Wisconsin Poison Center Intravenous N-acetylcysteine Dosing Recommendations in Acetaminophen Toxicity

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Abstract

The Wisconsin Poison Center (WPC) is the regional poison center serving the state of Wisconsin. Recently, this center developed new recommendations for intravenous N-acetylcysteine (IV NAC) dosing. Previously on a case-by-case basis, the WPC recommended that selected patients at risk for severe acetaminophen (APAP)-induced toxicity receive higher doses of NAC. The higher dose exceeds the FDA-approved dosing of IV NAC for prophylaxis and treatment against the development of severe toxicity. The WPC has now revised its recommendations for routine dosing of IV NAC, and the rationale for this recommendation deserves additional clarification, particularly for pharmacists who may be asked to modify formulations in order to comply. The purpose of this article is to communicate with hospital administrators, healthcare providers, and pharmacists about the new recommendations. However, it should be emphasized that enteral NAC remains the preferred dosing and route.

Despite the lack of randomized controlled trials, intravenous N-acetylcysteine (IV NAC) is a safe and effective treatment for acetaminophen (APAP) poisoning.[1,2] IV NAC is the treatment of choice when the oral route is unavailable. However, even with this safe and effective antidote, hepatoxicity and death can occur.[2,3] The Food and Drug Administration (FDA)-approved IV NAC dosing is 150 mg/kg IV over 1 hour, followed by 50mg/kg IV over 4 hours, followed by 100mg/kg IV over 16 hours. An alternative approach to this dosing is 150mg/kg IV over 1 hour, 12.5mg/kg/hr for 4 hours, then 6.25mg/kg/hr over for 16 hours. This original dosing regimen was designed for a minority of acetaminophen poisoned patients.[4] This minority were patients who present early (most within 10 hours), ingested a minimally toxic dose of APAP, and few other co-ingestants.[4] The FDA-approved regimen has even been described by the original investigator as suboptimal.[5] IV NAC is only approved for a 21-hour duration, however, longer durations are needed in many cases of APAP poisoning and thus it is frequently being used "off-label" with guidance of a toxicologist or a poison center.[1] Recently, the Wisconsin Poison Center (WPC) has been informing clinicians who treat patients with APAP overdose about updated dosing guidelines for N-acetylcysteine (NAC).

Rationale

No randomized, controlled trials were ever performed for IV NAC, and safety and efficacy were established with simple prospective studies.[2] The FDA-approved IV NAC regimen is complex, which makes it prone to medication errors.[6,7] A British study found that use of the FDA-approved dosing regimen for IV NAC resulted in compounding dosing errors of at least 20% in almost 33% of patients treated and 8% of treatments led to a dosing error greater than 50%.[6] Hayes et. al. reported that similar errors occurred in 33% of patients.[7] The authors also found a 5% incorrect infusion rate and 18.6% of those enrolled experienced greater than 1 hour of interruption in therapy.[7] The use of a "3-bag" system for the FDA-approved dosing (one bag for each infusion period) likely contributes to these errors.

Recently, alternative dosing regimens for IV NAC have been explored.[8,9] Regimens utilizing two bags have been described which resulted in fewer adverse effects.[10-12] One retrospective pediatric study used an increased dosing protocol (150mg IV bolus followed by 10mg/kg/hr IV for 20 hours) and found no administration errors.[13] Another recent pediatric study used a two-bag regimen with increased dosing (150mg/kg IV followed by 15mg/kg/hr IV) and found it to be safe and effective, with fewer reconstitution and administration errors, leading to improved patient safety.[14] The maintenance infusion continued until serum APAP concentrations were less than 10mg/L and the liver transaminases remained normal or were trending downward. The longest duration of maintenance IV NAC was 89 hours, with a median of 26.3 hours.[14] A prospective, observational study found that doubling the dose of the last NAC bag (200mg/kg over 16 hours) was associated with a significant decrease in hepatoxicity.[15] Lastly, a simplified regimen described using an infusion at 14 mg/kg/hr over 1 hour following the completion of the bolus.[16] Guidelines for acetaminophen poisoning in Australia and New Zealand discuss using increased dosing of IV NAC.[17] Whatever the case and whenever feasible, oral NAC has and will remain preferred over IV NAC (see table 1).[18]

Discussion Of The WPC Recommendations

Oral NAC is preferred due to favorable absorption, higher cumulative dosing leading to higher levels in the liver, and less expense. However, recent evidence and a trend in best practice development led the WPC to revise recommendations for IV NAC dosing. These recommendations are consistent with recent literature describing a two-bag regimen to decrease adverse effects, medication errors, and complications after APAP poisoning. **We recommend a loading dose of 150 mg/kg IV over 1 hour, followed by a continuous infusion at 12.5 mg/kg/hr. If no liver injury develops (i.e. a normal AST and total bilirubin throughout), then the infusion continues until the APAP level is non-detectable. If there is evidence of hepatic injury, then the infusion continues until recovery, transplant, or demise.** For obese patients, we recommend capping the dose calculation at a weight of 100 kg. Boluses for adults can be made in 200 milliliters (mL) of D5W or 0.45% sodium chloride (NaCl) and boluses for pediatric patients can be made up by following the package insert.[1] Concentrations of continuous IV bags may vary between institutions and individual patients, however, an easy approach for the continuous infusion is to mix 6,000 mg or 12,000 mg (1 or 2 vials) of IV NAC into 500 mL of D5W or 0.45% NaCl. More concentrated solutions can be used for patients at risk for volume overload,[1,16] but a less concentrated approach may decrease waste, depending on the patient's clinical status. These concentrations can also be used for pediatric patients since the infusions following from the package insert total approximately 4-8 mg/mL. To decrease osmolarity and risk of hyponatremia for pediatrics, 0.45% NaCl can be used as the diluent. With current application of the electronic medical record and prescriber order entry, we suggest standardizing dosing protocols within your own institution or health system.

Conclusion

The Wisconsin Poison Center is recommending all patients with confirmed or suspected APAP poisoning who are treated with IV NAC should receive 150 mg/kg IV over 1 hour followed by 12.5 mg/kg/hr until recovery, transplant, or death. This will ease compounding, dosing, and timing complications that have been reported with the "3 bag" NAC regimen. Oral NAC remains our preferred choice due to safety, efficacy, and cost. Please feel free to call the Wisconsin Poison Center at 1-800-222-1222 if you have further questions or concerns. A guideline is available for downloading at www.wisconsinpoison.org.

TABLE 1. NAC Recommendations

Product	*Route*	*Regimen*	*Comments*
NAC (WPC preferred)	Oral	140mg/kg load followed by 70mg/kg every 4 hours	Provides 490mg/kg in first 24 hours
NAC (Acetadote®)	IV	150mg/kg load followed by 12.5mg/kg/hr over 4 hours, followed by 6.25mg/kg/hr over 16 hours or longer	Provides 300mg/kg in first 21 hours
WPC recommended NAC	IV	150mg/kg load followed by 12.5mg/kg/hr for 20 hours or longer	Provides 400mg/kg in first 21 hours

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