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Desipramine

Updated: January 3, 2018.

OVERVIEW

Introduction

Desipramine is an oral tricyclic antidepressant that widely used in the therapy of depression. Desipramine can cause mild and transient serum enzyme elevations and is rare cause of clinically apparent acute cholestatic liver injury.

Background

Desipramine is a dibenzazepine derived tricyclic antidepressant which acts by inhibition of serotonin and norepinephrine reuptake within synaptic clefts in the central nervous system, thus increasing brain levels of these neurotransmitters. Desipramine is indicated for therapy of depression and was approved for this indication in the United States in 1964. Desipramine is available in generic forms and under the brand names of Norpramin in 10, 25, 50, 75, 100 and 150 mg tablets. The usual recommended dose for depression in adults is 100 to 200 mg daily in one or two divided doses. Desipramine can also be given as a single nighttime dose. Common side effects of tricyclic antidepressants include dizziness, headache, insomnia, somnolence, restlessness, confusion, gastrointestinal upset, increased appetite, weight gain, blurred vision, dry mouth and urinary retention.

Hepatotoxicity

Liver test abnormalities have been reported to occur in up to 16% of patients being treated with tricyclic antidepressants, 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 and without dose adjustment. Rare instances of clinically apparent acute liver injury have been reported due to desipramine, but far fewer than have been reported with amitriptyline or imipramine. The onset of jaundice is usually within 1 to 8 weeks of starting the antidepressant, and the pattern of serum enzyme elevations can be either hepatocellular or cholestatic. Features suggestive of hypersensitivity (fever, rash, eosinophilia) are common, but rarely severe. Autoantibody formation is unusual. These features are typical of tricyclic antidepressant hepatotoxicity.

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

Mechanism of Injury

The mechanism by which desipramine causes serum aminotransferase elevation is not known. It undergoes extensive hepatic metabolism (predominantly by CYP 2D6) and a possible cause of liver injury is production of

a toxic intermediate of metabolism. Many cases of acute liver injury have had features suggestive of a hypersensitivity reaction.

Outcome and Management

The serum aminotransferase elevations that occur on desipramine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. The acute liver injury caused by desipramine is typically self-limited and benign, and fatalities have not been reported in the published literature. Rechallenge with desipramine usually causes a prompt recurrence of the liver injury and should be avoided. Patients with clinically apparent desipramine induced liver injury may have cross sensitivity to injury from other tricyclic antidepressants and phenothiazines, but generally tolerate other antidepressants such as the selective serotonin reuptake inhibitors.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, Tricyclics: Amitriptyline, Amoxapine, Clomipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Desipramine – Norpramin®

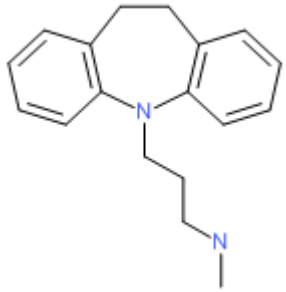
DRUG CLASS

Antidepressants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Desipramine	50-47-5	C18-H22-N2	

ANNOTATED BIBLIOGRAPHY

References updated: 03 January 2018

Zimmerman HJ. Tricyclic antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 495-8.

(Expert review of hepatotoxicity published in 1999 mentions that hepatic injury caused by tricyclic antidepressants is less frequent and less consistent than with monamine oxidase inhibitors).

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, 2013, pp. 443-62.

(Review of tricylic antidepressant hepatotoxicity; desipramine listed as causing hepatocellular liver injury with a latency of 1-4 weeks).

O'Donnell JM, Shelton RC. Drug therapy of depression and anxiety 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. 397-416.

(Textbook of pharmacology and therapeutics).

Powell WJ, Koch-Weser J, Williams RA. Lethal hepatic necrosis after therapy with imipramine and desipramine. JAMA 1968; 206: 642-5. PubMed PMID: 4234079.

(80 year old woman developed rash 2 weeks after starting imipramine and was switched to desipramine for 3 days when she developed jaundice, fever and desquamating rash [bilirubin 7.8 rising to 27 mg/dL, AST 330 U/L, Alk P 4 times ULN, atypical lymphocytes 6%], subsequently suffering hepatic coma, infections, hypotension and death).

Clarke AE, Maritz VM, Denborough MA. Phenothiazines and jaundice. Aust N Z J Med 1972; 2: 376-82. PubMed PMID: 4144624.

(Chlorpromazine and amitriptyline cause precipitation of proteins when added to human bile in vitro and hepatotoxicity of these agents may relate to this characteristic).

Fiori MG. Tricyclic antidepressants: a review of their toxicology. Curr Dev Psychopharmacol 1977; 4: 71-110. PubMed PMID: 340145.

(Review of cardiac, hepatic, neurological, fetal and psychotoxicity of tricyclic antidepressants; most cases of hepatotoxicity have been attributed to hypersensitivity, but tricyclics are taken up and extensively metabolized by hepatocytes).

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, psychotropic agents accounted for 93 cases, 54 of which were due to chlorpromazine; tricyclics were not specifically mentioned).

Price LH, Nelson JC, Waltrip RW. Desipramine-associated hepatitis. J Clin Psychopharmacol 1983; 3: 243-6. PubMed PMID: 6886037.

(Two women, ages 37 and 20 years developed asymptomatic rises in AST [peak values: 148 and 951 U/L] and GGT (376 and 2370 U/L) beginning 27 and 57 days after starting desipramine and falling to normal within 1-3 weeks of stopping).

Price LH, Nelson JC, Jatlow PI. Effects of desipramine on clinical liver function tests. Am J Psychiatry 1984; 141: 798-800. PubMed PMID: 6731623.

(Among 46 inpatients treated with desipramine for depression, there was no overall change in mean bilirubin, AST or Alk P levels; 5 patients had transient, minimal AST elevations).

Larrey D, Rueff B, Pessayre D, Algard M, Geneve J, Benhamou JP. Cross hepatotoxicity between tricyclic antidepressants. Gut 1986; 87-90. PubMed PMID: 3721296.

(39 year old woman developed abdominal pain 2 weeks after starting amineptine [a tricyclic antidepressant], with fever and eosinophilia [bilirubin 1.2 mg/dL, ALT 1360 U/L, Alk P 1.5 times ULN] resolving rapidly on stopping but recurring 7 days after starting clomipramine [ALT 1050 U/L, Alk P 1.5 times ULN], again resolving rapidly upon stopping).

Geneve J, Larrey D, Pessayre D, Benhamou JP. Structure tricyclique des medicaments et hepatotoxicite. Gastroenterol Clin Biol 1987; 11: 242-9. PubMed PMID: 2884161.

(Review of structural similarity and hepatotoxicity of tricyclic antidepressants focusing on amineptine, imipramine and amitriptyline).

Hoge SK, Biederman J. Liver function tests during treatment with desipramine in children and adolescents. J Clin Pharmacol 1987; 7: 87-9. PubMed PMID: 3584526.

(Among 42 children treated with desipramine for up to 2 years, there was no significant rise in mean AST, Alk P or bilirubin levels; 2 patients had minor, transient AST elevations).

Morrow PL, Hardin NJ, Bonadies J. Hypersensitivity myocarditis and hepatitis associated with imipramine and its metabolite, desipramine. J Forensic Sci 1989; 34: 1016-20. PubMed PMID: 2760582.

(Two patients with complicated medical histories [one on desipramine and one imipramine] died suddenly and were found to have myocarditis on autopsy, with liver showing eosinophils and lymphocytes in portal areas; no jaundice or information on ALT levels).

Pirmohamed MKL, Kittringham NR, Parkl BK. Idiosyncratic reactions to antidepressants: a review of the possible mechanism and predisposing factors. Pharm Ther 1992; 53: 105-25. PubMed PMID: 1641399.

(Review of idiosyncratic reactions to antidepressants, possible mechanism of injury being production of a chemically reactive metabolite that is either directly toxic or induces a hypersensitivity reaction).

Berson A, Fréneaux E, Larrey D, Lepage V, Douay C, Mallet C. Possible role of HLA in hepatotoxicity. An exploratory study. J Hepatol 1994; 20: 336-42. PubMed PMID: 8014443.

(Human leukocyte antigen [HLA] haplotypes done on 71 patients with drug induced liver disease; among 12 due to tricyclics [including 7 amineptine, 3 amitriptyline and 2 clomipramine], 6 [50%] were HLA A11 positive including 2 of the 3 amitriptyline cases; this allelle occurred in 12% in controls).

Remy AL, Larrey D, Pageaux GP, Desprez D, Ramos J, Michel H. Cross hepatotoxicity between tricyclic antidpressants and phenothiazines. Eur J Gastroenterol 1995; 7: 373-6. PubMed PMID: 7600146.

(65 year old woman developed fatigue and serum enzyme elevations [ALT ~1300 U/L; Alk P ~380 U/L] 1 month after starting trimipramine; 3 years later she developed nausea and ALT elevations 10 days after starting desipramine [ALT ~250 U/L], and 2 years later developed abdominal pain and fever and enzyme elevations [ALT ~1100 U/L, Alk P ~510 U/L] 8 days after starting cyamemazine; each time with rapid recovery and no jaundice).

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1686-96. PubMed PMID: 10553730.

(Systematic review of 81 articles on weight change with antipsychotics; using change after 10 weeks to compare: clozapine +5.7, olanzapine +4.2, chlorpromazine +4.2, risperidone +1.7, loxapine +0.6, haloperidol +0.5, ziprasidone +0.3, molindone -0.1, and pimozide -2.7 kilograms).

Grohmann R, Rüther E, Engel RR, Hippius H. Assessment of adverse drug reactions in psychiatric inpatients with the AMSP drug safety program: methods and first results for tricyclic antidepressants and SSRIs. Pharmacopsychiatry 1999; 32: 21-8. PubMed PMID: 10071179.

(Analysis of reporting of adverse events among inpatients in 29 German hospitals between 1993 to 1997; 896 severe adverse events occurred among 48,564 patients [1.8%], both total and hepatic events were more common with tricyclics than SSRIs).

Carvajal García-Pando A, García del Pozo J, Sánchez AS, Velasco MA, Rueda de Castro AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. J Clin Psychiatry 2002; 63: 135-7. PubMed PMID: 11874214.

(Analysis of cases of hepatotoxicity from antidepressants in Spanish Pharmacovigilance System from 1989-1999, identified 99 cases; among SSRIs, 26 due to fluoxetine, 14 paroxetine, 6 fluvoxamine, 5 sertraline, 3 venlafaxine and 2 citalopram; among tricyclics, 16 clomipramine 7 amitriptyline, 6 imipramine; among miscellaneous, 3 nefazodone and 1 trazodone; but all similar in rate ~1-3 per 100,000 patient-years of exposure, except for nefazodone=29/100,000; desipramine was not mentioned.).

Lucena M, Carvajal A, Andrade R, Velasco A. Antidepressant-induced hepatotoxicity. Expert Opin Drug Saf 2003; 2: 249-62. PubMed PMID: 12904104.

(Review of hepatotoxicity of antidepressants: antidepressant use has increased markedly between 1992 and 2002; account for 5% of cases of hepatotoxicity; tricyclics are less likely to cause injury than MAO inhibitors; predominantly cholestatic patterns of liver injury, with onset in first 2-3 weeks of starting; occasional reports of prolonged cholestasis).

Degner D, Grohmann R, Kropp S, Rüther E, Bender S, Engel RR, Schmidt LG. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry 2004; 37 Suppl 1: S39-45. PubMed PMID: 15052513.

(53,042 patients treated with antidepressants in 35 psychiatric hospitals in Germany from 1993-2000 were monitored for adverse drug reactions; increased liver enzymes reported in 16% on tricyclics, 5.5% on SSRIs and 12% of monamine oxidase inhibitors).

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 amitriptyline with a relative risk of 14.2: estimated frequency of 6 per 100,000 person-year exposures).

DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007; 41: 1201-11. PubMed PMID: 17609231.

(Review of drug induced liver injury and summary analysis of reports of injury from MAO inhibitors, SSRIs, tricyclics and atypical agents).

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 from 2004 to 2008, only 1 case was attributed to amitriptyline, no other tricyclic mentioned).

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 linked to tricyclic antidepressants).

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 amitriptyline but no other tricyclic antidepressant was listed).

Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf 2013; 8: 207-23. PubMed PMID: 23914755.

(Systematic review of the literature on hepatotoxicity of antidepressants discusses novel antidepressants and SSRIs, but not the tricyclics).

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. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to desipramine or other tricyclic antidepressant).

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, at least one case of which was attributed to amitriptyline but none to other tricyclic antidepressants).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014; 171: 404-15. PubMed Citation (Review of hepatotoxicity of antidepressants, mentions that cholestatic hepatitis can occur with desipramine and imipramine at an estimated rate of 4 per 100,000 patient years).

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, 20 cases [2%] were attributed to antidepressants, but none to desipramine and only one to a tricyclic - imipramine).

Friedrich ME, Akimova E, Huf W, Konstantinidis A, Papageorgiou K, Winkler D, Toto S, et al. Drug-induced liver injury during antidepressant treatment: results of AMSP, a drug surveillance program. Int J Neuropsychopharmacol 2016; 19. pii: pyv126. PubMed Citation

(Among 184,234 psychiatric inpatients from 80 hospitals, 149 cases [0.08%] of drug induced liver injury were reported in patients receiving antidipressants including 71 receiving tricyclics [0.14%], specifically 10 receiving amitriptyline [0.08%], 13 clomipramine [0.23%], 7 doxepine [0.06%], 2 nortriptyline [0.09%], and 18 trimipramine [0.15%]; numbers and rates for desipramine not listed).

Ferrajolo C, Scavone C, Donati M, Bortolami O, Stoppa G, Motola D, Vannacci A, et al.; DILI-IT Study Group. Antidepressant-induced acute liver injury: a case-control study in an Italian inpatient population. Drug Saf 2018; 41: 95-102. PubMed Citation

(Among 179 cases of hospitalizations for unexplained acute liver injury enrolled in an prospective study between 2010 and 2014, 17 had been exposed to antidepressants including one who received amitriptyline and one clomipramide, but none to desipramine or other tricyclics).