



Commentary

Acetylcysteine for paracetamol: Will one size ever fit all?

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From its first use in paracetamol (Acetaminophen, APAP) overdose, oral acetylcysteine (NAC) was controversial [1,2]. Intravenous (IV) NAC was initially no less provocative [3,4]. Yet, over a few short years both the 72-h oral, and the 20-h IV protocols rapidly became standard practices. Three facts likely hampered altering these regimens: (1) The case-fatality rate in untreated patients was very low. (2) The case-fatality rate in NAC-treated patients was even lower, suggesting efficacy. (3) Although some patients developed hepatotoxicity despite NAC, recovery was generally complete and uneventful. Additionally, legitimate concerns that delayed or prolonged methionine exacerbated hepatotoxicity prevented extending the IV protocol for over a decade [5]. Even when prolonged NAC was accepted for patients with fulminant hepatic failure, the initial protocols remained static.

NAC therapy, however, is not benign. The foul-smelling oral protocol commonly produced nausea and emesis, and the IV therapy caused more concerning anaphylactoid reactions. Combined with the complexity of the 3-bag IV protocol these adverse effects led to countless interruptions and premature terminations of care. Small changes occurred over time such as extending the 20-h protocol to 21 h in an attempt to the limit anaphylactoid events. Also, although discussions regarding tailoring NAC regimens to various patient scenarios arose, they rarely gained traction.

The nature of APAP overdose also evolved as preparations that combined APAP with anticholinergics or opioids as well as modified release products were introduced. This added complexity as delayed peak concentrations, multiple peak concentrations, patients who crossed from below treatment thresholds to above, and prolonged elimination phases were all recognized. Treatment decisions were further complicated by the introduction of multiple variations of Rumack–Matthew nomogram [6] notwithstanding the fact that it was nearly flawless in thousands of cases.

Finally, after decades of use, the first major modification to NAC therapy was introduced when the SNAP (Scottish and Newcastle antiemetic pre-treatment for paracetamol poisoning) study demonstrated that a novel 12-hour IV NAC regimen reduced adverse reactions and interruptions of therapy [7]. Since then, multiple alternative doses, rates, and duration of NAC therapy have modified clinical practice, the most notable of which is increasing the dose in patients with massive ingestions [8].

Nevertheless, for most common patients whose blood APAP concentration requires treatment based on whatever modification of the Rumack–Matthew nomogram is used, current regimens could be tailored to lower doses, shorter durations, or modifications designed to minimize adverse events and streamline care. In the current issue of the Journal, Wong and colleagues explore one of those options. They combine the first IV NAC dose (150 mg/kg given over 15–60 min) and the second dose (50 mg/kg given over 4 h) into a single 200 mg/kg dose given over 4 h with the remaining 100 mg/kg dose given over 16 h as in the traditional IV protocol. While the initial goal of this regimen was to reduce adverse events and simplify the 3-bag protocol, the present study examines clinical outcomes. Within the limitations of the study design, the 2-bag regimen met criteria for non-inferiority. Wong and colleagues are not alone as a 2-bag regimen is now routinely used in the UK, parts of the United States [9], Denmark [10], and likely elsewhere.

The 2-bag regimen is not without its own controversy [11]. Clearly for most patients this simplification will likely reduce adverse events and interruptions. Can more be done? If survival is the only desired outcome the 2-bag regimen will succeed, as no therapy and virtually any NAC therapy will suffice for most patients. For some, however, reductions in rates of hepatotoxicity, hepatic failure, and intensive care unit utilization are more meaningful endpoints. Unfortunately, small non-randomized studies are unlikely to address these outcomes. Readers are reminded that the original definition of APAP-induced hepatotoxicity was an ALT or AST over 1000 U/L [12]. Although somewhat arbitrary, this definition is valuable since historical patients with lower peak aminotransferases uniformly did well with no therapy at all. While patients with elevated aminotransferases that remain below 1000 U/L must have hepatic injury, this endpoint is likely inconsequential. Though for many clinicians it triggers continued NAC therapy, that decision may be arbitrary. Most concerning are patients with very high APAP concentrations who might benefit from the high initial NAC concentrations delivered by the standard IV protocol. Until this group is studied in randomized controlled trials using patient-centered definitions of hepatotoxicity it is premature to universally adopt the 2-bag

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regimen. That being said, the work by Wong and colleagues represents a significant advance that could benefit the vast majority of APAP poisoned patients.

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