U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Nalmefene. [Updated 2020 Mar 24].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Nalmefene

Updated: March 24, 2020.

OVERVIEW

Introduction

Nalmefene is an opiate receptor antagonist which is used to treat acute opioid overdose and to help in the management of alcohol dependence and addictive behaviors. Nalmefene has not been linked to serum enzyme elevations during therapy or to clinically apparent liver injury.

Background

Nalmefene (nal' me feen) is a semisynthetic opiate receptor antagonist which is similar structurally to naltrexone and oxymorphone. Nalmefene is distinctive in having antagonist activity against all three types of opiate receptors – μ, κ and δ. When given intravenously or intramuscularly, nalmefene causes rapid onset of withdrawal symptoms in opioid dependent persons and has been used successfully to treat acute opioid overdose. It is also used to reverse opioid actions in the postoperative period. It has a longer duration of action than naloxone and better oral availability. Nalmefene was approved for use in the United States in 1995 as a therapy of opioid overdose. Oral formulations, which have been used to treat alcohol dependence and other addictive behaviors, have not been approved for this use in the United States. Nalmefene is available in solutions for injection in concentrations of 100 μg/mL (for postoperative use) and 1 mg/mL (for management of known of suspected opioid overdose) under the trade name Revex. Side effects of parenterally administered nalmefene in opioid dependent patients include mood changes, sweating, anxiety, restlessness, trembling, dizziness, flushing, headache, nausea, vomiting, cardiac tachyarrhythmias, seizures, chest pain and acute pulmonary edema—symptoms of acute opioid withdrawal. In persons not taking opioids, nalmefene has minimal effects. Nalmefene is not a controlled substance, but its use is sometimes restricted to medical staff trained in emergency medicine or anesthesia.

Hepatotoxicity

Therapy with nalmefene has not been linked to serum enzyme elevations or to idiosyncratic acute, clinically apparent liver injury. Nalmefene is extensively metabolized in the liver, but largely by glucuronidation rather than transformation to a different metabolite. Patients with opioid overdose often have underlying chronic liver diseases such as alcoholic liver disease, hepatitis B or C, but treatment with nalmefene does not appear to exacerbate those conditions.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Drug Class: Opioid Antagonists; see also Substance Abuse Treatment Agents

Other Drugs in the Class: Naloxegol, Naloxone, Naltrexone

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nalmefene – Revex®

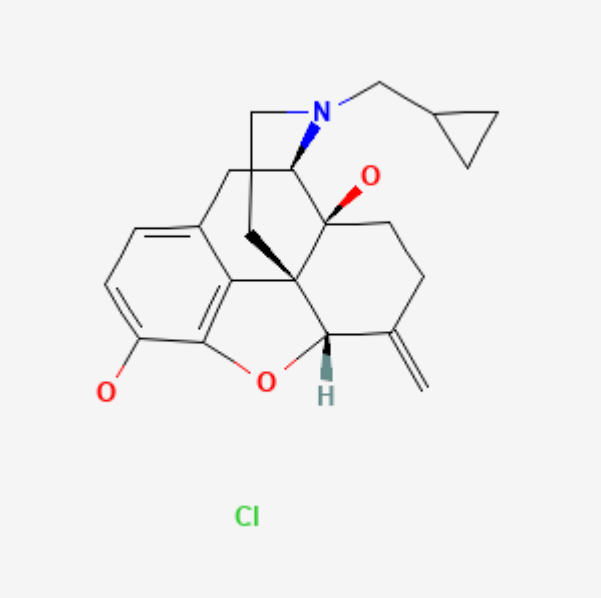
DRUG CLASS

Opioid Antagonists

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Nalmefene HCl	58895-64-0	C21-H25-N-O3.Cl-H	

ANNOTATED BIBLIOGRAPHY

References updated: 24 March 2020

Zimmerman HJ. Narcotic analgesics. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 710-11.

(Expert review of hepatotoxicity published in 1999; mentions that trials of naltrexone have reported serum aminotransferase elevations in up to 30% of recipients, an effect that appeared to be partially dose dependent; nalmefene not discussed).

Larrey D, Ripault MP. Illegal and recreational compounds. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 456-7.

(Review of hepatotoxicity discusses buprenorphine, an orally available morphine analogue, which has been linked to cases of severe acute liver injury, usually as a result of intravenous administration; nalmefene not discussed).

Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. 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. 355-86.

(Textbook of pharmacology and therapeutics).

Dixon R, Gentile J, Hsu HB, Hsiao J, Howes J, Garg D, Weidler D. Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. J Clin Pharmacol. 1987;27:233–9. PubMed PMID: 3680580.

(Phase 1 study of safety of single injections and 7 day courses of nalmefene in different doses found no increases in serum aminotransferase levels).

Kaplan JL, Marx JA. Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: a pilot study. Ann Emerg Med. 1993;22:187–90. PubMed PMID: 8427429.

(Among 53 patients with suspected opioid overdose who were treated with 1-10 boluses of either 0.5 and 1.0 mg of intravenous nalmefene, no serious adverse events were found; side effects possibly related to nalmefene were vomiting, dizziness and diarrhea).

Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, Mantero-Atienza E. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res. 1994;18:1162–7. PubMed PMID: 7847600.

(Controlled trial of 12 weeks of nalmefene or placebo in 21 alcohol dependent patients found no difference in laboratory measures during therapy, serum ALT levels decreasing in abstinent patients).

Bergasa NV, Schmitt JM, Talbot TL, Alling DW, Swain MG, Turner ML, Jenkins JB, et al. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. Hepatology. 1998;27:679–84. PubMed PMID: 9500694.

(Open label trial of nalmefene for 2-26 months in 14 patients with liver disease and pruritus found "no consistent effect of nalmefene on the severity of cholestasis, as assessed by routine serum biochemical markers").

Kaplan JL, Marx JA, Calabro JJ, Gin-Shaw SL, Spiller JD, Spivey WL, Gaddis GM, Zhao N, Harchelroad FP Jr. Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. Ann Emerg Med. 1999;34:42–50. PubMed PMID: 10381993.

(Controlled trial of two doses of nalmefene vs naloxone in 118 patients with suspected opioid overdose found similar rates of response and adverse events; the most common ones attributed to nalmefene were vomiting, tachycardia, nausea and myoclonus).

Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol. 2004;24:421–8. PubMed PMID: 15232334.

(Among 270 recently abstinent alcohol dependent subjects treated with one of 3 doses of nalmefene or placebo for 12 weeks, side effects of nausea, dry mouth, insomnia, dizziness and confusion were more common in nalmefene treated patients; no mention of ALT and AST results).

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 to nalmefene, naltrexone or other agents used to treated substance abuse).

van den Brink W, Aubin HJ, Bladström A, Torup L, Gual A, Mann K. Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. Alcohol Alcohol. 2013;48:570–8. PubMed PMID: 23873853.

(Retrospective analysis of 667 alcohol dependent patients treated with nalmefene or placebo on an as-needed basis for 6 months found decrease in average GGT and ALT values during the study, with greater decrease in nalmefene treated subjects).

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 nalmefene or other opioid antagonists).

van den Brink W, Sørensen P, Torup L, Mann K, Gual A; SENSE Study Group. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. J Psychopharmacol. 2014;28:733–44. PubMed PMID: 24671340.

(Among 675 alcohol dependent patients treated with nalmefene (18 mg) or placebo once daily for 1 year, decreases in alcohol intake were greater with nalmefene at 1 year (but not 6 months), and there were no differences in the incidence of clinically relevant laboratory values between the 2 treatment groups" except in ALT and AST values, but specific differences were not described).

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 nalmefene or other opioid antagonists).

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, none were attributed to nalmefene or other opioid antagonists).

van den Brink W, Strang J, Gual A, Sørensen P, Jensen TJ, Mann K. Safety and tolerability of as-needed nalmefene in the treatment of alcohol dependence: results from the Phase III clinical programme. Expert Opin Drug Saf. 2015;14:495–504. PubMed PMID: 25652768.

(Among 1123 patients treated with "as needed" nalmefene and 824 with placebo for alcohol dependency in 3 controlled trials, adverse events more frequent with nalmefene included nausea [22 vs 6%], dizziness [18% vs 6%, insomnia [13% vs 5%] and headache [12% vs 8%], but not ALT or AST elevations above 3 times ULN [3.8% vs 3.9%] and there were no episodes of clinically apparent liver injury).

Johansen KGV, Tarp S, Astrup A, Lund H, Pagsberg AK, Christensen R. Harms associated with taking nalmefene for substance use and impulse control disorders: A systematic review and meta-analysis of randomised controlled trials. PLoS One. 2017;12:e0183821. PubMed PMID: 28850596.

(Metaanalysis of 8 controlled trials found similar rates of serious adverse events and deaths in nalmefene vs placebo recipients but higher rates of discontinuation because of adverse events; no mention of ALT elevations or hepatotoxicity).

Castera P, Stewart E, Großkopf J, Brotons C, Brix Schou M, Zhang D, Steiniger Brach B, et al; PICASO Study Investigators. Nalmefene, given as needed, in the routine treatment of patients with alcohol dependence: an interventional, open-label study in primary care. Eur Addict Res. 2018;24:293–303. PubMed PMID: 30485854.

(Among 378 patients with alcohol dependency treated with open-label "as-needed" nalmefene, side effects included nausea (18%) and dizziness (18%), and one patient died of decompensated cirrhosis that was considered unrelated to the therapy and there were no other "clinically relevant changes" in laboratory values).

Chaignot C, Zureik M, Rey G, Dray-Spira R, Coste J, Weill A. Risk of hospitalisation and death related to baclofen for alcohol use disorders: Comparison with nalmefene, acamprosate, and naltrexone in a cohort study of 165 334 patients between 2009 and 2015 in France. Pharmacoepidemiol Drug Saf. 2018;27:1239–48. PubMed PMID: 30251424.

(Analysis of the French Health Insurance claims database of patients initiating alcohol use disorder therapies found an increased risk of hospitalization [+13%] and death [+31%] compared to exposure to approved drugs such as acamprosate, naltrexone and nalmefene).

Opioids for pain. Med Lett Drugs Ther. 2018;60(1544):57–64. PubMed PMID: 29664446.

(Concise review of the efficacy, safety and costs of opioids used for pain mentions that the 3 opioid antagonists that are used to treat opioid induced constipation-methylnaltrexone, naloxegol and nalmedine-have similar degrees of efficacy and toxicities).

Miyata H, Takahashi M, Murai Y, Tsuneyoshi K, Hayashi T, Meulien D, Sørensen P, et al. Nalmefene in alcohol-dependent patients with a high drinking risk: Randomized controlled trial. Psychiatry Clin Neurosci. 2019;73:697–706. PubMed PMID: 31298784.

(Among 594 Japanese patients with alcohol dependency treated with as-needed nalmefene or placebo for 12 weeks, alcohol use was less with nalmefene treatment while adverse events were more frequent; although "there were no clinically significant laboratory findings", one patient discontinued nalmefene therapy because of chronic hepatitis).

López-Pelayo H, Zuluaga P, Caballeria E, Van den Brink W, Mann K, Gual A. Safety of nalmefene for the treatment of alcohol use disorder: an update. Expert Opin Drug Saf. 2020;19:9–17. PubMed PMID: 31868031.

(Review of the safety of nalmefene as therapy of alcohol use disorders mentions that while "there is no evidence of hepatotoxicity associated with nalmefene, there is a lack of data involving patients with advanced liver disease").