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Isocarboxazid

Updated: April 8, 2020.

OVERVIEW

Introduction

Isocarboxazid is a monoamine oxidase inhibitor (MAO inhibitor) used in therapy of severe depression. Isocarboxazid therapy is associated with rare instances of clinically apparent acute liver injury.

Background

Isocarboxazid (eye" soe kar box' a zid) is a hydrazine antidepressant that acts through inhibition of monoamine oxidase, an enzyme that inactivates several neurotransmitter amines such as norepinephrine and serotonin. By inhibition of catabolism of serotonin and norepinephrine, isocarboxazid increases brain levels of these neurotransmitters which probably underlie its antidepressant effects. Isocarboxazid was approved for use as therapy of depression in the United States in 1959, but it is now rarely used because of the availability of more potent and better tolerated antidepressants such as the tricyclic antidepressants and the selective serotonin reuptake inhibitors. Isocarboxazid is available in generic forms and under the brand name of Marplan as tablets of 10 mg. The usual initial adult dose of isocarboxazid is 10 mg twice daily, with increase in the dose based upon efficacy and tolerance to a maximum of 60 mg per day. Common side effects include drowsiness, dizziness, headache, insomnia, tremor, dry mouth, nausea, increased appetite, weight gain and sexual dysfunction. Isocarboxazid interacts with many medications as well as many foods and beverages, and patients require careful monitoring and education. Rare but potentially severe adverse events associated with MAO inhibitors include suicidal ideation and behavior, hypertensive crises, serotonin syndrome, activation of mania, withdrawal syndrome, and hypersensitivity reactions.

Hepatotoxicity

Isocarboxazid, like most monoamine oxidase (MAO) inhibitors, can cause transient serum aminotransferase elevations in a proportion of patients. These elevations are usually mild, asymptomatic and self-limited and do not require dose modification. MAO inhibitors have been associated with rare cases of acute, clinically apparent liver injury but isocarboxazid has not specifically been implicated. The time to clinical onset of liver injury due to MAO inhibitors is typically 1 to 4 months after starting and the usual pattern of serum enzyme elevations is hepatocellular, although cholestatic injury has also been described. Immunoallergic features (rash, fever, eosinophilia) are uncommon as is autoantibody formation. Isocarboxazid has not been directly implicated in cases of drug-induced liver injury but it has had limited clinical use.

Likelihood score: E* (unproven, but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which isocarboxazid 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.

Outcome and Management

The serum aminotransferase elevations that occur on isocarboxazid and on other MAO inhibitor therapy are usually self-limited and do not require dose modification or discontinuation of therapy. The acute liver injury caused by MAO inhibitors is typically self-limited, but progressive and fatal instances of acute hepatitis have been reported with phenelzine. Rechallenge usually causes a prompt recurrence of the liver injury and should be avoided. Patients with isocarboxazid induced liver injury are likely to have cross sensitivity to other monoamine oxidase inhibitors, but should be able to tolerate tricyclic antidepressants or selective serotonin reuptake inhibitors.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, MAO Inhibitors: Phenelzine, Tranylcypromine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Isocarboxazid – Generic, Marplan®

DRUG CLASS

Antidepressant Agents

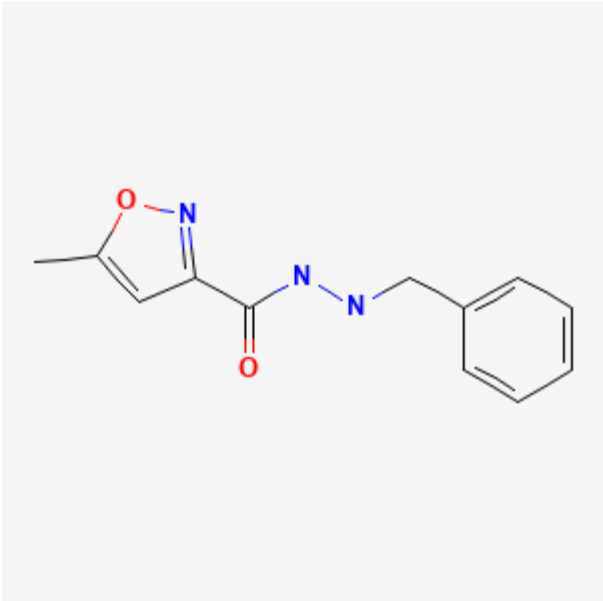
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE

Table continued from previous page.

Isocarboxazid	59-63-2	C12-H13-N3-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 08 April 2020

Abbreviations: MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

Zimmerman HJ. Antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 493-8.

(Expert review of hepatotoxicity of antidepressants published in 1999; hepatic injury caused by MAO inhibitors is similar to that of isoniazid with which they share structural similarity as hydrazines; the pattern of injury is typically hepatocellular and arises within 1-6 months of starting therapy; cases of fatal acute liver failure have been described, most commonly with iproniazid and less commonly with phenelzine and isocarboxazid, and least commonly with the nonhydrazide MAO inhibitor, tranylcypromine).

Larrey D, Ripault M-P. 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 MAO inhibitors and liver injury which was most common with iproniazid, which has been withdrawn; isocarboxazid is not mentioned).

O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. 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. 267-77.

(Textbook of pharmacology and therapeutics; the MAO inhibitors were the first antidepressants in clinical medicine, but inhibit both MAO-A and MAO-B which results in major drug and food interactions; specific MAO-B inhibitors are used for Parkinson disease, specific MAO-A inhibitors have been developed but are not available in the US).

Rosenblum LE, Korn RJ, Zimmerman HJ. Hepatocellular jaundice as a complication of iproniazid therapy. Arch Intern Med. 1960;105:583–93. PubMed PMID: 14438978.

(Classic paper on iproniazid hepatotoxicity; review of 90 patients; more common in women, ages 25-75 years, onset in 1-4 months [~95%], usually hepatocellular pattern similar to viral hepatitis, 22% mortality and demonstration that this is higher than in acute viral hepatitis).

Crisp AH, Hays P, Carter A. Three amine-oxidase inhibitor drugs in the treatment of depression. Relative value and toxic effects. Lancet. 1961;1:17–8. PubMed PMID: 13696480.

(Prospective study of liver test abnormalities during courses of iproniazid [n=17], nialamide [18] and peniprazine [20], with minor increases noted; no data on frequency of levels above normal).

Knight JA. Drug-induced hepatic injury. Marplan hepatitis. Am J Psychiatry. 1961;118:73–4. PubMed PMID: 13757117.

(23 year old woman developed jaundice 4 months after starting isocarboxazid [bilirubin 6.8 mg/dL, ALT 540 U/L, Alk P 3 time ULN], resolving within a few months of stopping).

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

(Cases of drug induced liver disease seen at Royal Free Hospital from 1959-65; 11 cases of acute liver failure due to drugs including iproniazid [n=3], phenelzine [2], phenoxypropazine [2], prochlorperazine [1] and halogenated anesthetics [3]; 20 cases of cholestatic hepatitis due to drugs, 18 due to chlorpromazine, 1 perphenazine and 1 nitrofurantoin).

Steingart AB, Cotterchio M. Do antidepressants cause, promote, or inhibit cancers? J Clin Epidemiol. 1995;48:1407–12. PubMed PMID: 7490604.

(Conflicting data from animal studies and epidemiological surveys have provided little evidence of a link between antidepressant use and breast, liver or other cancer after control for confounding variables).

Lucena MI, Carvajal A, Andrade RJ, 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; MAO inhibitors were first antidepressants developed; iproniazid caused a severe hepatitis and was withdrawn; phenelzine is still is in use, but has been associated with severe cases of hepatitis and development of cirrhosis).

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 2 to antidepressants [venlafaxine and fluoxetine], but none to MAO inhibitors).

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

(Review of the commonly used antidepressants and their potential for causing liver injury does not discuss the MAO inhibitors).

Shulman KI, Herrmann N, Walker SE. Current place of monoamine oxidase inhibitors in the treatment of depression. CNS Drugs. 2013;27:789–97. PubMed PMID: 23934742.

(History of the discovery that hydrazine-based drugs had potent antidepressant activity and subsequent development of nonspecific and specific, irreversible and reversible MAO A and B inhibitors which have similar antidepressant effects but different relative risks for complications such as hypertension from dietary intake of tyramine [as in aged cheese] and serotonin syndrome from use of a second serotonin-enhancing agent, such as a tricyclic, SSRI or SNRI as well as some opiates).

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, one of which was attributed to an tricyclic antidepressant [amitriptyline], but none to MAO inhibitors).

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 reports of hepatoxicity and rates of ALT elevations due to MAO inhibitors including iproniazid, phenelzine and modobemide, but not isocarboxazid).

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 MAO inhibitors).

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:pyv126. pii. PubMed PMID: 26721950.

(Among 184,234 psychiatric inpatients from 80 hospitals, 149 cases [0.08%] of drug induced liver injury were reported, with 3 cases occurring among 3860 subjects receiving MAO inhibitors, all 3 receiving tranylcypromine [0.08%]).

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 PMID: 28770534.

(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 most commonly citalopram, paroxetine and sertraline; none were taking an MAO inhibitor).

Drugs for depression. Med Lett Drugs Ther. 2020;62(1592):25–32. PubMed PMID: 32320387.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of drugs for depression, mentions that tricyclics and MAO inhibitors remain valuable alternatives for treatment of moderate-to-severe depression, despite concerns about their safety; hepatotoxicity is mentioned only for nefazodone [now rarely used because of severe hepatotoxicity] and duloxetine [in heavy drinkers]).