J. Med. Toxicol.
DOI 10.1007/s13181-016-0542-z

POSITION STATEMENT

ACMT Position Statement: Duration of Intravenous Acetylcysteine Therapy Following Acetaminophen Overdose

American College of Medical Toxicology[1]

Received: 15 February 2016 / Accepted: 19 February 2016

Keywords Position Statement · Acetaminophen · APAP · *N*-Acetylcysteine · NAC

Disclaimer

While individual practitioners may differ, this is the position of the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

Acetylcysteine (previously called *N*-acetylcysteine (NAC)—the abbreviation NAC is used throughout to avoid confusion with activated charcoal) for the treatment of potentially toxic acetaminophen (APAP) ingestion is available in oral and intravenous (IV) formulations. The FDA approved a 72-h oral NAC regimen in 1985. However, evidence supports using shorter oral NAC courses provided that liver enzymes and synthetic function are normal or improving, and plasma APAP concentration is undetectable [1, 2]. Intravenous NAC (Acetadote®, Cumberland Pharmaceuticals) was approved by the FDA in 2004 and is indicated to prevent or lessen hepatic injury after potentially toxic APAP ingestion.

The prescribing information for IV NAC recommends administering the drug within 8 h of APAP ingestion for maximal efficacy, and to administer as soon as possible for patients who present later than 8 h [3]. The NAC treatment regimen described in the prescribing information was developed in the UK in the 1970s and delivers NAC 300 mg/kg, with half given as a loading dose, and the remainder infused over 20 h. The primary mechanism of action involves enhanced detoxification of *N*-acetyl-*p*-benzoquinone imine, a hepatotoxic APAP metabolite. Later investigations demonstrated improved mortality in APAP-induced liver failure, presumably via other mechanisms, even when IV NAC was administered after APAP had been eliminated from the blood [4, 5].

Since approval of IV NAC in the USA, several reported cases have documented rising hepatic aminotransferase concentrations or persistent serum APAP concentrations despite 21 h of treatment [6–8]. With a short elimination half-life after therapeutic dosing, APAP is typically eliminated within 21 h after an acute overdose. However, hepatic injury can slow acetaminophen metabolism and prolong its apparent half-life [9]. In addition, altered absorption following massive ingestion [6] or coingestants that slow gastrointestinal motility [7] can result in persistently elevated acetaminophen concentrations.

In APAP poisoning, elevations in aminotransferases (AST or ALT equal or greater than 1000 U/L) precede laboratory markers of hepatic dysfunction. In APAP poisoning, many predictors of poor prognosis have been described. In practice, decreased pH, increases in phosphate, increased lactate, increases in prothrombin time/INR, and increases in serum creatinine are the most readily available predictors of poor prognosis [8, 10, 11]. Treatment with 21 h of IV NAC is highly effective at preventing hepatotoxicity in most patients following acute APAP overdose and in reducing mortality in those with established hepatotoxicity [12].

The administration of an additional NAC bolus or extending the duration of the 6.25 mg/kg/h infusion *may be appropriate* in certain clinical scenarios [13–16]. Treatment beyond 21 h is indicated when patients have evidence of hepatotoxicity evidenced by elevations in aminotransferases, abnormalities in predictors of poor prognosis, or persistent

✉ American College of Medical Toxicology
positionstatements@acmt.net;

[1] Phoenix, AZ, USA

Published online: 08 March 2016

APAP detected by laboratory testing. Laboratories use different reporting limits for APAP concentrations. Because the scientific literature does not establish one APAP reporting cutoff to be superior to another (e.g., 5 versus 15 μg/mL), we recommend the use of "undetectable" APAP as an indication to stop therapy.

The presence of rising liver aminotransferases, markers of poor prognosis, or persistent acetaminophen concentrations should prompt continued IV NAC administration.

The American College of Medical Toxicology (ACMT) strongly recommends all of the following criteria be present for discontinuation of IV NAC:

- Undetectable acetaminophen concentration
- Improving hepatic aminotransferases
- Improving prognostic markers (e.g., creatinine, lactate, pH, prothrombin time/INR, phosphate)

ACMT supports the principle of individualizing therapy, guided by patients' clinical condition, in consultation with a medical toxicologist or other expert.

The development of hepatotoxicity or liver failure despite IV NAC therapy should prompt evaluation and monitoring of acid–base status, coagulation parameters, renal function, and level of consciousness. Consider consultation with a medical toxicologist, a regional poison center (1-800-222-1222), and/or individual or institution with expertise in managing patients with severely compromised hepatic function.

Acknowledgments ACMT would like to acknowledge the members of the Position Statement and Guidelines Committee for the authorship of this statement: Andrew Stolbach (Chair), Jeffrey Brent, Peter Chase, Howard Greller, Ronald Kirchner, Thomas Kurt, Charles McKay, Sean Rhyee, Silas Smith, Brandon Warrick.

Compliance with Ethical Standards

Conflict of Interest None

Sources of Funding None

References

1. Woo OF, Mueller PD, Olson KR, Anderson IB, Kim SY. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. Ann Emerg Med. 2000;35:363–8.
2. Betten DP, Cantrell FL, Thomas SC, Williams SR, Clark RF. Prospective evaluation of shortened course oral N-acetylcysteine for acute acetaminophen poisoning. Ann Emerg Med. 2007;50:272–9.
3. United States Food and Drug Administration. Acetadote (acetylcysteine) Package Insert.http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021539s004lbl.pdf). Accessed 8/11/15
4. Harrison PM, Keays R, Bray GP, Alexander GJ, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet. 1990;335:1572–3.
5. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ. 1991;303:1026–9.
6. Smith SW, Howland MA, Hoffman RS, Nelson LS. Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous N-acetylcysteine therapy. Ann Pharmacother. 2008;42:1333–9.
7. Hendrickson RG, McKeown NJ, West PL, Burke CR. Bactrian ("double hump") acetaminophen pharmacokinetics: a case series and review of the literature. J Med Toxicol. 2010;6:337–44.
8. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97:439–45.
9. Prescott LF, Wright N. The effects of hepatic and renal damage on paracetamol metabolism and excretion following overdosage. A pharmacokinetic study. Br J Pharmacol. 1973;49:602–13.
10. Cholongitas E, Theocharidou E, Vasianopoulou P, Betrosian A, Shaw S, Patch D, et al. Comparison of the sequential organ failure assessment score with King's College Hospital criteria and the model for end-stage liver disease score for the prognosis of acetaminophen-induced acute liver failure. Liver Transpl. 2012;18:405–12.
11. Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. Hepatology. 2002;36(3):659–65.
12. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008;359(3):285–92.
13. Doyon S, Klein-Schwartz W. Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. Acad Emerg Med. 2009;16:34–9.
14. Klein-Schwartz W, Doyon S. Intravenous acetylcysteine for the treatment of acetaminophen overdose. Expert Opin Pharmacother. 2011;12:119–30.
15. Smilkstein MJ, Bronstein AC, Linden C, Augenstein WL, Kulig KW, Rumack BH. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med. 1991;20:1058–63.
16. Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol. 2012;50:91–8.