Patient-Tailored Acetylcysteine Administration

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Acetylcysteine is a familiar friend of emergency physicians, intensivists, and medical toxicologists. There are 2 broad categories of acetaminophen toxicity that receive acetylcysteine therapy: acute single overdose ingestion and repeated supratherapeutic (“chronic”) ingestion. Since the 1970s, we have used acetylcysteine to reduce liver injury and death in patients with an acute overdose ingestion of acetaminophen.1 The introduction of an intravenous formulation of acetylcysteine in the United States has fostered the adaptation of a shorter period of acetylcysteine administration, 20 hours instead of 72 hours. Both of these time-based protocols imply that all cases of acetaminophen toxicity receive the same duration of therapy. However, clinical experience indicates that a patient who presents late (>8 hours after ingestion) or who already has manifested liver injury after a single acute overdose needs a longer duration of acetylcysteine therapy than a patient who presents soon (within 8 hours) after acute overdose ingestion. Further, in many patients who receive acetylcysteine, the exact time of acute ingestion is unknown, or the ingestion has occurred during an unknown period. Although a variety of dosage regimens has been proposed for the various patterns of acetaminophen overdose, the optimal duration of acetylcysteine therapy is unknown. Currently, the administration of acetylcysteine is determined by the individual physician, with very little information to guide the decision.

In this issue of Annals, Betten et al2 report a poison center study of truncated acetylcysteine therapy for acute overdose ingestion of acetaminophen. Their results indicate that treatment with oral acetylcysteine for 20 to 48 hours was associated with excellent outcomes. The study has weaknesses, but the authors addressed major concerns, particularly the concern that poor outcomes may have been missed in patients lost to follow-up.

We believe the implications by Betten et al2 go farther, exposing a more fundamental issue of medical importance. The concepts of patient-tailored therapy and goal-directed therapy have enjoyed growing acceptance in recent years. The concept involves treating the patient’s condition only as long as necessary, as determined by their clinical condition. Betten et al2 used a compound clinical endpoint to recommend termination of acetylcysteine therapy. Defining treatment as a period (eg, 20 hours) is much different from treatment to a clinical endpoint. For example, the 20-hour protocol for intravenous administration of acetylcysteine does not take clinical findings into consideration. It simply dictates “treat 20 hours and then stop,” which is an admirably simple procedure, but it addresses only 1 group of patients with acetaminophen poisoning: those with a single, acute ingestion and a known time of ingestion. Further, the omission of clinical information may lead to premature termination of acetylcysteine treatment. For example, we recently treated a patient with an acute single ingestion and a persistently increased acetaminophen level of 100 mg/L at the end of a 20-hour infusion of acetylcysteine. If we had terminated the infusion at that time, it seems likely that the patient would have had liver injury. We are aware of anecdotal reports of patients who did indeed have serious liver injury when the 20-hour protocol was used without attention to the serum acetaminophen concentration.

In contrast, treating to a defined clinical endpoint incorporates clinical information. It implies that we can define the conditions needed to ensure that further liver injury does not occur, thereby allowing discontinuation of acetylcysteine treatment. Unfortunately, these conditions have not been well defined, although the rationale presented by Betten et al2 seems to be accepted by most toxicologists. The fundamental concept is the role of the acetaminophen metabolite, N-acetyl-p-benzoquinonemine (NAPQI), in initiating the injury of acetaminophen. It is commonly accepted that no further injury from the reactive intermediate should occur once acetaminophen has been eliminated because this would prevent the metabolism of acetaminophen to NAPQI. Further acetylcysteine therapy may be unneeded.

There are some obvious problems with this simple approach. The first is that liver injury from acetaminophen, like most causes of hepatic injury, takes time to manifest. Although the serum acetaminophen concentration may provide information about continued production of NAPQI, how do we assess injury that has already occurred but is not yet apparent? Toxicity from acetaminophen is generally defined as an alanine aminotransferase (ALT) level of 1,000 IU/L or greater.1 The period needed for ALT to reflect any increase above the upper limit of normal is at least several hours3 and in most cases may not be significant until approximately 24 hours. Serial measurement of ALT typically results in a peak between 72 and 96 hours. The delay until alteration of ALT levels and the delay to peak are observed regardless of whether the patient is treated.
with acetylcysteine, although those patients who are treated with acetylcysteine have a lower peak ALT.

The period needed for the serum ALT to increase after acetaminophen injury is unknown but is at least several hours.\textsuperscript{3} To assess liver effect, therefore, it would be wise to require that the serum ALT be normal (or at least decreasing rather than increasing) if one is to terminate acetylcysteine therapy. Another concern is that the serum ALT does not measure liver synthetic activity. Betten et al\textsuperscript{2} included the international normalized ratio. This may be a prudent inclusion, particularly if this approach ultimately becomes widespread.

Another concern is the patient’s overall clinical condition. Acetaminophen-induced liver failure does not occur in a vacuum. Often other drugs are involved or the patient may have other effects such as renal or pulmonary injury. Many practitioners would choose to continue acetylcysteine until the patient’s condition improved, although the medical rationale for this approach is not established. It is important for the clinician to have a clinical override in case the numbers look good but the patient looks bad.

If the appropriate compound clinical endpoint could be established, it would allow efficient and individualized treatment of patients with acetaminophen poisoning. We would simply administer acetylcysteine until the clinical endpoint was fulfilled and then terminate the acetylcysteine treatment. It is time to test such a regimen. For the past few years, we have been treating with acetylcysteine until a clinical endpoint was reached. The endpoint is similar to that used by Betten et al.\textsuperscript{2} Acetylcysteine is initiated as a loading dose, and then maintenance is provided until the patient meets 3 criteria. First, the acetaminophen level must be zero or near zero. Second, the serum ALT must be normal or improving. The term “improving” is defined as impressive improvement (ie, ALT decreasing from 1,500 IU/L to 500 IU/L). Finally, the patient must be clinically well. If the patient has other clinical effects, such as altered mental status or renal failure, then the acetylcysteine is continued until we are certain that the cause is not acetaminophen.

An important potential advantage of goal-directed therapy is that it can be applied to all patients receiving acetylcysteine therapy. For example, we currently use the approach described above for patients with acute ingestion, repeated (chronic) supratherapeutic ingestion, and in patients with an unknown pattern of ingestion. If the endpoint of acetaminophen level, ALT, acceptable clinical condition, and perhaps INR (or perhaps other factors) proves to be useful for one pattern of ingestion, it seems likely that it will be effective for all patterns of ingestion.

Lack of adequate power has always been a chronic problem in toxicology studies. Poisoning is an unpredictable event that evolves quickly, making patient enrollment difficult. Nevertheless, it is crucial that study of acetylcysteine be powered to detect any decrease in efficacy, which will require close follow-up to ensure that poor outcomes are not missed. It is also important to understand that most patients with a “toxic” acetaminophen level do not develop serious toxicity. For example, only 7.7% of patients whose initial serum acetaminophen concentration was above the nomogram line at 4 to 10 hours postingestion developed a serum ALT or AST greater than 1,000 U/L.\textsuperscript{4} Thus, a large number of patients will be required to detect any potential decrease in the effectiveness of acetylcysteine.

Acetylcysteine has been used effectively for 35 years, but we lack prospective studies on how to tailor its use in many situations. We propose that the paradigm for acetylcysteine administration be changed from one of treatment length to one tailored to the patient’s clinical condition. Acetylcysteine should be used in the same manner for all acetaminophen cases: until the liver is well or improving and there is no further acetaminophen left to metabolize.

Combined with the results of previous investigators, these data indicate that a shortened course can be safe and effective. It is time for a prospective trial that shortens the course of acetylcysteine therapy.

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\textbf{REFERENCES}