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NAC in NON- PCM LIVER FAILURE: NEW PROPOSED CRITERIA.

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Indian multicentric data of IAP-PED GASTRO/LIVER group on acute liver failure is eagerly awaited.

This vol 37 of pedgihep e-journal focuses on recently published papers on use of N-acetyl cystine in non PCM based acute Liver failure

Meta-analysis, text book references, adverse reactions of NAC, effect of NAC on normal subjects, Pharmacokinetics of NAC are discussed in details.

May I propose selective use of NAC in predetermined population in children for study purpose till further reports are available or published? Selective group included for using NAC are based on recently conducted trials.

Pharmacokinetics: NAC is deacetylated by the liver and intra-cellularly in most tissues to cysteine. Most of an acetylcysteine dose is expected to be metabolized and incorporated as cysteine into cellular pools. The mean terminal $t_{1/2}$ is 5.6 hours; clearance is 0.11 L/hr/kg. Renal clearance accounts for roughly 30% of total clearance. In patients with severe liver damage, the mean $t_{1/2}$ increases by 80% while the mean clearance decreases by 30% compared to a control group. The clearance of acetylcysteine was significantly reduced in patients with chronic liver disease compared with controls (Aliment Pharmacol Ther. 1997 Aug;11(4):787-91). Specific guidelines for dosage adjustments in hepatic impairment are not available; it is not known if dosage adjustments are needed. Although there was a 3-fold increase in acetylcysteine plasma concentrations in patients with hepatic cirrhosis, the published medical literature does not indicate that the dose of acetylcysteine in patients with hepatic impairment should be reduced. Specific guidelines for dosage adjustments in renal impairment are not available; it is not known if dosage adjustments are needed.

The mean elimination half-life of acetylcysteine is longer in newborns (11 hours) than in adults (5.6 hours).

Acceptable diluents include: 5% Dextrose, 0.45% Sodium Chloride injection (1/2 Normal Saline), and Water for Injection. Stability studies indicate that the diluted solution is stable for 24 hours at controlled room temperature. Photosensitivity of NAC is cannot be neglected .(drug insert)

The median duration of NAC administration in children with nonacetaminophen-induced acute liver injury is 5 days (range, 1 to 77 days) (Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal

S, Mieli-Vergani G, Dhawan A: **Safety and efficacy of *N*-acetylcysteine in children with non-acetaminophen-induced acute liver failure.** *Liver Transpl* 2008, **14:**25-30.)

EFFECT OF NAC in Normal controls:

N-acetylcysteine induced significant decreases in plasma levels of vitamin K dependent haemostatic proteins in vivo, being maximal at one hour following the start of infusion, with maximal decreases from 1.00 to 0.73 (0.67-0.79) (mean (95% confidence interval)), 0.66 (0.58-0.73), 0.81 (0.73-0.90), 0.64 (0.57-0.70), 0.74 (0.65-0.82), and 0.61 (0.54-0.67) for factor II, VII, IX, and X activities, protein C activity, and free protein S reactivity, respectively. N-acetylcysteine did not affect factor VIII or vWf in subjects without adverse reactions, and nor did it affect factor V or antithrombin in any of the subjects. Therapeutic doses of N-acetylcysteine cause abnormal haemostatic activity, and this should be taken into account when using haemostatic function tests as an indicator of hepatic injury.

Knudsen TT, Thorsen S, Jensen SA, Dalhoff K, Schmidt LE, Becker U, Bendtsen F - Gut - Apr 2005; 54(4); 515-21

Adverse Reactions

- anaphylactoid reactions
- bronchospasm
- drowsiness
- dysgeusia
- dyspnea
- edema
- erythema
- fever
- flushing
- hemoptysis
- hypotension
- nausea
- pharyngitis
- pruritus
- rash (unspecified)
- rhinorrhea
- sinus tachycardia
- stomatitis
- urticaria
- vomiting
- wheezing

TEXTBOOK REFRENCES 1:

STATEMENT:

N-Acetylcysteine has also been effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Nelson Textbook of Pediatrics , Nineteenth EditionRobert M. Kliegman, Bonita F. Stanton, Joseph W. St. Geme, Nina F. Schor, and Richard E. Behrman Chapter 356, 1412-1415.e1

TEXTBOOK REFRENCE 2:

N-acetylcysteine has been proposed as a potential treatment for non–acetaminophen-related acute liver failure on the basis of studies demonstrating improvements in tissue oxygenation and systemic hemodynamics and the drug's antioxidant properties. The benefit of *N*-acetylcysteine appeared to be limited to the subgroup of patients with grade 1 or 2 encephalopathy at entry (52% vs. 31%, P = 0.021). In addition, a single-center retrospective study of 170 children with nonacetaminophen acute liver failure demonstrated that treatment with *N*-acetylcysteine was associated with a shorter length of hospital stay and a higher rate of spontaneous recovery. study, *Liver Transpl* 14 (2008) , pp. 25-30 however, the untreated controls were not contemporaneous and had more severe illness at presentation. In both studies, *N*-acetylcysteine was generally well tolerated, with a low rate of side effects (e.g., rash, bronchospasm, arrhythmia). Additional studies of *N*-acetylcysteine for non–acetaminophen-related acute liver failure are in progress to identify which patients may benefit from this treatment.

Sleisenger and Fordtran's Gastrointestinal and Liver Disease:Pathophysiology/Diagnosis/Management , Ninth EditionMark Feldman, Lawrence S. Friedman, and Lawrence J. BrandtChapter 93, 1557-1568.e3

Journals review:

Statement 1:NAC did not improve 1-year survival in non-APAP PALF. 1-year LTx-free survival was significantly lower with NAC, particularly among those < 2 years old. These results do not support broad use of NAC in non-APAP PALF and emphasizes the importance of conducting controlled pediatric drug trials, regardless of results in adults

Method: adaptively allocated, doubly masked, placebo-controlled trial, A total of 184 participants were enrolled in the trial with 92 in each arm.

Study sample: pediatric age group.

PAPER1: Squires RH, Dhawan A, Alonso E, ETAL Hepatology. 2012 Aug 10.

Statement 2: NAC treatment of AOM mice led to reduced hepatic damage and improvement in neurological function, normalization of brain and hepatic glutathione levels as well as selective attenuation in expression of plasma proinflammatory cytokines. These findings demonstrate that the beneficial effects of NAC in experimental non-APAP-induced ALF involves both antioxidant and anti-inflammatory mechanisms.

Study sample: animals.

Method: Male C57BL/6 mice were treated with AOM (100 microg/g; i.p.) or saline and sacrificed at coma stage of encephalopathy in parallel with AOM mice administered NAC (1.2 g/kg; i.p.).

Paper 2: Bmeur C, Vaquero J, Desjardins P, Butterworth RF. Metab Brain Dis. 2010 Jun ; 25(2): 241-9

Statement 3: The use of NAC causes reduction in NAI-ALF mortality and its use was safe. A total of 34 (37.36%) patients survived; 22 (47%) in group 1 (NAC group) and 12 (27%) in group 2 (controls) ($P = 0.05$).

Study samples: adult based.

Method: 47 adult patients ,prospectively enrolled with NAI-ALF (group 1 or NAC group) and oral NAC given. 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).

Study 3: Role of *N*-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation Hepatology International Volume 3, Issue 4 , pp 563-570

Statement 4: 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.

Study samples 4: adult based. ClinicalTrials.gov number NCT00004467

Method 4:173 patients, 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.

Study 4 : Gastroenterology. 2009 September; 137(3): 856–864.e1. Published online 2009 June 12. doi: 10.1053/j.gastro.2009.06.006

STATEMENT 5: NAC does not improve transplant free survival by ameliorating the surge of pro-inflammatory cytokines in patients with non-APAP induced ALF. There were no differences in any serum cytokine concentrations or in SIRS in patients treated with NAC vs. placebo.

Study sample:Adult based, 90 patients from the randomized, placebo-controlled ALF Study Group NAC Trial
METHOD: randomized, placebo-controlled ALF Study Group NAC

STUDY 5: Relationship of Serum Cytokine Concentrations to Outcome, Complications and N-Acetylcysteine Treatment in Patients With Non-Acetaminophen-Induced Acute Liver Failure Mo1917. ASSLD abstracts. Gastroenterology 2012 :vol142:issue 5, supplement 1,S-999

Statement 6: NAC was associated with a shorter length of hospital stay, higher incidence of native liver recovery without transplantation, and better survival after transplantation.

Study sample: pediatric

Study group: 170 children presenting with nonacetaminophen-induced ALF between 1989 and 2004 ,retrospective.

Study:

Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal S, Mieli-Vergani G, Dhawan A - Liver Transpl. - Jan 2008; 14(1); 25-30

STATEMENT 7: N-acetylcysteine administration should be considered in all patients with acute liver failure.

STUDY SAMPLE: 7 Patients.

Method: pilot study, observation based.

Study: Ben-Ari Z, Vaknin H, Tur-Kaspa R - Hepatogastroenterology - ; 47(33); 786-9

Statement 8 : MEDLINE (1966-March 2003), International Pharmaceutical Abstracts (1970-2003), and Cochrane Library (2003, issue 3) databases : 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.

METHOD: METAREVIEW IN 2004

STUDY: Sklar GE, Subramaniam M - Ann Pharmacother - Mar 2004; 38(3); 498-500

Statement 9: N-acetylcysteine infusion increases cerebral perfusion pressure in pigs with fulminant hepatic failure.

Study sample: animal based.

Study: Crit Care Med. 2001 Oct;29(10):1989-95.

SUGGESTIONS:

The predictive model for early recognition of the risk of short-term development of hepatic encephalopathy (HE) or CLINICAL worsening in patients with symptomatic acute liver disease (ALD) unrelated to PCM poisoning has been well studied in literature. Earlier studies indicate that preservation of transplant-free survival of inpatients with non-PCM ALD is closely related to the ability to recognize early, often narrow window of opportunity.[1-5] We can stream-line use of NAC in selected group of patients accordingly.

King's college criteria (KCH)were established 20 years ago to predict survival rate lower than 20% among British patients with established non-P ALF (i.e. with HE) [6].

Study BY Y. Takikawa et al. [7]in Japanese patients Strongly support the view that the items used in KCH criteria (excluding the duration of jaundice before the onset of HE) to predict the short-term development of HE or clinical worsening. Takikawa and coworkers, from Japan, report the results of a 13-year prospective study that aimed to predict HE for inpatients with non-P ALD hence can be used as baseline reference for further studies. HE was predicted with 100% sensitivity and 69% specificity, or 62% sensitivity and 93% specificity, when taking cut-off values of HE-developing probability >20% or >50%, respectively;

The indications recommended by Jacques Bernuau, Franc_ois Durand [8] for referral of non-P ALD inpatients to a liver unit, ideally with LT (LIVER TRANSPLANT) facility with lesser degree of severity can be used as indications for use of NAC in non -pcm based liver failure with lower threshold at least till further RESULTS validated.
Review of KCH (King's college criteria), Takikawa eta al , Jacques Bernuau et al should guide us to direct poor prognostic patients with un-favourable etiologies of non -pcm based ALF for use of NAC.

PT ratio (% of control)	Additional characteristics of inpatients with non-P ALD
50–30	One of the following variables (1–8) is required for immediate transfer to a liver unit: (1) Children (<15 years)[a] (2) Adults >40 years[a] and unfavourable etiology[b] (3) Non-P ALD with fever >38 °C or uncommon etiology[c] (4) Post-operative ALD[d] (5) Pregnancy (6) ALD superimposed on chronic liver disease[e] (especially when the latter was previously stable and well compensated) (7) Comorbidity at special risk: diabetes mellitus, human immunodeficiency virus infection, previously cured cancer, malaria, severe acute renal failure (8) Hyperbilirubinemia >250 μmol/L [5,10]
<30	(1) Any non-P ALD patient[f] (especially patients[f] of age >40 years[a] or unfavourable etiology[b])

[a] Age: KCC for LT (age <10 or >40) [11]; Takikawa's criteria of increased HE risk (age >50) [10].
[b] Unfavourable etiology: KCC for LT [11]: drug-induced liver, undetermined etiology; Takikawa's criteria of increased HE risk [10]: acute flare-up of hepatitis B virus chronic infection, auto-immune hepatitis, undetermined etiology.
[c] ALD due to necrotizing herpesviruses (fever); (even still unclearly characterized) Wilson's disease, Budd–Chiari syndrome, post-aspirin Reye's syndrome.
[d] After non-hepatic surgery in patients not given anti-vitamin K therapy.
[e] The chronic liver disease may be previously diagnosed, or only suspected ("decompensated" cirrhosis is not included here).
[f] Except previously normal subjects with acute hepatitis type A, or C, or acute hepatic ischemia.

Poor Prognosis of such patients is known without liver Transplant. Liver transplant affordability is an important issue in our set up. Non- Liver Transplant based center may use following criteria for further studies to understand better use of NAC. Criteria for such use of NAC should be at lesser threshold than those for Liver Transplant for further studies.

Proposed Modified criteria for use of NAC with PT activity RATIO 50-30% of control (any one sufficient)

1. CHILDREN <10 year but > 2 years, modified after current PALF study :Squires RH, Dhawan A, Alonso E, ETAL Hepatology. 2012 Aug 10.
2. Children with un-favourable etiologies: Drug induced liver disease,autoimmune liver disease, idiopathic cause,flare of hepatitis B , modified as per KCH & Takikawa etal studies.
3. Children with un-common etiologies: Wilson, budd-chiari, reye's, HSV.
4. Post operative acute liver failure (non-hepatic surg in patients not given anti-vit K).
5. Acute on chronic liver disease: decompensated.
6. Sr bili > 250 umol/lt

I have not included the PT ACTIVITY <30 % as these patients are better transferred or given option of Liver transplant.

Above modified criteria is just a suggestion subject to initiate the discussion on the forum of IAP PED GASTRO AND LIVER GROUP.

Ref:

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6. (O'Grady JG, Alexander GJM, Hayller KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445
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