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Use of N-Acetylcysteine in the Management of Non-Acetaminophen Drug-Induced Liver Injury

Introduction

Approximately 11% of acute liver failure cases in the United States are caused by idiosyncratic drug-induced liver injury (DILI). Drug-induced liver injury refers to damage to the liver due to a medication, herbal product, or dietary supplement. Damage can range from elevated liver enzymes to acute liver failure, which is characterized by abnormal coagulation (international normalized ratio ≥ 1.5) and encephalopathy. Acetaminophen differs from many other causes of DILI because acetaminophen causes intrinsic DILI, meaning the liver injury is predictable when given in high doses and has the potential to affect everyone. In contrast, other medications cause idiosyncratic DILI, meaning the injury is unpredictable, not clearly dose-related, and affects those who are susceptible. The most common implicated agents in idiosyncratic or non-acetaminophen DILI are antibiotics and antiepileptic agents.

N-acetylcysteine

N-acetylcysteine, administered orally or intravenously, is approved by the Food and Drug Administration for the treatment of acetaminophen overdose. When used for acetaminophen toxicity, N-acetylcysteine works to restore depleted glutathione concentrations. The role of N-acetylcysteine for treatment of non-acetaminophen DILI is less clear. Although the mechanism of N-acetylcysteine in non-acetaminophen DILI is not well understood, the antioxidant and vasodilating actions of N-acetylcysteine are hypothesized to help with oxygen depletion in tissues.

Management of Drug-Induced Liver Injury

Management of non-acetaminophen DILI is difficult due to a number of factors, including the large number of causative agents, varied presentation, and lack of a definitive antidote. In patients with suspected non-acetaminophen DILI, the first step is to immediately discontinue the offending agent. The 2014 American College of Gastroenterology (ACG) guideline on the diagnosis and management of idiosyncratic DILI recognizes the lack of definitive treatments for idiosyncratic DILI, but recommends considering N-acetylcysteine in adults with early acute liver failure (conditional recommendation; low evidence level). However, the ACG does not recommend the use of N-acetylcysteine in pediatric patients with severe DILI (strong recommendation; low evidence level). The 2011 update to the American Association for the Study of Liver Diseases (AASLD) position paper on the management of acute liver failure states N-acetylcysteine may be beneficial in patients with DILI (grade I recommendation based on a randomized controlled trial).

Role of N-acetylcysteine in Non-Acetaminophen Drug-Induced Liver Injury

Literature Review

There are limited data evaluating the use of N-acetylcysteine in non-acetaminophen DILI. Hu et al conducted a meta-analysis of 4 clinical studies of 331 patients who received N-acetylcysteine compared to 285 patients who did not for non-acetaminophen acute liver failure. While there was no difference in the primary endpoint of overall survival between groups, survival without transplantation was significantly higher with use of N-acetylcysteine compared to the control group (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.11 to 2.34; *P* = 0.01). Survival after transplantation was also higher with use of N-acetylcysteine compared to the control group (OR, 2.44; 95% CI, 1.11 to 5.37; *P* = 0.03). Common adverse events associated with N-acetylcysteine included nausea, vomiting, diarrhea, and constipation. Other adverse events included rash, bronchospasm, and arrhythmia. The studies included in the meta-analysis are summarized below.

Lee at al conducted a prospective, double-blind, multi-center, placebo-controlled study evaluating the use of intravenous N-acetylcysteine in adults with acute liver failure. Patients were randomized to either 5% dextrose (placebo) or 5% dextrose with N-acetylcysteine at a dose of 150 mg/kg/hr for 1 hour, then 12.5 mg/kg/hr for 4 hours, and then 6.25 mg/kg as a continuous infusion for 67 hours. Eighty-one patients received N-acetylcysteine and 92 patients received placebo. The etiology of acute liver failure was DILI (n = 45), hepatitis B (n = 37), autoimmune hepatitis (n = 26), and indeterminate (n = 41). There was no difference in overall survival at 3 weeks in the N-acetylcysteine group compared to placebo (70% vs. 66%, respectively; *P* = 0.283). Significantly more patients

achieved transplant-free survival in the N-acetylcysteine group (40%) compared to the placebo group (27%; *P* = 0.043). When analyzed by coma grades, transplant-free survival was higher in patients with coma grades 1 to 2 with use of N-acetylcysteine compared to placebo (52% vs. 30%, respectively; *P* = 0.01); however, there was no statistical difference in transplant-free survival between groups in patients with coma grades 3 to 4. When outcomes were analyzed by etiology, the rate of transplant-free survival in patients with DILI was 58% with use of N-acetylcysteine compared to 27% in placebo; however, statistical significance was not determined due to a small sample size. Adverse events that occurred with higher frequency in the N-acetylcysteine group compared to placebo were nausea and vomiting (14% vs. 4%, respectively; *P* = 0.031). One patient in each group experienced bronchospasm. These results suggest that, while N-acetylcysteine did not improve overall survival, it improved transplant-free survival in patients with early coma grades (1 to 2).

A prospective study evaluated the use of N-acetylcysteine in 184 pediatric patients with non-acetaminophen acute liver failure. The use of intravenous N-acetylcysteine 150 mg/kg/day in 5% dextrose for 7 days did not improve survival at 1 year compared to placebo (73% vs. 82%, respectively; *P* = 0.19). A lower rate of transplant-free survival at 1 year occurred with use of N-acetylcysteine compared to placebo (35% vs. 53%, respectively; *P* = 0.03). This study is cited by the ACG guideline in its recommendation not to use N-acetylcysteine in children with severe DILI. However, an important limitation of this study is that none of the causes of acute liver failure in the N-acetylcysteine group were secondary to DILI.

Mumtaz et al conducted a cohort study that prospectively enrolled 47 adults who received N-acetylcysteine and compared them to 44 historical controls with acute liver failure not caused by acetaminophen. Oral N-acetylcysteine was administered every 4 hours at an initial dose of 140 mg/kg, then 70 mg/kg for 17 total doses. However, only 3 patients in the N-acetylcysteine group had drug-induced acute liver failure. Forty-seven percent of patients in the N-acetylcysteine group survived compared to 27% in the control group (*P* = 0.05). Conclusions that can be drawn from this study are limited due to the small number of patients included with acute liver failure secondary to DILI.

Kortsalioudaki et al conducted a retrospective study of pediatric patients with non-acetaminophen acute liver failure who received N-acetylcysteine (n = 111) compared with patients in the control group (n = 59). Patients received a continuous infusion of N-acetylcysteine 100 mg/kg/24 hr until INR < 1.4, liver transplantation, or death. The etiology of acute liver failure was DILI in 7 patients (6%) who received N-acetylcysteine. Survival without liver transplantation occurred in 43% of patients treated with N-acetylcysteine compared to 22% of those who did not receive N-acetylcysteine (*P* = 0.005). Of those who underwent liver transplantation, death occurred in 16% of patients who received N-acetylcysteine compared to 39% of patients in the control group (*P* = 0.02). N-acetylcysteine was discontinued in 1 patient due to an allergic reaction of bronchospasm and maculopapular rash.

Conclusion

Overall, evidence supporting the use of N-acetylcysteine in non-acetaminophen DILI is limited. A recent meta-analysis found that N-acetylcysteine is beneficial for the treatment of acute liver failure, but the analysis was not specific to acute liver failure secondary to DILI. One prospective study in adults showed that N-acetylcysteine improved transplant-free survival in patients with acute liver failure and grades 1 to 2 coma. Other studies evaluating the use of N-acetylcysteine in adult and pediatric patients are limited by a small number of patients who experienced acute liver failure secondary to DILI. N-acetylcysteine is safe and the most common adverse events include nausea, vomiting, diarrhea, and constipation. Bronchospasm is a rare, but more serious, adverse event. Based on these studies, N-acetylcysteine may benefit adults with DILI who are in early stages of acute liver failure. There are not enough data to support its use in pediatric patients.

Recommendations for Non-Statin Cholesterol Lowering Therapies

The American College of Cardiology (ACC) published an expert consensus decision pathway on the use of non-statin cholesterol lowering therapies for managing atherosclerotic cardiovascular disease (ASCVD) risk. These guidelines aim to build on the ACC/American Heart Association (AHA) guidelines that were published in 2013 by providing further guidance on the use of non-statin therapies for patients who may be intolerant to statins or need additional cholesterol lowering therapy.

According to the expert consensus, patients who do not achieve low density lipoprotein (LDL) lowering goals may be evaluated for additional therapies. Similar to the 2013 guidelines, goals for therapy are broken into groups and based on the ASCVD risk, comorbidities, age, and baseline LDL value. Workup for patients who do not achieve their LDL goals should include assessment of adherence, statin intolerance, lifestyle modifications, and intensification of the statin dose. Soluble dietary fiber and phytosterols may be added. Next, if goals are not met, a patient-provider discussion should determine whether to seek non-statin therapies. This discussion should include the ASCVD risk reduction, drug interactions, possible adverse events, and patient preferences. If the decision for a non-statin therapy is chosen, the ACC expert consensus recommends the options listed in Table 1 based on risk group.

Table 1. Risk groups and recommendations

Risk group	LDL goal	Non-statin therapy if LDL goal not reached
Adults with clinical ASCVD		
Without comorbidities	≥50% reduction from baseline or consider < 100 mg/dL	First-line: ezetimibe 10 mg daily Second-line: BAS* If unable to reach goals with ezetimibe, consider: PCSK9 inhibitor therapy
With comorbidities+	≥50% or consider < 70 mg/dL (or non-HDL < 100 in patients with DM)	First-line: ezetimibe Second-line: BAS* If unable to reach goals with ezetimibe, consider: PCSK9 inhibitor therapy
With baseline LDL ≥ 190 mg/dL	≥50% or consider < 70 mg/dL (or non-HDL < 100 in patients with DM)	Consider first-line: ezetimibe or PCSK9 inhibitor therapy Second-line: BAS*
Adults without clinical ASCVD		
With baseline LDL ≥ 190 mg/dL	≥50% or consider < 100 mg/dL	Consider: ezetimibe or PCSK9 inhibitor therapy Second-line: BAS*
Aged 40 to 75 years with DM, ASCVD risk < 7.5%, and LDL 70 to 189 mg/dL	≥50% or consider < 100 mg/dL (or non-HDL < 130 mg/dL patients with DM)	First-line: ezetimibe Second-line: BAS*
Aged 40 to 75 years without diabetes, LDL 70 to 189 mg/dL, and ASCVD risk score ≥ 7.5% at high risk^ NOT on high intensity statin	30 to 49% or consider < 100 mg/dL	Elevate to high intensity statin therapy
Aged 40 to 75 years without diabetes, LDL 70 to 189 mg/dL, and ASCVD risk score ≥ 7.5% at high risk^ ON high intensity statin	>50% or consider < 100 mg/dL	First-line: Ezetimibe Second-line: BAS*

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; PCSK9, proprotein convertase subtillsin/kexin type 9; TG, triglycerides
**If intolerant to ezetimibe and triglycerides < 300 mg/dL*
+Comorbidities include DM, ASCVD event within past 3 months, ASCVD event during statin therapy, poorly controlled ASCVD risk factors, elevated lipoprotein, chronic kidney disease not on dialysis, baseline LDL ≥ 190 mg/dL not due to secondary causes
#Higher risk includes ASCVD risk ≥ 7.5%, and LDL 70 to 189 mg/dL with CKD, albuminuria, retinopathy, evidence of subclinical atherosclerosis, elevated lipoprotein, or elevated hs-CRP
^High risk defined as 10-year ASCVD risk score ≥ 20%, primary LDL ≥160 mg/dL at baseline, poorly controlled major ASCVD risk factors, family history of premature ASCVD, accelerated subclinical atherosclerosis (eg, coronary artery calcification), elevated hs-CRP, concomitant conditions (eg, chronic kidney disease, human immunodeficiency virus, chronic inflammatory disorders)

The ACC expert consensus also provides recommendations on 3 specific patient populations: patients with symptomatic heart failure due to ischemic disease, patients on hemodialysis, and patients who plan on becoming pregnant. Use of a statin in patients with symptomatic heart failure is recommended if the expected survival is 3 to 5 years in order to see a benefit from statin therapy. The expert consensus recommends that these patients be considered in the clinical ASCVD plus comorbidities group listed in Table 1, except that proprotein convertase subtillsin/kexin type 9 (PCSK9) inhibitors are not recommended. In patients on maintenance hemodialysis, the expert consensus recommends an individual evaluation of risks and benefits. Women who are considering becoming pregnant should discontinue LDL-lowering therapy ideally 3 months before conception, or 1 month beforehand at the latest. However, a BAS may be continued but monitoring for vitamin K deficiency is recommended. Management of dyslipidemia in pregnancy should focus on lifestyle modifications.

Redefining Sepsis

Background

In an effort to facilitate earlier recognition and more timely management of patients with sepsis or those at risk of developing sepsis, key definitions and clinical criteria have recently been revised. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was the work of a multi-specialty task force of experts from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Key changes between current and previous definitions and clinical criteria are provided in Table 1. The last update to the definitions and clinical criteria were made in 1991 and 2001, respectively.

Terminology

Sepsis-3 defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The new definition shifts the focus away from inflammation, and gives a greater emphasis on the development of organ dysfunction. Another change in terminology is the removal of the term *severe sepsis*. The task force felt that this tem was redundant, and mislead clinicians into thinking that septic patients follow a continuum from sepsis to severe sepsis and septic shock.

Clinical criteria

In addition to updated definitions, clinical criteria for diagnosis of sepsis and septic shock have also changed. Use of the *systemic inflammatory response syndrome* (SIRS) criteria to help identify septic patients is no longer recommended, as it puts a disproportionate emphasis on inflammatory processes that may reflect an appropriate host response to infection. Additionally, new research has shown that when compared to other clinical scoring systems, SIRS criteria has a low predictive validity for hospital mortality both in and out of critical care areas. For these reasons, Sepsis-3 recommends 2 new scoring systems: the Sequential (sepsis-related) Organ Failure Assessment (SOFA) and quick SOFA (qSOFA). The SOFA scoring system was first described in the literature over 2 decades ago as a surrogate marker to predict mortality. The SOFA score consists of laboratory variables related to an organ system and/or intervention (see Table 2). Organ dysfunction is represented by a ≥ 2 point increase from baseline in SOFA score, which has an associated in-hospital mortality of > 10%. The intricacy of the SOFA scoring system largely limits use to patients being cared for in critical care areas.

For non-critical care settings such as emergency departments and hospital wards, the qSOFA score provides clinicians with a quick screening tool to identify possible organ dysfunction in patients with a suspected or confirmed infection. The qSOFA score allocates 1 point for each of the following criteria: altered mental status, systolic blood pressure ≤100 mm Hg, and respiratory rate ≥ 22 per minute. A qSOFA score of 2 or 3 should prompt the clinicians to consider possible organ dysfunction, and potential need for escalation of care.

Summary

The Sepsis-3 task force hopes that the new definitions and scoring system will improve patient outcomes, and offer greater consistency for epidemiologic studies and clinical trials reporting on sepsis. The Surviving Sepsis Campaign has endorsed the new definitions and clinical criteria, while continuing to stress the importance of early identification and treatment of possible infection. For all septic patients, utilization of the 3-hour and 6-hour bundle elements (i.e., Surviving Sepsis Campaign Bundles) also continues to be strongly recommended.

Table 1. Key changes to definitions and clinical criteria

	Previous	Current
Sepsis	A clinical syndrome defined by the presence of both infection and a systemic inflammatory response. • Extensive list of potential clinical criteria/laboratory abnormalities	Life-threatening organ dysfunction caused by a dysregulated host response to infection. • Suspected or documented infection *plus* acute increase of ≥2 SOFA points *or* qSOFA score 2 or 3
Severe sepsis	Sepsis complicated by organ dysfunction. • Extensive list of potential clinical criteria/laboratory abnormalities	Task force concluded that the term “severe sepsis” was redundant
Septic shock	A state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. • Arterial SBP <90 mm Hg, MAP < 60 mm Hg, or a reduction in SBP of > 40 mm Hg from baseline, despite adequate fluid resuscitation	A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. • Sepsis *plus* vasopressor therapy needed to maintain MAP ≥65 mm Hg *and* lactate >2 mmol/L (18 mg/dL), despite adequate fluid resuscitation

MAP=mean arterial pressure; qSOFA=quick Sequential [Sepsis-related] Organ Failure Assessment; SBP=systolic blood pressure; SOFA=Sequential [Sepsis-related] Organ Failure Assessment.

Table 2. The Sequential Organ Failure Assessment (SOFA) score

SOFA score	1	2	3	4
Respiration				
PaO_2/FIO_2, mm Hg	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation				
Platelets, $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin, mg/dL	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular[a]				
Hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any)	Dopamine 5.1 to 15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
CNS				
Glasgow Coma Score[b]	13-14	10-12	6-9	<6
Renal				
Creatinine, mg/dL	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine output, mL/day	-	-	<500	<200

CNS=central nervous system; FIO2=fraction of inspired oxygen; MAP=mean arterial pressure; PaO_2=partial pressure of oxygen.
[a]*Vasoactive mediations administered for at least 1 hr (catecholamine doses in* µg*/kg/min)*
[b]*Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.*

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