N-acyteylcysteine in conjunction with Methylprednisolone in patients with severe alcoholic hepatitis: a prospective, randomized, double blind, placebo-controlled trial

Wellington Veras

A. Study Purpose and Rationale

Alcoholic hepatitis, in its severest form, carries a very high mortality, with in-hospital mortality reaching as high as 65%.(1) Stratification of disease severity relies on the Maddrey discriminant-function (DF) score, calculated as 4.6(prothrombin time-control time (in seconds)+serum bilirubin). Severe alcoholic hepatitis is defined as a discriminant function score > 32. Current treatment of this disease relies on alcohol abstinence, supportive care, nutritional supplementation, and corticosteroid therapy. Multiple trials have evaluated the use of corticosteroids in the treatment of alcoholic hepatitis, with equivocal results.(2) Despite the results being equivocal, current guidelines recommend corticosteroid therapy for patients with severe alcoholic hepatitis.(3) Corticosteroids have many potential side effects, and therefore there is a need for alternative and/or complementary therapies. Current research is aimed at elucidating the pathogenesis of alcoholic hepatitis and liver failure with the hope that we can use that information for more targeted therapies.

The mechanism of hepatocyte damage in alcoholic hepatitis is not well understood. It is however thought to involve various mechanisms, including oxidative stress attributable to both an increased production of reactive oxygen species and a depletion of antioxidant defenses.(4) Nacetylcysteine (NAC) is an antioxidant that has been administered for fulminant hepatic failure of several causes, most notably acetaminophen toxicity. Given its antioxidant properties, it has been postulated that NAC might be of benefit in alcoholic hepatitis. This possibility has been explored in a pilot study of 16 patients w/ DF >32 given NAC for 7 or 14 days.(5) The results showed a significant improvement in some biochemical markers, including serum bilirubin level. Although promising, the study was not controlled and did not examine survival as an endpoint.

My proposed study will evaluate NAC, in conjunction with steroids, as a treatment for patients with severe alcoholic hepatitis. I will compare the efficacy of steroids plus placebo, against steroids plus NAC. Efficacy will be assessed via the change in serum bilirubin concentration.

B. Study Design and Statistical Analysis

The proposed study is a prospective, randomized, blinded, placebo controlled trial evaluating the efficacy of N-acetylcysteine in patients with severe alcoholic hepatitis that are also being treated with steroids. The primary endpoint will be serum bilirubin change at 7 days (defined as bilirubin level at day 7 lower than bilirubin level at first day of treatment). Previous studies have shown that bilirubin change at 7 days is a good prognostic indicator of survival at 1 and 6 months.(1) Secondary endpoints that will be analyzed include change in DF, change in MELD score (Model for End-Stage Liver Disease), and survival at 30 days.

Results of previous studies have shown that steroid therapy can decrease bilirubin levels in patients that respond by ainean of up 5mg/d1 with a standard deviation of 4.5. I expect that NAC will decrease bilirubin levels to a mean of 3.5. Using a paired t-test analysis we would need approximately 60 patients in each treatment arm to detect a change in the mean of 1.5 with 80% power. In anticipation of 10% mortality, withdrawal of steroids due to infections, progression to hepato-renal syndrome and withdrawal from study, we will plan to enroll 70 patients in each treatment group.

C. Study Procedure

Following informed consent patients will be randomized to receive either methylprednisolone 32mg Pony daily for 30 days and saline placebo, or methylprednisolone 32mg PO/IV for 30 days and NAC 300mg/kg IV for seven days. The saline and NAC preparations will be prepared by the pharmacist in identical 250cc packages. In order to ensure proper randomization, patients will be stratified according to DF (greater than or less than 50), serum bilirubin (greater than or less than 20), and serum creatinine (greater than or less than 1.5).

Daily blood will be drawn by the medical student and hand delivered to the laboratory for measurements of total hepatic panel including serum bilirubin; prothrombin time; serum electrolytes looking at BUN and creatinine; and complete blood count. Mean serum bilirubin levels at day 0 and day 7 will be compared and analyzed.

The liver transplant team at CPMC will be responsible for the day to day care of the patients, and they will determine if a patient needs to be withdrawn from the study. For our purposes, withdrawal from the study will refer to any situation in which corticosteroid therapy has to be interrupted, even if only temporary. The study drug has a benign side effect profile, and so decisions to withdraw a patient will be based mostly on the side effect profile of the corticosteroid. Patients will be withdrawn if they develop contraindications to steroid therapy such as gastrointestinal bleeding, bacterial infection, or renal failure. A member of the liver transplant service, not involved in the study, will be charged with monitoring for any unexpected complications arising from NAC therapy.

The study length will be 30 days. Patients that are discharged prior to completion of 30 days of steroids will obtain oral steroids and instructed to follow up at the liver transplant clinic to have their blood drawn at day 30. The data from patients who are unable to complete 7 days of NAC therapy will be analyzed in an intention-to-treat manner.

D. Study Drugs

N-acetylcysteine is a derivative of the amino acid cysteine. It is FDA approved as the antidote for acetaminophen toxicity and as a mucolytic agent. Due to its various mechanisms of action, NAC is used off-label for a variety of purposes including protection against doxorubicin toxicity, prevention of hemorrhagic cystitis caused by ifosfamide and cyclophosphamide, for paracetamol overdoses, as well as protection of renal function from radiocontrast dye.

The mechanism of interest in for our study is in NAC's ability to function as a free radical scavenger, and in repletion of glutathione stores preferentially in the liver, pancreas and lungs. The combined actions serve to decrease the amount of oxidative stress and free radical injury in the liver.

The most serious adverse effects reported with NAC were anaphylaxis and bronchospasm, with an incidence of 0.3-3%. The most common adverse effects include rashes, pruritis, and GI irritation including nausea, vomiting and diarrhea.

C. **Medical Device**

There will be no experimental medical devices in this study.

D. **Study Questionnaires**

No questionnaires will be used in this study.

E. Study Subjects

Enrolled patients will all be 18 years or older and have to meet the clinical definition of acute alcoholic hepatitis: a)long history of alcohol abuse, defined for this study as a woman who has more than three drinks every day or 21 drinks per week, or a man who has more than five drinks every day or 35 drinks per week; b) characteristic biochemical markers with an AST to ALT ratio of greater than 1; c) one or more of the following: jaundice, fever, leukocytosis >12k, hepatic encephalopathy, or palpable tender hepatosplenomegaly. MI Patients will have a DF score of 32 or higher.

Patients will be excluded from the trial if they have: a) active gastrointestinal bleeding (GIB) or recent GIB within past 48hrs, b) concomitant bacterial infection, c) Cr greater than 2.5, d) active viral hepatitis as determined by serology, e) prior documented serious adverse reaction to NAC, pregnancy.

Liver biopsy demonstrating histopathological features consistent with alcoholic liver disease will not be a requisite for inclusion into the study.

F. Recruitment of Subjects

Patients will be recruited from the CPMC emergency room and from the liver transplant ward service that have an admitting diagnosis of alcoholic hepatitis.

G. Confidentiality of Study Data

Patient data will be encoded and kept in a secure, central location. All information will be kept confidential in compliance with MB and HIPPA regulations.

H. Potential Conflict of Interest

No conflict of interest. None of the investigators have a financial stake in the results of the study.

I. Location of Study

Study will occur at Columbia-Presbyterian Hospital

J. Potential Risks

Potential risks of the study medication include serious and adverse effects as described under heading "Study Drugs".

K. Potential Benefits

Potential benefits to the patient are resolution of the acute hepatitis flare and potential reduction in mortality. However, the patient may not benefit at all from participation in this study. This study might also help the ongoing research seeking safer alternative therapies for alcoholic hepatitis.

L. Alternative therapies

Other alternative therapies such as Pentoxifylline are being investigated but are not currently accepted as standard of care in severe alcoholic hepatitis.

M. Compensation to Subjects

No compensation will be provided for participation.

N. Costs to Subjects

No costs will be incurred as a result of participation in the study.

O. Minors as research Subjects

Minors will be a part of the study.

P. Radiation or Radioactive Substances

There are no radioactive substances used in this study.

Q. References

1. Mathurin P, Abdelnour M, Raymond MJ, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003; 38: 1363-1369.
2. Mathurin P, Mendenhall CL, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe All. J Hepatol 2002; 36: 480-487.
3. McCullough AJ, O'Connor JF: Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. Am J Gastroenterol 1998 Nov; 93(11): 2022-36.
4. French SW: Mechanisms of alcoholic liver injury. Can J Gastroenterol 2000 Apr; 14(4): 32732.
5. Le Moine 0, Evrard S, Eisendrath P, Deschamps C, Deviere J. Treatment of alcoholic hepatitis with intravenous N-acetylcysteine: a pilot trial. Gastroenterology 2001; 120(suppl. 1):A-545.