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Clomipramine

Updated: October 15, 2017.

OVERVIEW

Introduction

Clomipramine is a tricyclic antidepressant used in the therapy of obsessive-compulsive disorder. Clomipramine can cause mild and transient serum enzyme elevations and is rare cause of clinically apparent acute liver injury.

Background

Clomipramine (kloe mip' ra meen) is a dibenzazepine derived tricyclic antidepressant which acts by inhibition of serotonin reuptake within synaptic clefts in the central nervous system, thus increasing brain serotonin levels. Clomipramine also has some blocking activity at postsynaptic dopamine receptors. Clomipramine is used in the therapy of obsessive-compulsive disorder and was approved for this indication in the United States in 1989. Clomipramine is available in generic forms and under the brand names of Anafranil in capsules of 25, 50 and 75 mg. The typical recommended dose for obsessive compulsive disorder is 25 mg daily, increasing to at least 100 mg daily with a maximum dose of 250 mg daily. Common side effects include dizziness, headache, insomnia, somnolence, gastrointestinal upset, increased appetite, weight gain, blurred vision, dry mouth and urinary retention. Rare, but potentially severe adverse events include suicidal ideation and behavior, worsening of depresssion or mania, glaucoma, serotonin syndrome, hypersensitivity reactions and seizures.

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. Serum aminotransferase elevations during clomipramine therapy are reported in 1% to 3% of patients and the abnormalities were usually mild, asymptomatic and transient, reversing even with continuation of medication. As with many tricyclic antidepressants, rare instances of clinically apparent acute liver injury have been reported in patients taking clomipramine. The clinical features of cases of drug induced liver disease from clomipramine have not been well defined. The acute liver injury caused by tricyclic antidepressants typically arises within 1 to 4 weeks of starting the medication and presents with fatigue followed by dark urine and jaundice. Both hepatocellular and cholestatic patterns of injury have been described. The injury is usually mild-to-moderate in severity and recovery is rapid when the tricyclic is discontinued. Immunoallergic features such as rash, fever and eosinophilia are not common and autoantibodies are generally not detected. Fatal cases are extremely rare.

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

Mechanism of Injury

The mechanism by which clomipramine causes serum aminotransferase elevation is not known. It undergoes extensive hepatic metabolism and a possible cause of liver injury is production of a toxic intermediate of metabolism that may be directly toxic or may induce a hypersensitivity reaction.

Outcome and Management

The serum aminotransferase elevations that occur on clomipramine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. The acute liver injury caused by clomipramine is typically self-limited and benign. Results of rechallenge after acute liver injury from clomipramine has not been reported, but rechallenge with tricyclic antidepressants usually causes a prompt recurrence of the liver injury that can be severe and therefore should be avoided. Patients with clinically apparent clomipramine induced liver injury can have cross sensitivity to other tricyclic antidepressants, but should be able to tolerate other antidepressants, the phenothiazines and atypical antipsychotics.

Drug Class: Antidepressant Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Clomipramine – Anafranil®

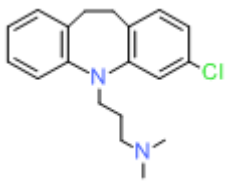
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Clomipramine	303-49-1	C19- H23-Cl-N2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 October 2017

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; 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 mentions that clomipramine has been implicated as a cause of hepatotoxicity with a latency of 1 week to 4 years and both hepatocellular and mixed patterns of injury).

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).

Klerman GL, Cole JO. Clinical pharmacology of imipramine and related antidepressant compounds. Pharmacol Rev 1965; 17: 101-41. PubMed PMID: 14294030.

(Extensive review of structure, pharmacology, clinical effects, mechanisms of action, drug interactions, and side effects of imipramine and related tricyclic antidepressants; jaundice is said to occur in 0.5 to 1% of treated patients and usually resolves rapidly with stopping).

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 and thus may produce a toxic or immunogenic intermediate).

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).

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).

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).

Alderman CP, Atchison MM, McNeece JI. Concurrent agranulocytosis and hepatitis secondary to clomipramine therapy. Br J Psychiatry 1993; 162: 688-9. PubMed PMID: 8149124.

(67 year old man developed elevations in ALT [510 U/L], but normal bilirubin and Alk P one month after starting clomipramine, with transient neutropenia lasting 14 days before recovery).

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 were determined in 71 patients with drug induced liver disease, 12 due to tricyclics, including 7 amineptine, 3 amitriptyline and 2 clomipramine; 6 [50%] were A11 positive including 2 of the 3 amitriptyline cases, but only 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 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 were 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).

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, accounting for 5% of cases of hepatotoxicity; tricyclics less likely to cause injury than MAO inhibitors; predominantly cholestatic patterns with onset in first 2-3 weeks; 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 antidepressant 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 anticonvulsants and CNS agents; 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).

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, but none were attributed to a tricyclic antidepressant).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014; 171: 404-15. PubMed PMID: 24362450.

(Review of hepatotoxicity of antidepressants, mentions 2 case reports of liver injury due to clomipramine with latency of about 1 month, hepatocellular pattern of injury and recovery in both: DeSanty [2007] and Larrey [1986]).

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 Citation

(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 were due to clompiramine).

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 PMID: 26721950.

(Among 184,234 psychiatric inpatients from 80 German, Austrian or Swiss hospitals, 149 cases [0.08%] of drug induced liver injury were reported, of which 13 occurred in 5,657 patients taking clomipramine [0.23%], which was higher than rates with other tricyclics, but most represented serum enzyme elevations without jaundice).

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 1 who received clomipramine [bilirubin 4.5 mg/dL, ALT 389 U/L, Alk P not given]; outcomes not provided).