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LETTER TO THE EDITOR

Intravenous *N*-acetylcysteine in dengue-associated acute liver failure

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We read with interest the article by Mumtaz et al. [1] on the role of oral *N*-acetylcysteine (NAC) in adults with non-acetaminophen-induced acute liver failure. We agree that their findings are of particular relevance to many developing countries, where liver transplantation is neither available nor affordable. There has been another recent study in which intravenous NAC has been shown to improve transplant-free survival in early-stage non-acetaminophen-induced acute liver failure in adults [2]. We report our initial experience in treating acute liver failure caused by dengue infection with NAC. Use of NAC in this situation has not been previously described.

Sri Lanka is experiencing its worst-ever dengue epidemic yet, with more than 250,000 reported cases and more than 250 deaths, mainly adults, since January 2009. Severe hepatic and cardiac complications and a higher than usual mortality have been notable features of this epidemic. Mild–moderate elevations in serum aminotransferase levels are very common in dengue, but acute liver failure can also occur [3] and has a poor outcome, with case fatality rates of up to 50% in children [4]. There is little information on the management of dengue-associated acute liver failure. There are isolated reports of rapid improvement in the biochemical profile and encephalopathy with molecular adsorbent recirculating system [5]. Liver transplantation is difficult because of hemodynamic instability, bleeding manifestations, and organ dysfunction caused by the infection itself, and may not be a treatment option in most countries where dengue is prevalent.

We retrospectively analyzed the outcome of eight consecutive adult patients (5 men and 3 women; age range, 28–64 years) presenting during the current epidemic with serologically confirmed dengue-associated acute liver failure. In addition to other supportive management [6, 7], they received NAC 150 mg/kg loading dose by intravenous administration over 15 min followed by 12.5 mg/kg/h for 4 h and then 6.25 mg/kg/h for up to 72 h. Two patients had dengue hemorrhagic fever [6], six had dengue shock syndrome [6], seven had pleural effusions, and five had ascites. Five patients had early-stage pretreatment hepatic encephalopathy (coma grades I–II), and three had advanced encephalopathy (coma grades III–IV). Time from disease onset to appearance of encephalopathy was 5–8 days. Worst recorded pretreatment value ranges for the eight patients were as follows: platelet count = 6,000–30,000/mm^3; international normalized ratio = 1.6–3.2; serum bilirubin = 2.7–12.2 mg/dL; alanine aminotransferase = 4,070–19,800 IU/L; aspartate aminotransferase = 4,455–26,500 IU/L; serum albumin = 2.7–3.9 g/dL; serum globulin = 3.1–3.9 g/dL; and serum creatinine = 0.7–2.5 mg/dL. None had taken acetaminophen more than the prescribed therapeutic dose, used hepatotoxic drugs, or had a history of alcohol abuse. Serology was negative for hepatitis A, B, C, and E, leptospira, and rickettsiae. All patients underwent computerized tomography of the brain to exclude intracranial hemorrhage and cerebral edema. All five patients with coma grades I–II recovered completely and were well at follow-up after at least 2 months, whereas the three patients with coma grades III–IV died. No patient had adverse effects attributable to NAC.

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Liver dysfunction in dengue infection may be a direct viral effect on liver cells, an adverse consequence of dysregulated host-immune responses against the virus, ischemic hepatic injury due to circulatory collapse in dengue shock syndrome, or a combination of any of these factors [3]. NAC may benefit patients with nonacetaminophen acute liver failure by improving systemic hemodynamics, by tissue oxygen delivery, or via other favorable effects on the acutely injured liver [2, 8, 9]. Lee et al. [2] conclude that benefit is seen when NAC is used in the early stages of liver failure but not when it is advanced. Our preliminary observations support their view and suggest that the intravenous administration of NAC in the early stages of dengue-associated liver failure is safe and may benefit patients. Larger randomized clinical trials must investigate this further, but until then, we recommend its use, especially in situations in which liver transplantation is not available.

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