Dosage of N-Acetyl Cysteine in Acute Liver Failure Not Related to Acetaminophen

We thank Dr Saurabh for his interest in the article INASL-Consensus Statement on Acute Liver Failure (Part-2)-Management of Acute Liver Failure[1] and for pointing out the printing error.

The use of N-acetyl cysteine (NAC), a glutathione precursor, was initially introduced in the 1970s for the treatment of acetaminophen-induced ALF, and its safety/efficacy is well established in this fatal condition.[2,3] NAC has also been shown to provide beneficial effect in non-Acetaminophen ALF (NA-ALF).[4] Various prospective studies and meta-analyses have also shown a beneficial effect of NAC in improving overall survival (OS), transplant-free survival (TFS) or even post-transplant survival (PTS).[5] A few studies have, however, failed to show significant improvement in overall survival when compared to placebo.[2,6] In a recent meta-analysis of seven studies, the use of NAC was associated with improvement in OS, TFS, and PTS in patients with NA-ALF.[7] There was a significant reduction in the duration of hospital stay. In this meta-analysis, the most common etiology of ALF was acute viral hepatitis. It was concluded that NAC should be used in all patients with NA-ALF especially in nontransplant centers and for optimal outcomes it is preferable to initiate treatment in the early stages of ALF.

NAC is available as Intravenous (200 mg/mL, 10 mL ampoule) and oral liquid formulation (10% and 20%) of NAC.[8] Traditionally dosage protocol for NAC for acetaminophen-induced ALF includes a 21-h intravenous protocol, which includes (a) 150 mg/kg of NAC 20% in 200 mL 5% dextrose over 60 min followed by (b) 12.5 mg/kg/hour in 500 mL 5% dextrose for 4 h and then (C) 6.25 mg/kg/hour in 1000 mL 5% dextrose for 16 h). Instead of 5% dextrose, 0.9% normal saline can also be used.[9] For children less than 12 years a body weight of more than 20 kg, the recommended volumes of 5% dextrose are 100 mL, 250 mL, and 500 mL for three dosages, respectively. In children with a body weight of less than 20 kg, the diluting volumes of 5% dextrose at 3 mL/kg, 7 mL/kg, and 14 mL/kg, respectively, have been used. At the end of 21 h infusion, it has been suggested that infusion be continued till encephalopathy resolves and INR normalizes.[10]

In the older studies, NAC has been used either by intravenous route or orally in patients with NA-ALF. The intravenous route has been preferred by many.[11] A systemic review comparing oral and intravenous NAC showed a similar level of hepatotoxicity in rats with acetaminophen overdose, and the route of dosing did not make much difference.[7] One fears that oral NAC may have impaired absorption in, poor tolerance (due to nausea and vomiting), delayed gastric emptying and intestinal failure in the setting of ALF.[11] A prospective study that included the sick patients with ALF failed to show any significant benefit (in terms of OS and duration of hospital stay) using NAC by oral route.[3] Therefore intravenous administration of NAC was preferred over the oral route by the INASL consensus document. INASL has recommended the dosage used by most of the studies.[5,12,13] The safety and tolerability of NAC is well established and minor adverse events reported include allergic reactions (Bronchospasm, rash), cardiac arrhythmias and peripheral edema.[7] A summary of these studies have been provided in Table 1.[1,3,5,12–17]

INASL consensus document for ALF, after due deliberation, recommended that NAC be administered intravenously in all patients with NA-ALF. The recommended regimen should read (a) 150 mg/kg body weight in 250 mL of 5% dextrose over 1 h followed by (b) 50 mg/kg over 4 h and then (c) 100 mg/kg over 16 h. The latter dose, i.e., 100 mg/kg over 16 h, may be repeated till encephalopathy and INR normalize. The time period of 16 h was wrongly printed as 6 h. We duly acknowledge this unintentional printing mistake, which may be corrected. An erratum has also been requested to be published in the upcoming issue of the journal.

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Table 1 Various Dosage Schedules for the Use of NAC for Non-acetaminophen Acute Liver Failure.

Study reference	Etiology of ALF	NAC regimen used	Route of administration
Kortsalioudaki et al, 2008[14]	Infective/AIH/ Metabolic/DILI/ Indeterminate	100 mg/kg/24 h infusion until normalization of INR, death or LT. Median duration of treatment-5 (1–77) days	Intravenous
Lee et al, 2009[5]	DILI/AIH/HBV/ Indeterminate	150 mg/kg body weight followed by 12.5 mg/kg/hour over 4 h and then 6.25 mg/kg/hour over 16 h. Continued for remaining 67 h	Intravenous
Kumarasena et al, 2010[15]	Dengue infection	150 mg/kg body weight followed by 12.5 mg/kg/hour over 4 h and then 6.25 mg/kg/hour up to72 h	Intravenous
Mumtaz et al, 2009[3]	Infective/DILI/AFLP	140 mg/kg, followed by 70 mg/kg, for a total of 17 doses, 4 h apart starting within 6 h of admission.	Oral
Soteolo et al, 2009[16]	HAV	100 mg/kg every 4 h × 16 h, followed by 100 mg/kg every 6–8 h depending on clinical/laboratory improvement	Oral
Parkash et al, 2016[17]	HAV/HEV/Non-A to E	100 mg/kg/24 h continuous infusion till normalization of INR or death, median duration of treatment-15.5 days	Intravenous
Darweesh et al 2017[12]	Infective/DILI/ Pregnancy related	150 mg/kg infusion over 30 min followed by 70 mg/kg over 4 h, then 70 mg/kg over 16 h Afterwards 150 mg/kg/24 h till 2 INR reports are normal	Intravenous
Nabi et al, 2017[13]	Infective/DILI/AIH	150 mg/kg body weight followed by 12.5 mg/kg/hour over 4 h and then 6.25 mg/kg/hour over 16 h, continued for remaining 67 h	Intravenous
INASL Consensus recommendation[1]	ALF all etiologies	(a) 150 mg/kg body weight in 250 mL of 5% dextrose over 1 h followed by (b) 50 mg/kg over 4 h and then (c) 100 mg/kg over 16 h. The latter dose, i.e. 100 mg/kg over 16 h, may be repeated till encephalopathy and INR normalize.	Intravenous

Note: ALF, acute liver failure; NAC, N-acetyl cysteine; AIH, autoimmune hepatitis; DILI, drug-induced liver injury; HBV, hepatitis B virus; HAV, hepatitis A virus; AFLP, acute fatty liver of pregnancy.

CONFLICTS OF INTEREST

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