PMID: 26844013.

(Description of mechanistic simulation models of the metabolism and toxicity of tolcapone and entacapone which predicted their differential hepatotoxicity).

Lv X, Wang XX, Hou J, Fang ZZ, Wu JJ, Cao YF, Liu SW, et al. Comparison of the inhibitory effects of tolcapone and entacapone against human UDP-glucuronosyl-transferases. Toxicol Appl Pharmacol 2016; 301: 42-9. PubMed PMID: 27089846.

(Comparison of the inhibitory effects of tolacapone and entacapone against recombinant human UGTs showed more potent inhibtion by tolacapone for most isoforms).