

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

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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 PubMed 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.

Key words. N-acetylcysteine. Acute hepatic failure. Antidote. Critically ill.

INTRODUCTION

Acute liver failure (ALF) affects 2,000 individuals annually in the United States; while ALF is relatively uncommon, it is a fatal syndrome.¹ Overall, short-term survival of patients with ALF has dramatically increased from 3-18% to 67% partly as a result of advances in liver transplantation.² The leading cause of ALF in both children and adults is acetaminophen overdose followed by viral infections, autoimmune disease, and other drugs or toxins.¹

Despite the heterogenic etiologies of ALF, common clinical features include a sudden loss of hepatocellular function leading to a severe systemic inflammatory response with multi-system failure if left untreated. The American Association for the Study of Liver Disease developed a standard definition of ALF which includes, evidence of abnormal

coagulation, usually characterized by an International Normalized Ratio (INR) of 1.5 or greater, along with any degree of encephalopathy in a patient without preexisting cirrhosis, with the length of illness less than 26 weeks in duration.³

Treatment of ALF is challenging because of the rapid progression to coma and death in addition to lack of proven therapies. Supportive measures aimed at attenuating hemodynamic instability, reversing coagulopathy, preventing or controlling infections, prompt administration of an antidote where one exists, and early consideration for liver transplantation should occur.³ The use of acetylcysteine as a glutathione precursor in the early treatment of acetaminophen-induced ALF is well established. Although this is an off-label use of the medication, beneficial effects of acetylcysteine have also been observed in the treatment of non-acetaminophen-induced acute liver failure (NAI-ALF) where glutathione loss is not the problem. The mechanism by which acetylcysteine improves liver function in NAI-ALF has not been fully elucidated; however, the resultant tissue hypoxia observed is believed to be ameliorated by acetylcysteine's antioxidant and vasodilating effects. Small studies including patients with ALF have demonstrated an improvement in the

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consumption of oxygen and oxygen-extraction ratio, derangements observed in ALF, when intravenous acetylcysteine was administered.^{4,5} Furthermore, the antioxidant properties of acetylcysteine may potentiate nitric oxide, thereby increasing renal circulation.⁶ Acetylcysteine has also been used off label for the treatment of carbon tetrachloride, chloroform, penny royal oil toxicity.⁷

In 2004, Sklar and Subramaniam published the results of a literature search investigating the effectiveness of acetylcysteine in the treatment of NAI-ALF.⁸ The authors concluded the evidence did not support the routine use of acetylcysteine in patients with NAI-ALF. Further, they recommended that larger, randomized, double-blind, controlled studies be conducted prior to using acetylcysteine as first-line treatment for NAI-ALF. This recommendation was based on available studies at that time, plagued by small sample sizes and inconclusive results. Other limitations of the available studies up to 2003 were:

- Only conducted in countries with access to IV acetylcysteine.
- Lack of definitive clinical outcomes, and
- Lack of consensus as to the effective dosing, administration, and appropriate patient population.

The purpose of this review article is to evaluate more recent literature on the use of acetylcysteine for NAI-ALF.

DATA SOURCES

A search of MEDLINE April 2003 through May 2012 using the PubMed database was conducted for the keywords acetylcysteine and non-acetaminophen-induced acute liver failure or acetylcysteine and liver failure. Two reviewers (IS, SLKG) performed the search independently to identify articles. There were a total of 263 articles identified during this broad search and the abstracts were reviewed for the inclusion criteria of NAI-ALF. All human case reports, case series, and research articles that discussed the use of acetylcysteine for NAI-ALF were evaluated. Eleven articles were included for review in this article.

ASSESSMENT OF LITERATURE

Since 2004, there have been eight case reports or case series suggesting the beneficial effects of acetylcysteine in ALF not caused by acetaminophen. The description of the cases, treatment regimens used,

and clinical course are described in Table 1.⁹⁻¹⁶ Two notable case reports were published describing the use of intravenous acetylcysteine in infants developing ALF following unintentional overdoses of clove oil.^{9,10} In both cases, the infants had improvements in their liver function and made a full recovery without any long-term sequelae. The mechanism of hepatic injury from clove oil is similar to that seen with acetaminophen. Hepatotoxicity results from the formation of a quinone intermediate when clove oil is metabolized by the hepatic cytochrome P-450 enzyme system.¹⁰ Animal models have demonstrated the enhanced toxicity of clove oil when glutathione stores were depleted and prevention of hepatotoxicity with the administration of either glutathione or acetylcysteine.^{17,18} The relationship between acetylcysteine administration and improved liver function coupled with biological plausibility suggests acetylcysteine can be useful in cases of clove oil poisoning; however, it is difficult to ascertain whether the reversal of ALF in these patients was solely due to the administration of acetylcysteine therapy.

A retrospective study by Kortsalioudaki and colleagues was conducted in children diagnosed with NAI-ALF to determine the effectiveness of acetylcysteine therapy.¹⁹ Fifty-nine patients who did not receive acetylcysteine admitted from 1989-1994 were compared with 111 patients admitted from 1995-2004 who received routine acetylcysteine therapy. All patients received standard therapy with intravenous dextrose, antimicrobials, and stress ulcer prophylaxis. acetylcysteine was administered as a continuous infusion of 100 mg/kg/24 h until normalization of the INR, death, or liver transplant. The two groups were similar in terms of etiology of ALF; however, there were significant differences in the presence of jaundice, ascities, other vital laboratory parameters in the group not receiving acetylcysteine therapy suggesting that this group may have presented with more advanced liver disease. Overall, patients who received acetylcysteine had a greater survival with their native liver as compared to patients who did not receive acetylcysteine therapy (43% vs. 22%, respectively; $p = 0.005$) and an increased rate of survival after liver transplantation. In addition, patients receiving acetylcysteine had a significantly shorter hospital length of stay when compared to patients not receiving acetylcysteine.

Mumtaz, *et al.* conducted a prospective study to determine if the administration of acetylcysteine therapy would impact mortality in patients with NAI-ALF.²⁰ A total of 47 adult patients with NAI-ALF were enrolled from 2004-2007 and compared

Table 1. Case reports or case series of acetylcysteine for non-acetaminophen-induced acute liver failure.

Reference	Patient(s) (n)	Cause of ALF	Case description	Acetylcysteine regimen (concomitant interventions)	Study outcome
Eisen (2004)	1	Clove Oil	3-month-old girl developed ALF ~26 h after consuming less than 8 mL of clove oil.	Intravenous: 150 mg/kg x1, followed by 12.5 mg/kg/h x 4 h, followed by 6.25 mg/kg/h x 48 h (total 52 h of acetylcysteine therapy).	Liver function and clinical status improved with full recovery.
Janes (2005)	1	Clove-oil	15-month-old boy who developed ALF 15 h after injecting 10-20 mL of clove oil.	150 mg/kg.	Improvement in ALT within 6 h. His liver function and status improved over the next eight days.
Daram (2005)	1	Iron	18-year-old woman developed ALF after an intentional overdose of ~100 ferrous sulfate tablets.	Oral: 140 mg/kg followed by a 70 mg/kg dose every 4 h (gastric lavage and deferoxamine).	The patient was minimally symptomatic and eventually had a full recovery.
Assy (2007)	1	Ischemia	56-year-old man developed ALF two days after admission for an exacerbation of severe heart failure.	Intravenous: 150 mg/kg over 15 min, followed by 12.5 mg/kg/h x 4 h, followed by 6.25 mg/kg/h x 16 h.	Three days later the patient showed improvement; liver profile and enzyme levels improved and the signs and symptoms of CHF were reduced. The patient was discharged with no evidence of hepatic dysfunction.
Soteol (2009)	12	Hepatitis A	12 patients age ranging from 5-17 years developing ALF.	Oral: 100 mg/kg every 4 h x 16 h, followed by 100 mg/kg every 6-8 h depending on the clinical and laboratory improvement.	All cases had satisfactory progress.
Tuccori (2010)		Ethanol	54-year-old mandeveloped ALF ~10 h after transurethral resection with 10 liters of glycine 1.5% and ethanol 1% used for irrigation during procedure.	Intravenous: 150 mg/kg (hypertonic saline infusion and intravenous furosemide).	Liver function improved over a few days and recovered completely within 30 days.
Kumzrzzena (2010)	8	Dengue infection	All 8 patients developed ALF; 5 patients had coma grades I-II whereas 3 had coma grades III-IV.	Intravenous: 150 mg/kg over 15 min, followed by 12.5 mg/kg/h x 4 h, followed by 6.25 mg/kg/h for up to 72 h.	All patients with coma grades I-II had complete recovery; all patients with coma grades III-IV died.
Cheung (2011)	1	Ifosfamide	61-year-old woman developed ALF 1 day after a three-day treatment of ifosfamide and doxorubicin.	Intravenous: 150 mg/kg over 16 h x 4 days.	Encephalopathy and biochemical tests were reversed 10 days after treatment.

with 44 historical controls from 2000-2003. Patients received oral acetylcysteine at a dose of 140 mg/kg, followed by 70 mg/kg every 4 h, for a total of 17 doses, within 6 h of admission. Patients in both groups received standard supportive care. Baseline characteristics between the two groups were similar except the baseline bilirubin was significantly higher in the control group. Of note, the majority of the patients in both groups had acute hepatitis E infection as the cause of ALF. Survival rates for patients in the acetylcysteine group were significantly higher than the control group. Interestingly, the authors identified five independent prognostic risk factors predicting mortality including patients who did not receive acetylcysteine [OR 10.3; 95% CI (1.6-65.7)], older than 40 years of age [OR 10.3; 95% CI (2.0-52.5)], prothrombin times greater than 50 seconds [OR 15.4; 95% CI (3.8-62.2)], requiring mechanical ventilation [OR 20.1; 95% CI (3.1-130.2)], and an interval of onset between jaundice and hepatic encephalopathy of more than 7 days [OR 5.0; 95% CI (1.3-19.1)].

The two previous trials suggest a survival benefit from acetylcysteine therapy in children and adults in patients admitted with ALF not caused by acetaminophen; however, there are several limitations.^{19,20} Both studies were single-center and enrolled small numbers of patients. One study used an oral regimen of acetylcysteine early in the course of ALF for a specific duration, whereas the other study used an inconsistent duration of acetylcysteine as an intravenous infusion.^{19,20} Most importantly, both studies used a design that involves a historical control group. Because these two groups are not compared at the same time point, differences in survival between these two groups may have been a result of advances in the care of the critically ill patient.

Lee, *et al.* performed a prospective, randomized, double-blind multicenter study to determine whether IV acetylcysteine improves overall survival at 3 weeks after study enrollment in patients with NAI-ALF.²¹ One hundred seventy three patients were randomized to receive intravenous acetylcysteine at 150 mg/kg/h over one hour, 12.5 mg/kg/h for 4 h, followed by 6.25 mg/kg/h for the remaining 67 h or placebo. Results indicated that survival at 3 weeks was not significant between the two groups; however, transplant-free survival was significantly higher in the acetylcysteine group *vs.* placebo (40% *vs.* 27%, respectively; $p = 0.043$). Transplant-free survival was found to be significant for patients with coma grades I-II as compared to grades III-IV

(52% *vs.* 30%, respectively; $p = 0.01$). In spite of these results, 40% of the study population required liver transplantation. Additionally, this study was conducted over a period of eight years (1998-2006) during which time advances in the care of ALF patients may have influenced the results.

ADVERSE EFFECTS

Oral and intravenous acetylcysteine therapy was well tolerated in large clinical studies.¹⁹⁻²¹ Adverse effects noted in the studies include nonspecific maculopapular rash, transient bronchospasm, arrhythmias (tachycardia and bradycardia), dizziness, and peripheral edema.^{19, 20} Anaphylactoid reactions, which are typically infusion rate related, have also been reported with the use of acetylcysteine.^{19,20} In the largest, randomized controlled trial to date, the only significant difference observed was an increased incidence of nausea and vomiting in the acetylcysteine group *vs.* placebo (14% *vs.* 4 %, respectively; $p = 0.03$).²¹

DISCUSSION

Since 2003, there have been several contributions to the literature that provide further insight to the use of acetylcysteine in the treatment of ALF not caused by acetaminophen. Advances in the care have improved the overall outcome of ALF; however, liver transplantation is definitive therapy in advanced cases. Despite the marginal benefit from IV acetylcysteine therapy in NAI-ALF with coma grades I-II, the routine use of acetylcysteine cannot be recommended; however, may be considered in non-transplant centers while awaiting referral or when transplantation is not an option. Current data are limited by timing of therapy and the inclusion of a heterogeneous patient population. In addition, any improvements in mortality may be offset by the failure of other organ systems in these critically ill patients. Finally, studies to date do not account for advances in clinical practice that affect the ability to correctly interpret the magnitude of benefit of acetylcysteine therapy in ALF not related to acetaminophen. Future studies are required to determine the optimal dose, route and duration of therapy, and to establish guidelines regarding patient selection.

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CONFLICT OF INTEREST

Authors have no conflict of interest to disclose.

ABBREVIATIONS

- **ALF:** acute liver failure.
- **INR:** International Normalized Ratio.
- **NAI-ALF:** non-acetaminophen-induced acute liver failure.

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