



Date of Search: 29 Dec 2016

Sources Searched: Medline, Embase, Cochrane Library, NICE Evidence

Acetylcysteine and Liver Failure/Fatty Liver Disease

SUMMARY:

For patients whose disease appears to be caused by etiologies other than acetaminophen, N-acetylcysteine may improve outcomes. In a [randomized, controlled trial](#), NAC appeared to improve spontaneous survival when given during early coma stages (grades I and II) in the setting of non-acetaminophen acute liver failure including, for example, drug-induced liver injury and hepatitis B.

Source: AASLD Position Paper: *The Management of Acute Liver Failure* (2011) [Last Accessed 30/12/2016] **URL:** http://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf

The Cochrane Collaboration has published a protocol for a systematic review (March 2016) which will investigate the use of [N-acetylcysteine in non paracetamol- induced liver failure](#).

Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: A meta-analysis of prospective clinical trials

Author(s): Hu J.; Sun Z.; Quan Q.; Zhang Q.; Ren X.

Source: *Clinics and Research in Hepatology and Gastroenterology*; Oct 2015; vol. 39 (no. 5); p. 594-599

Publication Date: Oct 2015

Publication Type(s): Journal: Article

Abstract:Background: Acute liver failure (ALF) is a rare but highly mortal condition without liver transplantation (LT). N-acetylcysteine (NAC), a glutathione precursor that detoxifies the reactive metabolite of acetaminophen and replenishes hepatic glutathione stores, is a highly effective drug for the prevention of ALF caused by acetaminophen. However, therapeutic use of NAC in non-acetaminophen-induced ALF (NAI-ALF) including alcohol intoxication, hepatitis virus infection, or drug and toxin-related hepatotoxicity is still inconclusive. The aim of this article is using meta-analysis method to analyze recent prospective clinical trials for the safety and efficacy of NAC in patients with ALF not caused by acetaminophen poisoning. Methods: Prospective clinical trials comparing efficacy and safety between NAC and control in the treatment of NAI-ALF were identified by searching Pubmed (2000-2014) and EMBASE (2000-2014) using the search terms acetylcysteine or NAC and NAI-ALF. The primary outcome was overall survival. Secondary outcomes included liver transplantation-free survival, post transplantation survival, length of ICU and hospital stays, and the relationship with coma grade. The safety profiles were also analyzed. Results: Four clinical trials were selected for meta-analysis. A total of 331 patients receiving treatment with NAC (oral or intravenously) and 285 patients in control group were included for meta-analysis. No statistical difference was identified between NAC group and control group for overall survival [236/331 (71%) vs 191/285 (67%); 95% CI 1.16 (0.81-1.67); P = 0.42]. However, there were significant differences between NAC group and control group regarding the survival with native liver [112/273 (41%) vs 68/226 (30%); 95% CI 1.61 (1.11-2.34); P = 0.01] and post-transplantation survival [78/91 (85.7%) vs 50/70 (71.4%); 95% CI 2.44 (1.11-5.37); P = 0.03]. The identified side effects of NAC included nausea, vomiting, and diarrhea or constipation. Rarely, it could cause rashes, fever, headache, drowsiness, low blood pressure, and elevated serum transaminase levels in a patient with cystic fibrosis. At the

dose used for acetaminophen toxicity, acetylcysteine does not have hepatotoxic effects. Conclusion: NAC is safe for NAI-ALF. It can prolong patients' survival with native liver without transplantation and survival after transplantation, but it cannot improve the overall survival. Copyright © 2015.

N-Acetylcysteine Use in Non-Acetaminophen-Induced Acute Liver Failure.

Author(s): McPheeters, Chelsey M; VanArsdale, Vanessa M; Weant, Kyle A

Source: Advanced emergency nursing journal; 2016; vol. 38 (no. 3); p. 183-189

Publication Date: 2016

Publication Type(s): Journal Article

Available in full text at [Advanced Emergency Nursing Journal](#) - from Ovid

Abstract:This article will review the available evidence related to the management of non-acetaminophen induced acute liver failure with N-acetylcysteine. Randomized controlled trials and a meta-analysis were included in this review. The efficacy of N-acetylcysteine in the treatment of acute liver failure from causes other than acetaminophen toxicity was evaluated. The efficacy of N-acetylcysteine in non-acetaminophen-induced acute liver failure is limited to specific patient populations. Patients classified as Coma Grade I or II are more likely to benefit from the use of this agent. The use of N-acetylcysteine is associated with improved transplant-free survival, not overall survival, in adults. N-Acetylcysteine does not improve the overall survival of patients with non-acetaminophen-induced acute liver failure but may be beneficial in those patients with Coma Grades I-II. Liver transplantation remains the only definitive therapy in advanced disease.

Database: Medline

N-acetylcysteine for non-paracetamol drug-induced liver injury: a systematic review.

Author(s): Chughlay MF; Kramer N; Spearman CW; Werfalli M; Cohen K

Source: British journal of clinical pharmacology; Jun 2016; vol. 81 (no. 6); p. 1021-1029

Publication Date: Jun 2016

Publication Type(s): Journal Article; Review

PubMedID: 26757427

Available in full text at [British Journal of Clinical Pharmacology](#) - from John Wiley and Sons

Abstract:AIMS: N-acetylcysteine (NAC) may be useful in the management of non-paracetamol drug-induced liver injury (DILI). Our objective was to review systematically evidence for the use of NAC as a therapeutic option for non-paracetamol DILI.METHODS: We searched for randomized controlled trials (RCTs) and prospective cohort studies. We searched several bibliographic databases, grey literature sources, conference proceedings and ongoing trials. Our pre-specified primary outcomes were all cause and DILI related mortality, time to normalization of liver biochemistry and adverse events. Secondary outcomes were proportion receiving liver transplant, time to transplantation, transplant-free survival and hospitalization duration.RESULTS: We identified one RCT of NAC vs. placebo in patients with non-paracetamol acute liver failure. There was no difference in the primary outcomes of overall survival at 3 weeks between NAC [70%, 95% confidence interval (CI) = 60%, 81%, n = 81] and placebo (66%, 95% CI = 56%, 77%, n = 92). NAC significantly improved the secondary outcomes of transplant-free survival compared with placebo: 40% NAC (95% CI = 28%, 51%) vs. 27% placebo (95% CI = 18%, 37%). A subgroup analysis according to aetiology found improved transplant-free survival in patients with non-paracetamol DILI, NAC (58%, n = 19) vs. placebo (27%, n = 26), odds ratio (OR) 0.27 (95% CI = 0.076, 0.942). Overall survival was similar, NAC (79%) vs. placebo (65%);, OR 0.50 (95% CI = 0.13, 1.98).CONCLUSION: Current available evidence is limited and does not allow for

any firm conclusions to be made regarding the role of NAC in non-paracetamol DILI. We therefore highlight the need for further research in this area.

Database: PubMed

Protective effect of ursodeoxycholic acid, resveratrol, and N-acetylcysteine on nonalcoholic fatty liver disease in rats.

Author(s): Ali, Mahmoud Hussein Hassan; Messiha, Basim Anwar Shehata; Abdel-Latif, Hekma Abdel-Tawab

Source: Pharmaceutical biology; Jul 2016; vol. 54 (no. 7); p. 1198-1208

Publication Date: Jul 2016

Publication Type(s): Journal Article

Abstract: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. Resveratrol (RSV) and N-acetylcysteine (NAC) are safe representatives of natural and synthetic antioxidants, respectively. The objective of this study was to evaluate protective effects of RSV and NAC, compared with ursodeoxycholic acid (UDCA), on experimental NAFLD. NAFLD was induced by feeding rats a methionine choline-deficient diet (MCDD) for four cycles, each of 4 d of MCDD feeding and 3 d of fasting. Animals were divided into normal control, steatosis control, and five treatment groups, receiving UDCA (25 mg/kg/d), RSV (10 mg/kg/d), NAC (20 mg/kg/d), UDCA + RSV, and UDCA + NAC orally for 28 d. Liver integrity markers (liver index and serum transaminases), serum tumor necrosis factor- α (TNF- α), glucose, albumin, renal functions (urea, creatinine), lipid profile (total cholesterol; TC, triglycerides, high density lipoproteins, low density lipoproteins; LDL-C, very low density lipoproteins, leptin), and oxidative stress markers (hepatic malondialdehyde; MDA, glutathione; GSH, glutathione-S-transferase; GST) were measured using automatic analyzer, colorimetric kits, and ELISA kits, supported by a liver histopathological study. RSV and NAC administration significantly improved liver index (RSV only), alanine transaminase (52, 52%), TNF- α (70, 70%), glucose (69, 80%), albumin (122, 114%), MDA (55, 63%), GSH (160, 152%), GST (84, 84%), TC (86, 86%), LDL-C (83, 81%), and leptin (59, 70%) levels compared with steatosis control values. A combination of RSV or NAC with UDCA seems to ameliorate their effects. RSV and NAC are effective on NAFLD through antioxidant, anti-inflammatory, and lipid-lowering potentials, where as RSV seems better than UDCA or NAC.

Database: Medline

Use of acetylcysteine for non-acetaminophen-induced acute liver failure

Author(s): Sales I.; Smithburger P.L.; Kane-Gill S.L.; Dzierba A.L.; Rowe D.

Source: Annals of Hepatology; 2013; vol. 12 (no. 1); p. 6-10

Publication Date: 2013

Publication Type(s): Journal: Review

Available in full text at [Annals of Hepatology](#) - from Free Access Content

Abstract: The purpose of this review was to evaluate the effectiveness of acetylcysteine in the treatment of acute liver failure not related to acetaminophen. A search of MEDLINE April 2003 through May 2012 using the Pub-Med database was conducted using the keywords acetylcysteine and non-acetaminophen-induced acute liver failure or acetylcysteine and liver failure. All human case reports, case series, and research articles that discussed the use of acetylcysteine for non-acetaminophen induced liver failure were evaluated. A total of 263 articles were identified during this broad search with 11 articles included for review in this article; eight case reports, two retrospective trials, and one prospective, randomized, double-blind multicenter study. In conclusion,

the data suggest marginal benefit of IV acetylcysteine in NAI-ALF with coma grades I-II; however, the routine use of acetylcysteine cannot be recommended. It may be considered in non-transplant centers while awaiting referral or when transplantation is not an option. Further studies are necessary to determine optimal dosing, duration, and criteria for patient selection.

Database: EMBASE

Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review.

Author(s): Socha, Piotr; Horvath, Andrea; Vajro, Pietro; Dziechciarz, Piotr; Dhawan, Anil; Szajewska, Hania

Source: Journal of pediatric gastroenterology and nutrition; May 2009; vol. 48 (no. 5); p. 587-596

Publication Date: May 2009

Publication Type(s): Journal Article Review

Available in full text at [Journal of pediatric gastroenterology and nutrition](#). - from Ovid

Abstract:Uncertainty exists regarding the treatment of patients with nonalcoholic fatty liver disease (NAFLD) who are unable to lose weight and/or change lifestyle. The present study assesses the effectiveness and safety of pharmacological and dietary supplement interventions for NAFLD. MEDLINE, EMBASE, and the Cochrane Library were searched for randomized controlled trials (RCTs) both in adults and in children. Fifteen (2 pediatric patients and 13 adults) RCTs met the inclusion criteria. A significant effect on normalization of alanine transaminase was found in patients treated with metformin compared with vitamin E, and in those treated with high-dose (3 g) carnitine vs diet. In contrast, there was no difference in patients treated with pioglitazone combined with vitamin E versus vitamin E alone, ursodeoxycholic acid (UDCA) combined with vitamin E or alone versus placebo, or UDCA versus combination of vitamin E and vitamin C, and in patients treated with vitamin E, probucol, N-acetylcysteine, low doses of carnitine, or Yo Jyo Shi Ko compared with placebo. Aspartate aminotransferase normalization was significantly higher in those treated with UDCA combined with vitamin E versus UDCA alone or placebo, and in those treated with metformin. Small number of subjects, high drop-out rates, and numerous interventions in 1 study limit the value of many studies. Only 7 RCTs analyzed biopsy specimens, but most of them have significant methodological limitations. Pioglitazone had reduced liver necrosis and inflammation in 1 large study. Limited data do not allow one to draw firm conclusions on the efficacy of various treatments for NAFLD.

Database: Medline

Oxidative stress and inflammation in hepatic diseases: Therapeutic possibilities of N-acetylcysteine

Author(s): de Andrade K.Q.; Moura F.A.; Santos J.C.F.; dos Santos J.M.; de Araujo O.R.P.; Goulart M.O.F.

Source: International Journal of Molecular Sciences; Dec 2015; vol. 16 (no. 12); p. 30269-30308

Publication Date: Dec 2015

Publication Type(s): Journal: Review

Available in full text at [International Journal of Molecular Sciences](#) - from National Library of Medicine

Abstract:Liver disease is highly prevalent in the world. Oxidative stress (OS) and inflammation are the most important pathogenetic events in liver diseases, regardless the different etiology and natural course. N-acetyl-L-cysteine (the active form) (NAC) is being studied in diseases characterized

by increased OS or decreased glutathione (GSH) level. NAC acts mainly on the supply of cysteine for GSH synthesis. The objective of this review is to examine experimental and clinical studies that evaluate the antioxidant and anti-inflammatory roles of NAC in attenuating markers of inflammation and OS in hepatic damage. The results related to the supplementation of NAC in any form of administration and type of study are satisfactory in 85.5% (n = 59) of the cases evaluated (n = 69, 100%). Within this percentage, the dosage of NAC utilized in studies in vivo varied from 0.204 up to 2 g/kg/day. A standard experimental design of protection and treatment as well as the choice of the route of administration, with a broader evaluation of OS and inflammation markers in the serum or other biological matrixes, in animal models, are necessary. Clinical studies are urgently required, to have a clear view, so that, the professionals can be sure about the effectiveness and safety of NAC prescription. Copyright © 2015 by the authors; licensee MDPI, Basel, Switzerland.

Database: EMBASE

N-acetylcysteine improves liver function in patients with non-alcoholic Fatty liver disease.

Author(s): Khoshbaten, Manouchehr; Aliasgarzadeh, Akbar; Masnadi, Koorosh; Tarzamani, Mohammad K; Farhang, Sara; Babaei, Hosain; Kiani, Javad; Zaare, Maryam; Najafipoor, Farzad

Source: Hepatitis monthly; 2010; vol. 10 (no. 1); p. 12-16

Publication Date: 2010

Publication Type(s): Journal Article

Available in full text at [Hepatitis Monthly](#) - from National Library of Medicine

Abstract:Non-alcoholic fatty liver change is a common disease of the liver in which oxidative stress plays a basic role. Studies are largely focused on protecting the liver by means of anti-oxidative material. The aim of this study is to evaluate the role of N- acetylcysteine in the process of liver injury. Thirty patients with non-alcoholic fatty liver steatosis were randomly selected to receive either N-acetylcysteine or vitamin C. Liver function tests (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) were measured as well as the grade of steatosis, the pattern of its echogenicity, the span of the liver and the spleen and the portal vein diameter before the intervention. Patients were followed up using the same method of evaluation repeated in the first, second and third months. The mean age (SD) was 40.1(12.4) in patients receiving NAC and 46(10.4) years in patients receiving vitamin C (P = 0.137). NAC resulted in a significant decrease of serum alanine aminotransferase after three months, compared to vitamin C. This effect was independent of the grade of steatosis in the initial diagnosis. NAC was able to significantly decrease the span of the spleen. N-acetylcysteine can improve liver function in patients with non-alcoholic fatty liver disease. Better results may be achievable in a longer follow up.

Database: Medline

Are N-acetylcysteine and adalimumab effective for non-alcoholic steatohepatitis?

Author(s): Yalcin M.; Kiyak M.A.; Akarsu M.; Bengi G.; Celik A.; Sagol O.

Source: Gastroenterology Insights; 2016; vol. 7 (no. 1)

Publication Date: 2016

Publication Type(s): Journal: Article

Abstract:Background-Objectives: Due to the lack of effective medical treatment for non-alcoholic steatohepatitis (NASH), we aimed to evaluate new treatment options. In particular, our goal was to investigate and compare the effects of N-acetylcysteine (NAC) and Adalimumab treatment on tumor necrosis factor alpha (TNF-alpha) and oxidative stress during the development of NASH in a rat model of the disease. Materials and Methods: Our study included a total of 35 female Wistar albino

rats that were divided into 5 groups of 7 each, and evaluated over a 6 week period. One group received a normal diet, while the other four groups received a methionine and choline deficient (MCD) diet. One of the groups receiving the MCD diet did not take any medicine, while the other three were administered NAC, adalimumab, or a NAC/adalimumab combination therapy. Results: NASH was successfully established in the MCD diet group. Levels of TNF-alpha were effectively suppressed in the three groups that received therapy. Even though adalimumab significantly enhanced suppression of TNF-alpha, the NASH score was suppressed to a more statistically significant extent in the groups receiving NAC. Conclusions: Our study showed that TNF-alpha and oxidative stress play an important role in NASH pathogenesis. The antioxidant agent, NAC, was found to be superior to the anti-TNF agent, Adalimumab, in the improvement of total NASH score. Although these drugs did not prevent the development of NASH, it was shown that they mildly reverse the NASH histopathology score, suggesting improvement of and overall liver function.

Database: EMBASE

An established dosing of n-acetylcysteine in non-acetaminophen-induced acute liver failure

Author(s): Kinney J.; Cho N.

Source: Critical Care Medicine; Dec 2016; vol. 44 (no. 12); p. 224

Publication Date: Dec 2016

Publication Type(s): Journal: Conference Abstract

Available in full text at [Critical Care Medicine](#) - from Ovid

Abstract: Learning Objectives: Non acetaminophen induced acute liver failure (NAI-ALF) has significant mortality and need for transplantation. A decrease in total bilirubin, ALT, and INR have shown to reduce mortality and transplantation in this population. Recent evidence has demonstrated N-acetylcysteine (NAC) to improve systemic hemodynamics, tissue oxygen delivery, and hepatic blood flow in NAI-ALF. Currently, there is not an established dose of NAC for NAI-ALF. The primary endpoint is the effect of NAC (dosed as in acetaminophen toxicity) on total bilirubin, ALT, and INR in patients with NAI-ALF. Methods: Single center, retrospective study of patients admitted between 2012 and 2015. The inclusion criteria were: adults, treated with NAC (dosed as in acetaminophen toxicity), and had ALF*. Patients were excluded for ALF as a result of acetaminophen toxicity or shocked/ischemic liver. SPSS statistical software was used for data analysis. Results: 15 patients were included in the NAC group and 17 in the non-NAC. Differences in baseline characteristics observed in the NAC arm were higher AST (1118.3 vs 235.5, U/L; p=0.050), ALT (677.9 vs 139.2, U/L; p=0.025), and number of males (11/15 vs 6/17; p=0.042). Despite this, the patients' liver functions were shown similar by the calculated MELD scores (29.6 vs 28.3; p=0.721), rates of jaundice (7/15 vs 13/17; p=0.144), and cirrhosis (9/15 vs 13/17; p=0.691). The results showed a significant decrease in the NAC group's ALT from baseline and Day 1 of treatment (677.9 and 717.8 to 245.8, U/L; p=0.022 and p=0.013) versus the non-NAC patients (139.2 to 128.2, U/L; p=0.861). Plus, survival was nearly 20% higher in those who received NAC (9/15 vs 7/17; p=0.479). Conclusions: Treatment with NAC, at this established dose, showed a reduction in ALT; a known predictor of mortality and transplant. As of now, there is inadequate evidence whether this population should receive NAC empirically. But, at a safe and well-studied dose, in a high risk population; it is worth considering for the possible benefits. Further study will provide greater insight into the positive impact of NAC in NAI-ALF.

Database: EMBASE

Co-administration of metformin and N-acetylcysteine with dietary control improves the biochemical and histological manifestations in rats with non-alcoholic fatty liver.

Author(s): El-Lakkany, Naglaa Mohamed; Seif El-Din, Sayed Hassan; Sabra, Abdel-Nasser Abdel-Aal; Hammam, Olfat Ali; Ebeid, Fatma Abdel-Latif

Source: Research in pharmaceutical sciences; Oct 2016; vol. 11 (no. 5); p. 374-382

Publication Date: Oct 2016

Publication Type(s): Journal Article

Available in full text at [Research in Pharmaceutical Sciences](#) - from National Library of Medicine

Abstract:Non-alcoholic fatty liver disease (NAFLD) is a burgeoning health problem that affects 1/3 of the adult population and an increasing number of children in developed countries. Oxidative stress and insulin resistance are the mechanisms that seem to be mostly involved in its pathogenesis. This study was conceived in a NAFLD rat model to evaluate the efficacy of both metformin (MTF) and N-acetylcysteine (NAC) with dietary control on biochemical and histologic liver manifestations. Rats were classified into nine groups; normal (I), NAFLD-induced by feeding high-fat diet (HFD; II) for 12 weeks, NAFLD switched to regular diet (RD; III), NAFLD-HFD or -RD treated with MTF in a dose of 150 mg/kg (IV, V), NAC in a dose of 500 mg/kg (VI, VII) or MTF+NAC (VIII, IX) respectively for 8 weeks. After 20 weeks, the rats in group II showed notable steatosis, lobular inflammation, fibrosis accompanied with elevated ($P < 0.05$) serum alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (γ -GT), cholesterol, triglycerides, LDL, VLDL, leptin, tumor necrosis factor (TNF- α), transforming growth factor (TGF- β 1) and hepatic malondialdehyde (MDA) compared with group I. Meanwhile, hepatic superoxide dismutase (SOD), glutathione GSH with serum HDL, adiponectin were significantly decreased ($P < 0.05$). These changes were to a less extent in group III. MTF or NAC individually resulted in improvement of most of these biochemical and histological parameters. These improvements were more pronounced in the combined groups VIII and IX versus each drug alone. NAC supplementation concomitant with MTF could be beneficial for the treatment of NAFLD and prevention of nonalcoholic steatohepatitis (NASH).

Database: Medline

Protective effect of ursodeoxycholic acid, resveratrol, and N-acetylcysteine on nonalcoholic fatty liver disease in rats.

Author(s): Ali MH; Messiha BA; Abdel-Latif HA

Source: Pharmaceutical biology; Jul 2016; vol. 54 (no. 7); p. 1198-1208

Publication Date: Jul 2016

Publication Type(s): Journal Article

PubMedID: 26134756

Abstract:CONTEXT: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. Resveratrol (RSV) and N-acetylcysteine (NAC) are safe representatives of natural and synthetic antioxidants, respectively.OBJECTIVE: The objective of this study was to evaluate protective effects of RSV and NAC, compared with ursodeoxycholic acid (UDCA), on experimental NAFLD.MATERIALS AND METHODS: NAFLD was induced by feeding rats a methionine choline-deficient diet (MCDD) for four cycles, each of 4 d of MCDD feeding and 3 d of fasting. Animals were divided into normal control, steatosis control, and five treatment groups, receiving UDCA (25 mg/kg/d), RSV (10 mg/kg/d), NAC (20 mg/kg/d), UDCA + RSV, and UDCA + NAC orally for 28 d. Liver integrity markers (liver index and serum transaminases), serum tumor necrosis factor- α (TNF- α), glucose, albumin, renal functions (urea, creatinine), lipid profile (total cholesterol; TC, triglycerides, high density lipoproteins, low density lipoproteins; LDL-C, very low density lipoproteins,

leptin), and oxidative stress markers (hepatic malondialdehyde; MDA, glutathione; GSH, glutathione-S-transferase; GST) were measured using automatic analyzer, colorimetric kits, and ELISA kits, supported by a liver histopathological study. RESULTS: RSV and NAC administration significantly improved liver index (RSV only), alanine transaminase (52, 52%), TNF- α (70, 70%), glucose (69, 80%), albumin (122, 114%), MDA (55, 63%), GSH (160, 152%), GST (84, 84%), TC (86, 86%), LDL-C (83, 81%), and leptin (59, 70%) levels compared with steatosis control values. A combination of RSV or NAC with UDCA seems to ameliorate their effects. DISCUSSION AND CONCLUSION: RSV and NAC are effective on NAFLD through antioxidant, anti-inflammatory, and lipid-lowering potentials, where as RSV seems better than UDCA or NAC.

Database: PubMed

Vitamin B5 and N-Acetylcysteine in Nonalcoholic Steatohepatitis: A Preclinical Study in a Dietary Mouse Model

Author(s): Machado M.V.; Kruger L.; Jewell M.L.; Michelotti G.A.; Pereira T.A.; Xie G.; Moylan C.A.; Diehl A.M.

Source: Digestive Diseases and Sciences; Jan 2016; vol. 61 (no. 1); p. 137-148

Publication Date: Jan 2016

Publication Type(s): Journal: Article

Available in full text at [Digestive Diseases and Sciences](#) - from Springer Link Journals

Abstract:Background: Nonalcoholic fatty liver disease (NAFLD) is the number one cause of chronic liver disease and second indication for liver transplantation in the Western world. Effective therapy is still not available. Previously we showed a critical role for caspase-2 in the pathogenesis of nonalcoholic steatohepatitis (NASH), the potentially progressive form of NAFLD. An imbalance between free coenzyme A (CoA) and acyl-CoA ratio is known to induce caspase-2 activation. Objectives: We aimed to evaluate CoA metabolism and the effects of supplementation with CoA precursors, pantothenate and cysteine, in mouse models of NASH. Methods: CoA metabolism was evaluated in methionine-choline deficient (MCD) and Western diet mouse models of NASH. MCD diet-fed mice were treated with pantothenate and N-acetylcysteine or placebo to determine effects on NASH. Results: Liver free CoA content was reduced, pantothenate kinase (PANK), the rate-limiting enzyme in the CoA biosynthesis pathway, was down-regulated, and CoA degrading enzymes were increased in mice with NASH. Decreased hepatic free CoA content was associated with increased caspase-2 activity and correlated with worse liver cell apoptosis, inflammation, and fibrosis. Treatment with pantothenate and N-acetylcysteine did not inhibit caspase-2 activation, improve NASH, normalize PANK expression, or restore free CoA levels in MCD diet-fed mice. Conclusion: In mice with NASH, hepatic CoA metabolism is impaired, leading to decreased free CoA content, activation of caspase-2, and increased liver cell apoptosis. Dietary supplementation with CoA precursors did not restore CoA levels or improve NASH, suggesting that alternative approaches are necessary to normalize free CoA during NASH. Copyright © 2015, Springer Science+Business Media New York.

Database: EMBASE

Liver disease in pregnancy

Author(s): Frise C.; Williamson C.

Source: Medicine (United Kingdom); Nov 2015; vol. 43 (no. 11); p. 636-638

Publication Date: Nov 2015

Publication Type(s): Journal: Article

Available in print at [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#) - from Medicine

Abstract:The presence of abnormal liver function is common in pregnancy. It can be a challenge to elucidate the cause. The history and clinical assessment provide useful tools for distinguishing between pregnancy-related causes, such as pre-eclampsia, acute fatty liver of pregnancy and obstetric cholestasis, and non pregnancy-related causes such as non-alcoholic fatty liver disease, acute viral infection, autoimmune liver disease and Budd-Chiari syndrome. Pregnancy may also affect the natural course of liver conditions, for example, by increasing the risk of haemorrhage from a hepatic adenoma, or the severity of hepatitis E infection. It is important for clinicians to be aware of the impact that liver disorders and the drugs used to treat them have on pregnancy and to understand the influence of pregnancy on specific liver disorders. Copyright © 2015 Elsevier Ltd.

Database: EMBASE

Effects of N-acetylcysteine on cytokines in non-acetaminophen acute liver failure: Potential mechanism of improvement in transplant-free survival

Author(s): Stravitz R.T.; Sanyal A.J.; Bajaj J.S.; Mirshahi F.; Cheng J.; Reisch J.; Lee W.M.

Source: Liver International; Oct 2013; vol. 33 (no. 9); p. 1324-1331

Publication Date: Oct 2013

Publication Type(s): Journal: Article

Available in full text at [Liver International](#) - from John Wiley and Sons

Abstract:Background: N-Acetylcysteine (NAC) improves transplant-free survival in patients with non-acetaminophen acute liver failure (ALF) when administered in early stages of hepatic encephalopathy. The mechanisms of this benefit are unknown. Aim: To determine whether NAC improves transplant-free survival in ALF by ameliorating the surge of pro-inflammatory cytokines. Methods: Serum samples were obtained from 78 participants of the randomized, ALF Study Group NAC Trial with grade 1 or 2 hepatic encephalopathy on randomization. Concentrations of ten cytokines, chosen to represent a wide array of inflammatory responses, were determined by multiplex enzyme-linked immunosorbent assay ELISA. Results: In univariate analysis, predictors of transplant-free survival included NAC administration ($P = 0.012$), admission bilirubin ($P = 0.003$), international normalized ratio INR ($P = 0.0002$), grade 1 vs. grade 2 encephalopathy ($P = 0.006$) and lower admission interleukin (IL)-17 concentrations ($P = 0.011$). IL-17 levels were higher in patients with grade 2 vs. grade 1 encephalopathy on randomization ($P = 0.007$) and in those who progressed to grade 3 or grade 4 encephalopathy over the following 7 days ($P < 0.01$). Stepwise multivariate logistic regression analysis identified only NAC administration and lower IL-17 concentrations as independent predictors of transplant-free survival. In patients with detectable IL-17 concentrations on admission, 78% of those who received NAC vs. 44% of those who received placebo had undetectable levels by day 3-5 ($P = 0.042$), and the mean decrease in IL-17 concentrations between admission and late samples was significantly greater in patients who received NAC vs. placebo ($P = 0.045$). Conclusions: N-acetylcysteine (NAC) may improve transplant-free survival in patients with non-acetaminophen ALF by ameliorating the production of IL-17, which is associated with

progression of hepatic encephalopathy and poor outcome. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Database: EMBASE

Intravenous acetylcysteine for indications other than acetaminophen overdose

Author(s): Bass S.; Zook N.

Source: American Journal of Health-System Pharmacy; Sep 2013; vol. 70 (no. 17); p. 1496-1501

Publication Date: Sep 2013

Publication Type(s): Journal: Article

Available in full text at [American Journal of Health-System Pharmacy](#) - from EBSCOhost

Abstract: Purpose. The use of intravenous acetylcysteine for off-label indications, specifically non-acetaminophen-induced acute liver failure (NAI-ALF), severe alcoholic hepatitis, and contrast-induced nephropathy (CIN), is reviewed. Summary. I.V. acetylcysteine is most often used as an antidote for acetaminophen overdose due to its ability to increase levels of glutathione; however, it is also used to treat NAI-ALF and severe alcoholic hepatitis and to prevent CIN. Although the i.v. and oral formulations of acetylcysteine have been evaluated for these indications, most studies have examined the i.v. form. I.V. acetylcysteine is used in the treatment of NAI-ALF to improve oxygenation to the liver. One large randomized trial of 173 adults with NAI-ALF from any etiology and of any grade encephalopathy demonstrated overall improvement in transplant-free survival, particularly for patients with low-grade encephalopathy, though overall survival was not improved. When used to treat severe alcoholic hepatitis, i.v. acetylcysteine serves as an antioxidant and glutathione source. A trial of 174 patients with severe alcoholic hepatitis revealed that patients had 28-day survival benefit when treated with acetylcysteine; improvement in patients with hepatorenal syndrome was also noted. When used for the prevention of CIN, i.v. acetylcysteine provides antioxidants and vasodilation. The benefit for this indication is limited to surrogate markers such as serum creatinine and in patients with multiple risk factors for the development of CIN. Conclusion. Data regarding the use of i.v. acetylcysteine for the treatment of NAI-ALF and severe alcoholic hepatitis and in the prevention of CIN are inconclusive, though some evidence supports its use in certain populations. Copyright © 2013, American Society of Health-System Pharmacists, Inc. All rights reserved.

Database: EMBASE

Improvements in hepatic serological biomarkers are associated with clinical benefit of intravenous N-acetylcysteine in early stage non-acetaminophen acute liver failure

Author(s): Singh S.; Hynan L.S.; Lee W.M.

Source: Digestive Diseases and Sciences; May 2013; vol. 58 (no. 5); p. 1397-1402

Publication Date: May 2013

Publication Type(s): Journal: Article

Available in full text at [Digestive Diseases and Sciences](#) - from ProQuest

Abstract: Background: N-acetylcysteine (NAC) improves transplant-free survival in early coma grade (I-II) patients with non-acetaminophen induced acute liver failure (ALF). We determined whether the clinical benefit was associated with improvements in hepatic function. Methods: In a prospective, double blind trial, 173 ALF patients without evidence of acetaminophen overdose were stratified by coma grade (I-II vs. III-IV) and randomly assigned to receive either intravenous NAC or dextrose (placebo) for 72 h, resulting in four patient groups. INR, ALT, bilirubin, creatinine, and AST obtained

on admission (day 1) and subsequent days (days 2-4) were used for secondary analysis performed by fitting longitudinal logistic regression models to predict death or transplantation or transplantation alone. Results: Treatment group and day of study in models including bilirubin or ALT were predictors of transplantation or death (maximum $p < 0.03$). Those patients with early coma grade who were treated with NAC showed significant improvement in bilirubin and ALT levels when compared to the other three groups (maximum $p < 0.02$ for NAC 1-2 vs. the 3 other treatments) when predicting death or transplantation. Treatment group, day of study, and bilirubin were predictors of transplantation (maximum $p < 0.03$) in ALF patients. Conclusion: The decreased risk of transplantation or death or of transplantation alone with intravenous NAC in early coma grade patients with non-acetaminophen induced ALF was reflected in improvement in parameters related to hepatocyte necrosis and bile excretion including ALT and bilirubin, but not in INR, creatinine, or AST. Hepatic recovery appears hastened by NAC as measured by several important lab values. © 2013 Springer Science+Business Media New York.

Database: EMBASE

Role of N-Acetylcystiene in acute hepatic failure

Author(s): Alvi H.; Talib A.; Khan F.W.

Source: Medical Channel; 2012; vol. 18 (no. 1); p. 37-40

Publication Date: 2012

Publication Type(s): Journal: Article

Available in full text at [Medical Channel](#) - from ProQuest

Abstract:Introduction: Acute liver failure (ALF) may be fulminant. Fulminant hepatic failure is characterized by the development of hepatic encephalopathy within 8 weeks after the onset of acute liver disease. Coagulopathy is invariably present. A thiol-containing agent, N-acetylcysteine (NAC) scavenges free radicals of oxygen and nitrogen. Its use in Non acetaminophen induced (NAI) ALF is still not being used as regular practice due to variable results of studies. This study was designed to evaluate the outcomes of NAC in NAI-ALF patients in terms of their early recovery, ICU stay and safety index of the drug. Methods: A cross-sectional prospective study was done in two private hospitals from March 2007 to February 2008. Group I included patients with NAC and conventional treatment and Group II consisted of conventional treatment only. Results: Total of 55 patients with acute hepatic failure without drug intoxication were admitted during the study period. They were randomly divided into two groups. Out of 55 patients, 30 were in Group I and 25 were in Group II. In Group I out of 30 patients 3 died with a success of treatment in 90.0% cases and in group II out of 25 patients 4 died with the success rate of 84%. Conclusion: Role of N-Acetylcysteine in Acute Hepatic Failure is encouraging. Therefore it is recommended that patients with acute hepatic failure may preferably be given NAC along with conventional treatment rather than treating them with conventional regimen alone.

Database: EMBASE

Relationship of serum cytokine concentrations to outcome, complications and N-acetylcysteine treatment in patients with non-acetaminophen-induced acute liver failure

Author(s): Todd Stravitz R.; Sanyal A.J.; Reisch J.; Lee W.M.

Source: Gastroenterology; May 2012; vol. 142 (no. 5)

Publication Date: May 2012

Publication Type(s): Journal: Conference Abstract

Available in print at [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#) - from Gastroenterology

Abstract: N-Acetylcysteine (NAC) improves transplant-free survival (TFS) in patients with non-acetaminophen (APAP) acute liver failure (ALF) when administered in early stages of hepatic encephalopathy (HE). The mechanisms of this benefit are unknown. We hypothesized that NAC may improve TFS by ameliorating the surge of pro-inflammatory cytokines leading to the systemic inflammatory response syndrome (SIRS). Objectives. To determine the effects of NAC administration on serum cytokine concentrations, and to relate cytokine concentrations to outcome, progression of HE, and the SIRS in patients with non-APAP-induced ALF. Methods. Serum samples from 90 patients from the randomized, placebo-controlled ALF Study Group NAC Trial were analyzed. Samples from 45 patients in each group were assayed, and serum cytokine concentrations were determined in multiplex SearchLight ELISA assays by ThermoFisher. Pro- and anti-inflammatory cytokines representing activation of Th1 (IL- 2, IFN γ , TNF α), Th2 (IL-4,6,10,13), and Treg (IL-17,23) classes of T-helper cells were chosen for assay. Results. The number of SIRS components on admission was a predictor of 21 day mortality ($p=0.02$ by ANOVA). Predictors of TFS in univariate analysis included NAC administration ($p=0.005$), admission bilirubin ($p<0.001$), INR ($p=0.085$), grade 1 vs. 2 HE ($p<0.02$) and higher admission IL-17 concentrations ($p=0.02$). However, there were no differences in any serum cytokine concentrations or in SIRS in patients treated with NAC vs. placebo. Stepwise multivariable logistic analysis identified each of these factors as independent predictors of TFS ($p<0.0001$). IL-17 levels were higher in patients with grade 2 vs. 1 HE ($p<0.01$) and in those who progressed to grade 3/4 HE ($p<0.02$). Patterns of elevated cytokines were observed, with levels of Th1 cytokines highly related ($r=0.75$, $p<0.0001$), and levels of pro- and anti-inflammatory cytokines also related (eg., IL-6 and IL-10; $r=0.48$, $p<0.001$). IL-6 and IL-10 concentrations were both related to number of SIRS on admission ($p<0.01$ and $p<0.001$) and inversely related to mean arterial pressure ($r=-0.35$ and -0.34 , respectively; $p<0.001$ for both). Conclusions. NAC does not improve TFS by ameliorating the surge of pro-inflammatory cytokines in patients with non-APAP-induced ALF. However, specific pro- and anti-inflammatory cytokine concentrations are associated with outcome, HE grade, and the SIRS. IL-17 may have an important role in HE progression and outcome.

Database: EMBASE

Limited therapeutic effect of N-acetylcysteine on hepatic insulin resistance in an experimental model of alcohol-induced steatohepatitis.

Author(s): Setshedi, Mashiko; Longato, Lisa; Petersen, Dennis R; Ronis, Martin; Chen, William C; Wands, Jack R; de la Monte, Suzanne M

Source: Alcoholism, clinical and experimental research; Dec 2011; vol. 35 (no. 12); p. 2139-2151

Publication Date: Dec 2011

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article

Available in full text at [Alcoholism: Clinical and Experimental Research](#) - from John Wiley and Sons

Abstract:Alcohol-related steatohepatitis is associated with increased oxidative stress, DNA damage, lipotoxicity, and insulin resistance in liver. As inflammation and oxidative stress can promote insulin resistance, effective treatment with antioxidants, for example, N-acetylcysteine (NAC), may restore ethanol-impaired insulin signaling in the liver. Adult male Sprague-Dawley rats were fed for 130 days with liquid diets containing 0 or 37% ethanol by caloric content, and simultaneously treated with vehicle or NAC. Chow-fed controls were studied in parallel. Liver tissues were used for histopathology, cytokine activation, and insulin/IGF-1 signaling assays. We observed significant positive trends of increasing severity of steatohepatitis ($p = 0.016$) with accumulation of neutral lipid ($p = 0.0002$) and triglycerides ($p = 0.0004$) from chow to control, to the ethanol diet, irrespective of NAC treatment. In ethanol-fed rats, NAC reduced inflammation, converted the steatosis from a predominantly microvesicular to a mainly macrovesicular histological pattern, reduced pro-inflammatory cytokine gene expression, ceramide load, and acid sphingomyelinase activity, and increased expression of IGF-1 receptor and IGF-2 in liver. However, NAC did not abrogate ethanol-mediated impairments in signaling through insulin/IGF-1 receptors, IRS-1, Akt, GSK-3 β , or p70S6K, nor did it significantly reduce pro-ceramide or GM3 ganglioside gene expression in liver. Antioxidant treatments reduce the severity of chronic alcohol-related steatohepatitis, possibly because of the decreased expression of inflammatory mediators and ceramide accumulation, but they do not restore insulin/IGF-1 signaling in liver, most likely due to persistent elevation of GM3 synthase expression. Effective treatment of alcohol-related steatohepatitis most likely requires dual targeting of oxidative stress and insulin/IGF resistance. Copyright © 2011 by the Research Society on Alcoholism.

Database: Medline

Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation.

Author(s): Mumtaz, Khalid; Azam, Zahid; Hamid, Saeed; Abid, Shahab; Memon, Sadik; Ali Shah, Hasnain; Jafri, Wasim

Source: Hepatology international; Dec 2009; vol. 3 (no. 4); p. 563-570

Publication Date: Dec 2009

Publication Type(s): Journal Article

Available in full text at [Hepatology international](#) - from ProQuest

Abstract:We aimed to study the role of N-acetylcysteine (NAC) in non-acetaminophen-induced acute liver failure (NAI-ALF). A total of 47 adult patients were prospectively enrolled with NAI-ALF (group 1 or NAC group) and oral NAC was given. The primary outcome was reduction in mortality with the use of NAC in NAI-ALF. The secondary outcomes were to evaluate safety of NAC and to assess factors predicting mortality. We compared these results with records of NAI-ALF patients admitted in our hospital from 2000 to 2003 ($n = 44$) who were not given NAC (group 2 or historical controls). The two groups were comparable for the etiology of ALF, prothrombin time (PT), alanine aminotransferase, creatinine, albumin, etc. The mean age in group 1 was 27.7 ± 11.8 years and in group 2 37.5 ± 18.8 years ($P = 0.004$). Bilirubin was 20.63 ± 11.03 and 14.36 ± 8.90 mg/dl in groups 1 and 2, respectively ($P = 0.004$). There were 8 (17%) and 1 (2.3%) pregnant ALF women with acute hepatitis E virus (HEV) infection in groups 1 and 2, respectively ($P = 0.031$). All patients were given supportive care, including mechanical ventilation. A total of 34 (37.36%) patients survived; 22 (47%) in group 1 (NAC group) and 12 (27%) in group 2 (controls) ($P = 0.05$). On multivariable regression analysis, patients not given NAC (odds ratio [OR] = 10.3, 95% confidence interval [CI] = 1.6-65.7), along with age older than 40 years (OR = 10.3, 95% CI = 2.0-52.5), PT more than 50 s (OR = 15.4, 95% CI = 3.8-62.2), patients requiring mechanical ventilation (OR = 20.1, 95% CI = 3.1-130.2), and interval between jaundice and hepatic encephalopathy (OR = 5.0, 95% CI = 1.3-19.1) were independent predictors of mortality. The use of NAC causes reduction in NAI-ALF mortality and its use was safe.

Database: Medline

Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure.

Author(s): Lee, William M; Hynan, Linda S; Rossaro, Lorenzo; Fontana, Robert J; Stravitz, R Todd; Larson, Anne M; Davern, Timothy J; Murray, Natalie G; McCashland, Timothy; Reisch, Joan S; Robuck, Patricia R; Acute Liver Failure Study Group

Source: Gastroenterology; Sep 2009; vol. 137 (no. 3); p. 856

Publication Date: Sep 2009

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Randomized Controlled Trial Multicenter Study Journal Article Research Support, U.s. Gov't, P.h.s.

Available in print at [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#) - from Gastroenterology

Abstract:N-acetylcysteine (NAC), an antidote for acetaminophen poisoning, might benefit patients with non-acetaminophen-related acute liver failure. In a prospective, double-blind trial, acute liver failure patients without clinical or historical evidence of acetaminophen overdose were stratified by site and coma grade and assigned randomly to groups that were given NAC or placebo (dextrose) infusion for 72 hours. The primary outcome was overall survival at 3 weeks. Secondary outcomes included transplant-free survival and rate of transplantation. A total of 173 patients received NAC (n = 81) or placebo (n = 92). Overall survival at 3 weeks was 70% for patients given NAC and 66% for patients given placebo (1-sided P = .283). Transplant-free survival was significantly better for NAC patients (40%) than for those given placebo (27%; 1-sided P = .043). The benefits of transplant-free survival were confined to the 114 patients with coma grades I-II who received NAC (52% compared with 30% for placebo; 1-sided P = .010); transplant-free survival for the 59 patients with coma grades III-IV was 9% in those given NAC and 22% in those given placebo (1-sided P = .912). The transplantation rate was lower in the NAC group but was not significantly different between groups (32% vs 45%; P = .093). Intravenous NAC generally was well tolerated; only nausea and vomiting occurred significantly more frequently in the NAC group (14% vs 4%; P = .031). Intravenous NAC improves transplant-free survival in patients with early stage non-acetaminophen-related acute liver failure. Patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation.

Database: Medline

Combination of N-acetylcysteine and metformin improves histological steatosis and fibrosis in patients with non-alcoholic steatohepatitis

Author(s): de Oliveira C.P.M.S.; Stefano J.T.; De Siqueira E.R.F.; Silva L.S.; de Campos Mazo D.F.; Lima V.M.R.; Furuya C.K.; Souza F.G.; Rabello F.; Santos T.E.; Nogueira M.A.; Carrilho F.J.; Mello E.S.; Alves V.A.F.; Caldwell S.H.

Source: Hepatology Research; Feb 2008; vol. 38 (no. 2); p. 159-165

Publication Date: Feb 2008

Publication Type(s): Journal: Article

Available in full text at [Hepatology Research](#) - from John Wiley and Sons

Abstract:Aim: There is no proven medical therapy for the treatment of non-alcoholic steatohepatitis (NASH). Oxidative stress and insulin resistance are the mechanisms that seem to be mostly involved in its pathogenesis. The aim of our study was to evaluate the efficacy of N-acetylcysteine (NAC) in combination with metformin (MTF) in improving the aminotransferases and histological parameters

(steatosis, inflammation, hepatocellular ballooning, and fibrosis) after 12 months of treatment. Methods: Twenty consecutive patients (mean age 53 +/- 2 years [36-68] and body mass index [BMI] 29 [25-35]) with biopsy-proven NASH were enrolled in the study. NAC (1.2 g/day) and MTF (850-1000 mg/day) were given orally for 12 months. All patients underwent evaluation of serum aminotransferases, fasting lipid profile and serum glucose, anthropometric parameters, and nutritional status at 0 and 12 months. A low calorie diet was prescribed for all patients. Results: Serum alanine aminotransferase, high-density lipoprotein, insulin, and glucose concentrations and the homeostasis model assessment-insulin resistance (HOMA-IR) index were reduced significantly at the end of study ($P < 0.05$). The BMI declined, but without statistical significance. Aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, cholesterol, and triglycerides levels were not altered with the treatment. Liver steatosis and fibrosis decreased ($P < 0.05$), but no improvement was noted in lobular inflammation or hepatocellular ballooning. The NASH activity score was significantly improved after treatment. Conclusion: Based on the biochemical and histological evidence in this pilot study, NAC in combination with MTF appears to ameliorate several aspects of NASH, including fibrosis. Further studies of this form of combination therapy are warranted to assess its potential efficacy. © 2007 The Japan Society of Hepatology.

Database: EMBASE

N-acetylcysteine attenuates oxidative stress and liver pathology in rats with non-alcoholic steatohepatitis.

Author(s): Thong-Ngam, Duangporn; Samuhasaneeto, Suchitra; Kulaputana, Onanong; Klaikeaw, Naruemon

Source: World journal of gastroenterology; Oct 2007; vol. 13 (no. 38); p. 5127-5132

Publication Date: Oct 2007

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Available in full text at [World Journal of Gastroenterology](#) - from Free Access Content

Abstract: To evaluate attenuating properties of N-acetylcysteine (NAC) on oxidative stress and liver pathology in rats with non-alcoholic steatohepatitis (NASH). Male Sprague-Dawley rats were randomly divided into three groups. Group 1 (control, n=8) was free accessed to regular dry rat chow (RC) for 6 wk. Group 2 (NASH, n=8) was fed with 100% fat diet for 6 wk. Group 3 (NASH+NAC(20), n=9) was fed with 100% fat diet plus 20 mg/kg per day of NAC orally for 6 wk. All rats were sacrificed to collect blood and liver samples at the end of the study. The levels of total glutathione (GSH) and hepatic malondialdehyde (MDA) were increased significantly in the NASH group as compared with the control group (GSH; 2066.7 +/- 93.2 vs 1337.5 +/- 31.5 micromol/L and MDA; 209.9 +/- 43.9 vs 3.8 +/- 1.7 micromol/g protein, respectively, $P < 0.05$). Liver histopathology from group 2 showed moderate to severe macrovesicular steatosis, hepatocyte ballooning, and necroinflammation. NAC treatment improved the level of GSH (1394.8 +/- 81.2 micromol/L, $P < 0.05$), it did not affect MDA (150.1 +/- 27.0 micromol/g protein), but led to a decrease in fat deposition and necroinflammation. NAC treatment could attenuate oxidative stress and improve liver histology in rats with NASH.

Database: Medline

Effects of N-acetylcysteine on oxidative stress in rats with non-alcoholic steatohepatitis.

Author(s): Samuhasaneeto, Suchittra; Thong-Ngam, Duangporn; Kulaputana, Onanong; Patumraj, Suthiluk; Klaikeaw, Naruemon

Source: Journal of the Medical Association of Thailand = Chotmaihet thangphaet; Apr 2007; vol. 90 (no. 4); p. 788-797

Publication Date: Apr 2007

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

Abstract: Prove the attenuated effects of N-acetylcysteine (NAC) on oxidative stress in rats with nonalcoholic steatohepatitis (NASH). Male Sprague-Dawley rats were randomly divided into five groups. Group 1 (normal control) was fed regular dry rat chow (RC) for 6 weeks. Group 2 (NASH) was fed 100% fat diet for 6 weeks. Group 3-5 were fed 100% fat diet for 6 weeks, and then switched to RC alone (NASH + diet ; group 3), to RC + 20 mg/kg/day of NAC orally (NASH + diet + NAC20; group 4) or to RC + 500 mg/kg/day of NAC orally (NASH + diet + NAC500; group 5) for 4 weeks, respectively. They were sacrificed to collect blood and liver samples at the end of the present study. Levels of total glutathione (GSH), serum cholesterol, and hepatic malondialdehyde (MDA) were increased significantly in the NASH group compared with normal control. Liver histopathology from group 2 showed moderate to severe macrovesicular steatosis, hepatocyte ballooning, and necroinflammation. Treatment with diet or diet plus NAC reduced the levels of GSH, cholesterol, and hepatic MDA back to normal. Liver sections from group 3-5 showed a decrease in fat deposition and necroinflammation in hepatocytes. However, no differences on all variables existed between diet alone and diet plus NAC groups. Our data indicate that diet or diet plus NAC treatment could attenuate oxidative stress and improve liver histopathology of NASH. However the addition of NAC is not better than diet treatment alone.

Database: Medline

Acetylcysteine treatment for non-acetaminophen-induced acute liver failure.

Author(s): Sklar, Grant E; Subramaniam, Malar

Source: The Annals of pharmacotherapy; Mar 2004; vol. 38 (no. 3); p. 498-500

Publication Date: Mar 2004

Publication Type(s): Journal Article Review

Abstract: To evaluate the effectiveness of intravenous acetylcysteine in the treatment of non-acetaminophen-induced acute liver failure (ALF). A search of MEDLINE (1966-March 2003), International Pharmaceutical Abstracts (1970-2003), and Cochrane Library (2003, issue 3) databases was conducted, using the search terms acetylcysteine, non-acetaminophen-induced hepatic failure, liver failure, intravenous, and treatment. All of the studies found were small and do not provide conclusive evidence that acetylcysteine benefits this subgroup of patients. Microvascular regional benefits were seen, but clinical outcomes have not been studied. Intravenous acetylcysteine should not be used routinely for treatment of non-acetaminophen-induced ALF. Further large-scale studies are needed to evaluate clinical outcomes.

Database: Medline

N-acetylcysteine in the treatment of non-alcoholic steatohepatitis.

Author(s): Pamuk, Gülsüm Emel; Sonsuz, Abdullah

Source: Journal of gastroenterology and hepatology; Oct 2003; vol. 18 (no. 10); p. 1220-1221

Publication Date: Oct 2003

Publication Type(s): Randomized Controlled Trial Letter Clinical Trial

Available in full text at [Journal of Gastroenterology and Hepatology](#) - from John Wiley and Sons

Database: Medline

N-acetylcysteine in acute hepatic failure (non-paracetamol-induced).

Author(s): Ben-Ari, Z; Vaknin, H; Tur-Kaspa, R

Source: Hepato-gastroenterology; 2000; vol. 47 (no. 33); p. 786-789

Publication Date: 2000

Publication Type(s): Journal Article

Abstract: Acute liver failure is a serious condition associated with poor prognosis. It may be associated with changes in systemic hemodynamics, i.e., tissue hypoxia, which contributes to multiple-organ failure. Recent studies have shown that N-acetylcysteine administered to patients with fulminant hepatic failure (paracetamol-induced) increases oxygen delivery and improves survival. The aim of this pilot study was to evaluate N-acetylcysteine administration to patients with non-paracetamol-induced acute liver failure and assess its effect on the clinical course and outcome. N-acetylcysteine was administered at presentation to 7 patients with non-paracetamol-induced acute liver failure. Patients were followed for changes in clinical parameters (grade of encephalopathy), coagulation factors, biochemical parameters and outcome. Clinically, 3 patients who initially had grade O/II encephalopathy, did not progress, and have fully recovered. The mean peak prothrombin time, serum factor V, aspartate aminotransferase and alanine aminotransferase levels, all significantly improved. Four patients (57%) have recovered fully (1 patient, although fully recovered, died later from an unrelated cause). Two patients required orthotopic liver transplantation and 1 patient died. N-acetylcysteine administration may have prevented progression to grade III/IV encephalopathy and improved serum coagulation factors. This may account for its beneficial effect on survival in patients who had poor prognostic criteria at base-line. No side effects of the drug were noted. This study suggests that N-acetylcysteine administration should be considered in all patients with acute liver failure.

Database: Medline

DISCLAIMER: Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

Strategy 106799

#	Database	Search term	Results
1	Medline	(Acetylcysteine).ti,ab	10083
2	Medline	("N-acetylcysteine").ti,ab	9327
3	Medline	("N-acetyl-L-cysteine").ti,ab	3374
4	Medline	exp ACETYLCYSTEINE/	11356
5	Medline	(1 OR 2 OR 3 OR 4)	17725
6	Medline	exp "NON-ALCOHOLIC FATTY LIVER DISEASE"/ OR exp "FATTY LIVER"/	23968
7	Medline	("fatty liver").ti,ab	17401
8	Medline	(6 OR 7)	30089
9	Medline	(pregn*).ti,ab	388149

10	Medline	exp PREGNANCY/	799047
11	Medline	(9 OR 10)	878437
12	Medline	(5 AND 8 AND 11)	1
13	Medline	(5 AND 8)	63
14	Medline	(8 AND 11)	1266
15	EMBASE	(Acetylcysteine).ti,ab	13140
16	EMBASE	("N-acetylcysteine").ti,ab	12056
17	EMBASE	("N-acetyl-L-cysteine").ti,ab	3875
18	EMBASE	exp ACETYLCYSTEINE/	31438
19	EMBASE	(15 OR 16 OR 17 OR 18)	33028
20	EMBASE	("fatty liver").ti,ab	27812
21	EMBASE	exp "FATTY LIVER"/	56019
22	EMBASE	(20 OR 21)	57869
23	EMBASE	(pregn*).ti,ab	536620
24	EMBASE	exp PREGNANCY/	716583
25	EMBASE	(23 OR 24)	856801
26	EMBASE	(19 AND 22 AND 25)	17
27	EMBASE	(15 AND 22 AND 25)	2
28	EMBASE	*ACETYLCYSTEINE/	9556
29	EMBASE	(22 AND 28)	53
30	EMBASE	(25 AND 28)	146
31	EMBASE	(acute).ti,ab	1324127

32	EMBASE	(22 AND 25 AND 31)	916
33	EMBASE	**"FATTY LIVER"/	14456
34	EMBASE	(preg*).ti	235404
35	EMBASE	(33 AND 34)	552
36	EMBASE	(19 AND 35)	4
37	Medline	("liver failure").ti	4393
38	Medline	exp "LIVER FAILURE"/	21058
39	Medline	(37 OR 38)	22025
40	Medline	(5 AND 11 AND 39)	5
41	EMBASE	("liver failure").ti	6838
42	EMBASE	exp "LIVER FAILURE"/	63209
43	EMBASE	(41 OR 42)	63412
44	EMBASE	(19 AND 25 AND 43)	44
45	EMBASE	**"ACUTE LIVER FAILURE"/	2510
46	EMBASE	(28 AND 45)	32
47	Medline	(5 AND 39)	213
48	PubMed	(Acetylcysteine).ti,ab	15926
50	PubMed	("liver failure" OR "fatty liver").ti,ab	48904
51	PubMed	(48 AND 50)	330