Modified two step N-acetylcysteine dosing regimen for the treatment of acetaminophen overdose a safe alternative

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ABSTRACT

Intravenous N-acetylcysteine (IV NAC) is currently the approved treatment for acetaminophen (APAP) overdose with a three-step regimen totaling 300 mg/kg over 21 hours. Due to the complexity of this regimen, some institutions have used simplified, off-label regimens to mitigate dosing errors, adverse effects and shorten treatment durations. This article describes a modified two-step IV NAC regimen 510 mg/kg over 25 hours. We performed a retrospective analysis of outcomes in APAP overdose treated with a modified two-step IV NAC regimen between January 1, 2009 and April 30, 2014. We identified patients using medication charges. We included 79 patients in the analysis whom received IV NAC for APAP overdose. We found no documentation of adverse events during infusions. The median time from ingestion to initiation of treatment was 7.5 hours (interquartile range 5, 12 hours) and the median duration of therapy was 32 hours (interquartile range 25, 49 hours). A modified two-step regimen (510 mg/kg over 25 hours), which provides almost twice the dose of the recommended FDA approved dose of 300 mg/kg over 21 hours, may be a less complex and safer alternative to the traditional regimen.

Introduction

The U.S. Food and Drug Administration (FDA) approved the N-acetylcysteine (IV NAC) product in 2004 with a three-step regimen totaling 300 mg/kg. The FDA approved regimen, which involves three different doses, volumes, and infusion times, introduces the risk of medication errors [1,2]. Error rates demonstrated in some studies are as high as 30% [3]. Although the FDA approved regimen appears to be effective at preventing acetaminophen (APAP) toxicity, experts agree there is uncertainty about the optimal dose, duration and route of NAC administration. Cases of hepatotoxicity, transplant and death despite early administration of IV NAC using the FDA approved dosing regimen have occurred, suggesting inadequate dosing with this protocol [4–7]. These uncertainties warrant investigation for alternative regimens that may also be safe and effective. Currently, some institutions are using a simplified, off-label, regimen in attempts to mitigate dosing errors, adverse effects and decrease treatment duration [1,8–11]. This study aims to describe a modified two-step IV NAC regimen.

Methods

Mission Health System (MHS) in Ashville, North Carolina uses a two-step IV NAC regimen with a 25-hour duration and higher total NAC dosage of 510 mg/kg than the traditional FDA approved regimen. This two-step regimen, based on a Poison Control Center recommendation, begins with an initial 150 mg/kg loading dose infused over 1 hour followed by 360 mg/kg (15 mg/kg/hr) infusion over 24 hours. Both products are prepared in 5% dextrose with the initial loading dose in 500 mL and the infusion in 1000 mL. Each patient receives the entire 25-hour infusion and hospital practice is to continue NAC therapy until APAP is undetectable with normal or declining AST and ALT concentrations.

We identified patients using pharmacy charges generated from receipt of IV NAC over the course of
the study period of January 1, 2009 through April 30, 2014. We excluded patients if they did not have a detectable APAP concentration, received IV NAC for a non-APAP overdose indication or if therapy initiation occurred at an outside hospital, or if APAP exposure could not be verified.

The objective of this study was to describe the following: delays in medication administration (defined by >1 hour of time between steps), incidence of adverse events (i.e., dermatologic, gastrointestinal, respiratory, anaphylactoid and/or status epilepticus symptoms) or delivery of rescue medications (i.e. antiemetics, epinephrine, bronchodilators, antihistamines, steroids), unplanned cessation of IV NAC therapy to mitigate adverse event symptoms, incidence of hepatic injury as evidenced by elevations in transaminases, incidence of liver transplantation during admission, requirement of renal replacement therapy secondary to APAP toxicity and 28-day mortality. Statistical analysis was descriptive in nature. The Institutional Review Board (IRB) reviewed and approved this retrospective study.

Results

We included 79 patients who received IV NAC for APAP overdose and had detectable APAP concentrations during their hospital admission in our study analysis. We summarized patient demographics and characterization of APAP overdoses in Table 1. Aggregated data implicated immediate release APAP products in 97% of ingestions.

We described treatment outcomes in Table 2. Delays in medication administration greater than 1 hour occurred in 11% of patients. However, there were no documented adverse outcomes associated with delays in therapy.

We found no documentation of adverse events during the IV NAC infusion. We reviewed the administration of rescue medications during the IV NAC infusion as a surrogate marker. Five patients required either an antiemetic or bronchodilator; however, IV NAC therapy was never discontinued for any patient.

Fifty eight percent of patients required continuation of therapy. Hospital practice is to continue NAC therapy until APAP is undetectable with normal or declining AST and ALT concentrations.

Peak AST concentrations were greater than 1000 in 22% of patients. One patient receiving the two-step regimen received a liver transplant. Six percent of patients required renal replacement therapy during admission. Three of those patients received unchanged IV NAC dosing of 15 mg/kg/hr, one patient had a dose increase to 37 mg/kg/hr rational for dose increase was not documented. In-hospital mortality for the cohort was 5%. The median peak serum creatinine was 0.9 mg/dL.

Discussion

This investigation describes a modified two-step IV NAC regimen. The standard FDA approved three-step regimen is prone to medication errors due to its complexity. Hayes et al analyzed the records of their regional poison center and found that 33% of patients experienced a medication error attributable to incorrect dose, rate or lack of indication with the FDA-approved regimen [3]. The most common type of error noted was an interruption in therapy of greater than 1 hour. Other studies have noted large variation in dosages received due to calculation and preparation errors [12]. Delays in IV NAC treatment or errors in dosing could potentially increase incidences of hepatotoxicity, increase durations or treatments, lengths
of stay and cost [2]. This investigation found that only 11% of patients experienced such a delay with a modified regimen. It is unclear if other dosing strategies aimed at mitigating delays in therapy are safe and provide the same clinical effectiveness in treating acetaminophen overdose. However, strategies such as the two-step regimen above and single bag regimens could mitigate therapy delays [13].

This study is limited by its retrospective nature, hence reducing the available data for collection and resulting in missing data points for some patients. This design may also have affected our ability to identify the incidence of adverse events and medication errors. Adverse events and medication errors were only able to be analyzed if noted by caregivers in the medical record. In addition, some symptoms such as nausea and vomiting may be difficult to distinguish from the clinical manifestations of APAP overdose.

Nausea and vomiting and anaphylactoid reactions are estimated to occur in about 30% of patients with rates of adverse events varying among studies; this is largely due to methodology of chart review, and prevalence of only severe reactions being documented [10].

MHS is not a liver transplant site; patients must be transferred if evaluation for liver transplantation secondary to the APAP overdose is required. These transfer records were not available for additional analysis.

Conclusions

A modified two-step IV NAC regimen (510 mg/kg over 25 hours) which provides almost twice the dose of the recommended FDA approved dose of 300mg/kg over 21 hours, may be a less complex and safer alternative to the traditional regimen. Reducing the number of bags administered can possibly reduce interruptions in therapy and reduce the likelihood for medication errors.

Disclosure statement

No potential conflict of interest was reported by the authors.

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