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ORIGINAL ARTICLE

Investigating a Novel Two-Bag N-Acetylcysteine Regimen for Acetaminophen Toxicity

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Abstract

Background Acetaminophen toxicity remains one of the most common causes of liver failure and is treated with a course of n-acetylcysteine (NAC). This exceptionally effective medication is traditionally administered using a complicated three-bag protocol that is prone to administration errors.

Objective We aimed to assess whether switching to a novel two-bag protocol (150 mg/kg over 1 h followed by 150 mg/kg over 20 h) reduced administration errors while not increasing liver injury or anaphylactoid reactions.

Methods This was a retrospective chart review of hospital encounters for patients with acetaminophen toxicity, comparing outcomes before and after the change from a three-bag protocol to a two-bag protocol at two affiliated institutions. The primary outcome was incidence of medication errors with secondary outcomes including acute liver injury (ALI) and incidence of non-anaphylactoid allergic reactions (NAAR). The study was approved by the health system's Institutional Review Board.

Results 483 encounters were included for analysis (239 in the three-bag and 244 in the two-bag groups). NAAR were identified in 11 patients with no difference seen between groups. Similarly, no differences were seen in ALI. Medication administration errors were observed significantly less often in the two-bag group (OR 0.24) after adjusting for confounders.

Conclusion Transitioning to a novel two-bag NAC regimen decreased administration errors. This adds to the literature that two-bag NAC regimens are not only safe but also may have significant benefits over the traditional NAC protocol.

Keywords Acetaminophen · N-acetylcysteine · Medication errors · Anaphylactoid reactions · Liver failure

Introduction

N-acetylcysteine (NAC) is an antidote for both chronic and acute acetaminophen toxicity [1]. Traditionally, this medication has been dosed intravenously utilizing a three-bag regimen (the Prescott protocol [2]) which is often modified so the initial bolus is given over one hour rather than 15 min [1]. Although this dosing regimen is quite effective in preventing liver damage related to acetaminophen toxicity, it is prone to administration errors owing to its convoluted approach [3]. With this in mind, there has been a move towards simplifying the three-bag regimen with the goal of not sacrificing effectiveness of liver protection while decreasing administration errors. Several studies have proposed various simplified approaches [4]– both "single-bag" formulations [5] and two-bag formulations [6–15]. These studies have shown that a simpler approach appears to be similar regarding the minimization of acute liver injury (ALI) [6, 7, 9, 10, 13], minimizing administration errors [12], minimizing treatment delays [10, 14], while decreasing the rate of non-allergic anaphylactoid reactions (NAARs) [6, 7, 9–11, 13].

Previous studies have largely focused on using a modified two-bag approach where an initial 200 mg/kg infusion is given over 4 h while the remaining 100 mg/kg is administered over 16 h, or a shortened 12 h approach where

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the initial administration is 100 mg/kg over 2 h followed by the remaining 200 mg/kg over 10 h [4]. The novel two-bag regimen implemented at our institution was developed to further reduce incidence of medication errors. In previous two-bag NAC regimens, the transition from bag one to bag two occurs 4 h after initiation of NAC. At this point, patients are often transitioning to different phases of care with different care team members, which presents a risk for incorrect doses and delays to dose administration. In our novel two-bag regimen, the transition from bag one to bag two occurs one hour after initiation of NAC. Although not always occurring in the same phase of care (due delays in transition from the emergency department related to staffing, boarding, etc.), it was thought that by having the transition occur sooner, most patients would be;, this may reduce dosing confusion, incidence of incorrect doses, and delayed administration of doses.

We present a study of our experience shifting from the traditional protocol (150 mg/kg over 1 h, 50 mg/kg over 4 h, and 100 mg/kg over 16 h) to this novel two-bag regimen that further simplifies dosing by using the same dose in both bags and only adjusting the duration of administration (150 mg/kg over 1 h followed by 150 mg/kg over 20 h). We aim to assess whether an even simpler approach decreases medication errors, as well as add to the growing body of evidence supporting the use of two-bag NAC protocols.

Methods

Study Design

This was a retrospective analysis of hospital encounters amongst patients suffering from acetaminophen toxicity treated with NAC. Two affiliated hospitals in a single metropolitan area were analyzed before and after the change was made from the three-bag to two-bag protocol. Hospital A is a 454-bed level 1 trauma center with a dedicated inpatient toxicology service while Hospital B is a 426-bed level 3 trauma center without a dedicated toxicology service. Both the initial and novel NAC protocols were identical at both institutions. Neither hospital has a liver transplantation service nor admits pediatric patients. NAC treatment was initiated based on the treatment threshold recommendations in the n-acetylcysteine package insert [16] and often in consultation with the toxicologists at Hospital A or with the regional Poison Control System at Hospital B. Outcome measures were compared between cohorts that received the traditional three-bag protocol and those that received the novel protocol regardless of the treating hospital.

Inclusion/Exclusion Criteria

All encounters where intravenous NAC was administered for acetaminophen toxicity were included from July 1st 2018 to December 31st 2022 and were identified by ICD-10 codes for acetaminophen toxicity (T39.1X). We selected dates of inclusion to obtain similar-sized groups in the pre- and post-protocol change groups. Patients were excluded if they had indicated that they did not want their data used for research or were pregnant at the recommendation of the local Institutional Review Board (IRB). Additional exclusion criteria included patients who were started on NAC at a transferring outside hospital, patients where NAC administration was deemed inappropriate and thus discontinued, and patients who did not initiate the final bag of NAC (because they were transferred to a liver transplant center, transferred to a pediatric hospital, left against medical advice, or because care was withdrawn by family).

Outcome Measures

The primary outcome was the incidence of medication errors in patients with acetaminophen toxicity treated with NAC. Secondary outcomes included incidence of ALI, NAARs, ICU admissions, and mortality. We defined ALI as either peak alanine transaminase (ALT) > 150 U/L during admission or a doubling of admission baseline ALT for presentations within 24 h post-overdose. We defined medication errors as either NAC ordered with the incorrect dose or administered greater than 60 min past the expected time. Although we did not expect that frequency of NAARs would be different between the groups given that the rate of the loading dose was identical between the groups, we included this variable as it has been reported elsewhere.

Data Collection

The institution's data informatics team identified all encounters. A portion of the data were collected directly from the electronic medical record (EMR) including patient age, sex, and weight; hospital length of stay; initial acetaminophen, aspartate transaminase (AST), alanine transaminase (ALT), international normalized ratio (INR), and creatinine levels; and ICU admission status. Four abstractors blinded to the aims of the study and to which cohort each encounter belonged abstracted the remainder of data. All abstractors were trained in utilizing a standard data abstraction protocol and then input into a REDcap database. This data included the intent of ingestion (accidental/unintentional, intentional, supratherapeutic, or unknown), the chronicity of ingestion (acute, chronic, or unknown), the hospital disposition (discharge, deceased, transfer to a liver transplant center, or

transfer to a pediatric center), coingested medications, incidence of NAAR, type of NAAR, and medications administered for NAARs. Further, the time and dosage of each administration of NAC was abstracted directly from the chart by hand. All cases of medication errors and NAARs were confirmed by the corresponding author for accuracy. We defined all outcomes and data analysis strategies *a priori*.

The study was approved by the hospital system's IRB.

Statistical Methods

Patient characteristics were analyzed using descriptive statistics and compared between groups using chi squared analyses of categorical data and *t*-tests for continuous data. Unadjusted odds ratios (ORs) were calculated for the primary and secondary outcomes. To adjust for potential confounders, a logistic regression model was developed to adjust for age, sex, weight, initial lab values (AST, ALT, creatinine), chronicity of ingestion, intent of ingestion, time of ingestion (prior to arrival), and treating hospital. All statistical analyses were completed using R software [17].

Results

We identified 548 hospital encounters that met the inclusion criteria. 65 encounters were excluded for a total sample of 483 encounters (Fig. 1) with 239 patients in the three-bag group and 244 in the two-bag group. Patient characteristics are displayed in Table 1. Patients were primarily female ($n=318$, 66%), acute ($n=334$, 65%), intentional ($n=320$, 60%) ingestions, and most were discharged ($n=448$, 94%). With regard to intent, most ingestions in both groups were acute. Relative to the three-bag group though, patients in the two-bag group were slightly less likely to have a chronic ingestion (22% vs. 28%). There were no other significant differences identified between the cohorts. There were 627 coingestants with the most frequent being ethanol, antihistamines, and opioids (Table 2).

Regarding the primary outcome, incidence of medication errors, there was a significant difference detected in medication error with the three-bag group having medication errors in 27% of cases ($n=65$), while the two-bag group had errors in 11% of cases ($n=27$). This represents an OR of 0.33 in the two-bag group relative to the three-bag group ($p=<0.005$) and a number needed to treat (NNT) of 6.25. In the adjusted analysis this difference held with an OR of 0.24 ($p=<0.005$). Among the medication errors, most were instances of wrong administered dose ($n=80$, 87%) versus delays in administration ($n=12$, 13%). In the two-bag group, delays represented 19% ($n=5$) of errors versus 11% ($n=7$) in the three-bag group. Regarding NAAR, there were 11 total reactions with no significant difference between the groups ($p=0.38$) in the unadjusted analysis. 2% of patients ($n=4$) in the three-bag group and 3% of patients in the two-bag group ($n=7$) experienced a NAAR and details regarding each instance are displayed in Table 3. Similarly, there were no differences in the secondary outcomes of ALI ($p=0.38$), mortality ($p=0.56$), or ICU admission ($p=0.31$). In the adjusted analysis these outcomes remained non-significant. These results – both adjusted and unadjusted – are displayed in Table 4.

Discussion

Due to the complexity of the Prescott protocol to treat acetaminophen toxicity, researchers and clinicians have been interested in moving to a simpler NAC protocol. In a single hospital system, the decision was made to move to a novel two-bag protocol (150 mg/kg over 1 h followed by

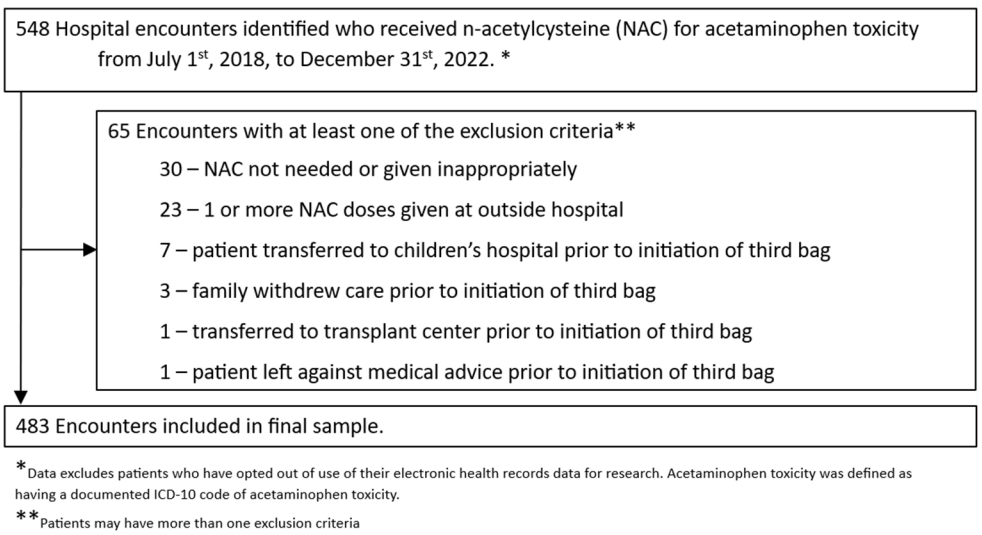

Fig. 1 Study sample inclusion and exclusion criteria

Table 1 Baseline characteristics

Continuous variables	Total (n=483)		3 bag (n=239)		2 bag (n=244)		p value
	median	SD	median	SD	median	SD	
Total NAC doses given	3.0	1.0	3.0	0.9	2.0	0.6	<0.005
Ingestion time (min prior to arrival)	180	716	120	785	240	652	0.86
Patient age (years)	37.0	18.2	37.0	19.1	36.5	17.3	0.22
Patient weight (kg)	73.2	24.0	72.7	23.6	75.0	24.5	0.42
Hospital length of stay (day)	3.6	7.6	3.0	6.9	4.1	8.2	0.31
Initial INR	1.1	0.8	1.1	0.9	1.1	0.7	0.87
Initial APAP (mcg/mL)	41	94	32	93	53	96	0.12
Initial AST (U/L)	28	1237	34	1432	25	1012	0.62
Initial ALT (U/L)	29	1532	29	1608	25	1354	0.70
Initial creatinine (mg/dL)	0.8	1.0	0.7	1.0	0.8	1.1	0.14
Max AST (U/L)	37	1579	40	1841	31	1271	0.69
Max ALT (U/L)	30	1890	32	2027	28	1749	0.84
Categorical variables	Total (n)		3 bag (n)	(%)	2 bag (n)		p value
Male sex	165		81	34%	84	0.9	
Chronicity of ingestion						0.18	
Acute	334		156	65%	178		
Chronic	122		68	28%	54		
Unkown	27		15	6%	12		
Intent of ingestion						<0.05	
Accidental\unintentional	9		7	3%	2		
Intentional	320		143	60%	177		
Supratherapeutic	116		63	26%	53		
Unknown	38		26	11%	12		
Disposition						0.21	
Discharge	448		225	94%	223		
Died	14		8	3%	6		
Transfer to liver transplant center	11		4	2%	7		
Transfer to children's hospital	10		2	1%	8		

150 mg/kg over 20 h). The analysis presented here reveals that switching from the traditional three-bag protocol did not increase NAAR, ALI, mortality, or ICU placement in this patient population. Furthermore, with regard to medication errors, we found a marked decrease (wrong dose, delay in administration).

The goal of utilizing simplified NAC protocols is to ensure safety of the antidote and efficacy at minimizing acetaminophen-induced hepatic injury. Previous studies utilizing two-bag protocols have shown no significant difference with regard to ALI relative to the traditional protocol, as we found in our study. In our patient population we found ALI in about a third of our patients with no significant difference between the groups. Bateman et al., in a randomized controlled trial of a modified two-bag approach (with an initial dose of 200 mg/kg over 4 h), found a lower rate of ALI (12.9%) although they used a narrower definition of ALI [6]. In retrospective cohorts of the same modified protocol, several researchers have found even lower rates of ALI (in the 1-5% range) using a similarly narrower definition of ALI [7, 9, 10, 13]. Regardless of the definition, it is reassuring that no statistically significant difference in ALI has been reported in these two-bag protocols, but it should be noted that these studies (including our own) are likely not powered to detect a difference if one exists. Further study is warranted.

Similarly, previous studies have assessed NAAR incidence between the traditional protocols and modified two-bag protocols. In our analysis, we found no difference between the groups with an overall NAAR incidence of 2.5%. This mirrors Sudanagunta et al., which also showed no difference in NAAR in a two-bag protocol (19% vs. 23%, $p=0.54$), albeit in a pediatric patient population [12]. Several other studies have shown decreases in NAAR incidence [7, 9, 10] with an overall prevalence of 0.5–31%. An almost seven-fold decrease in NAAR was found by Bateman et al. [6], and Wong et al. [13]. As with ALI, inconsistency in the definition of NAAR limits the direct comparison between the studies. In our study, although NAAR was broadly defined it was still relatively rare in both cohorts and generally appears to not be affected by which group they were in. This is likely because the maximum rate of NAC administration in all the two-bag regimens is lower than the initially described first bag (150 mg/kg over 15 min) and the same

Table 2 Coingestant frequencies*

Substance class	Frequency	Substances
Ethanol	111	
Antihistamines	85	Diphenhydramine, doxylamine, pyrilamine, promethazine, hydroxyzine, chlorpheniramine
Opioids	76	Oxycodone, hydrocodone, methadone, heroin, hydromorphone, tramadol, fentanyl
Ibuprofen	61	
Sedatives	35	Alprazolam, diazepam, lorazepam, clonazepam, butalbital, zolpidem, eszopiclone
SSRI, SNRI, TCA	32	Fluoxetine, citalopram, escitalopram, sertraline, venlafaxine, desvenlafaxine, duloxetine, atomoxetine, amitriptyline
Aspirin	29	
Antitussive	27	Dextromethorphan, benzonatate
Caffeine	19	
Stimulants	16	Amphetamine, methamphetamine, cocaine
Gabapentin	16	
Atypical antipsychotics	15	Quetiapine, mirtazapine, risperidone, aripiprazole, clozapine, olanzapine
Trazodone	13	
Antihypertensives	13	Lisinopril, losartan, hydralazine, furosemide, amlodipine, hydrochlorothiazide, clonidine, atenolol, propranolol
Muscle relaxant	11	Tizanidine, cyclobenzaprine, methocarbamol
Melatonin	9	
Antacids	8	Omeprazole, pantoprazole, calcium carbonate
Anticonvulsive	7	Valproic acid, topiramate, lamotrigine
THC	7	
Household products	6	Bleach, drain cleaner, acetone, dishwasher detergent
Buspirone	6	
Antimicrobial	6	Ciprofloxacin, cephalexin, terbinafine, tenofovir, oseltamivir
Other	6	regorafenib, montelukast, methotrexate, prednisone, metformin, levothyroxine
Toxic alcohols	5	Isopropyl, ethylene glycol, propylene glycol
Antithrombotic agents	4	Warfarin, cilostazol, clopidogrel, rivaroxaban
Alpha agonists	2	Tamsulosin, prazosin
Statin	2	Atorvastatin

*175 cases where thought to have involved acetaminophen alone

between the two groups in our analysis. Previous research has found that slowing this initial infusion is associated with fewer adverse events [6, 7, 18, 19, 20, 21].

The most significant difference between groups in our study was regarding medication errors. We chose to use a broad definition of medication errors– combining both delays in administration of over 60 min and dosing/rate error into a single composite variable. Utilizing this definition, we found a marked decrease in errors from 27 to 11% with an adjusted OR of 0.24. As noted above, these errors were more often wrong dose/rate errors rather than delays in administration. While dose/rate errors are related to the complexity of the protocol, delays in administration would likely be due to other nursing and pharmacy issues that may be independent of either protocol. This decrease in overall medication errors is not an unexpected finding given the relative simplicity of our protocol. As opposed to the traditional dosing strategy, there are only two opportunities for inappropriate dose choice and one opportunity for delay in administration rather than three and two in a three-bag regimen, respectively. Although several studies have reported medication errors in modified two-bag protocols [8, 10], only two studies assessed the difference in errors between traditional and two-bag protocols. Sudanagunta et al. reported a decrease in medication errors from 39 to 23% with a NNT of 7 [12] while O'Callaghan et al. found a decrease from 51 to 31% between groups with a NNT of 5 [14]. Our results represent a similar NNT of 6.25.

Considered together, we believe that this novel approach (2 doses of NAC at 150 mg/kg over 1 h and 20 h, respectively) may be similarly effective and safe as previously reported two-bag NAC regimens. That said, our results are limited in several ways. Most importantly, the interpretation of our study results is limited due to the retrospective nature of the design. Efforts were made to limit the bias inherent in retrospective research including using blinded abstractors (abstractors had no knowledge of the hypothesis or aim of the study until the data collection process was complete, nor were they given any explicit information about which cases were in each group), trained using a standard abstraction protocol, with *a priori* defined definitions of each outcome and variable. Nevertheless, limitations remain including the number and varied training level of the abstractors (4 were utilized with training ranging from first-year medical resident to medical toxicology fellow), how questions of interpretation were resolved (by a single individual, the corresponding author), and the lack of reliability analysis on the abstraction of the entire corpus of charts. Due to resource and time restraints, only the cases that met criteria for one of the primary or secondary outcomes (NAAR, ALI, administration errors) and cases marked for exclusion were reviewed by the corresponding author for accuracy. Our use

Table 3 Cases with NAAR*

Case	Scenario	Group	Reaction	Medication Administered
1	Acute intentional ingestion with diphenhydramine and ibuprofen coingestion	Three	Rash	None
2	Chronic supratherapeutic ingestion without coingestion	Three	Difficulty swallowing/breathing, hives	Epinephrine, methylprednisolone, diphenhydramine
3	Chronic accidental ingestion with oxycodone and ibuprofen coingestion	Three	Emesis	Prochlorperazine
4	Acute intentional ingestion with dextromethorphan, doxylamine, guaifenesin, phenylephrine, and ethanol coingestion	Two	Rash	Diphenhydramine
5	Acute intentional ingestion with no coingestion	Two	Skin flushing/heating, restlessness	Diphenhydramine, hydrocortisone
6	Acute intentional ingestion with no coingestion	Two	Hives	Diphenhydramine, methylprednisolone
7	Acute intentional ingestion with ibuprofen coingestion	Two	Nausea	Ondansetron
8	Acute accidental ingestion with no coingestion	Two	Stridor, angioedema	Diphenhydramine, famotidine, hydrocortisone
9	Chronic supratherapeutic ingestion with ethanol coingestion	Two	Itching, hives, nausea	Ondansetron
10	Chronic supratherapeutic ingestion with no coingestion	Two	Rash, flushing, difficulty breathing	Epinephrine, diphenhydramine, methylprednisolone
11	Acute ingestion of unknown intent with no coingestion	Three	Diaphoresis, periumbilical pain	None

*Severe reactions highlighted (cases 2,8,10)

of ICD-10 codes to identify patients for the study further limits interpretation, as this may miss or include patients with inappropriate or inaccurate codes. Our data regarding ingestion intent and chronicity is limited by the patient history documented in the chart, which may be similarly inaccurate or imprecise. Our results are further limited by not obtaining complete information regarding transferred patients– especially whether they received a transplant or not. We also did not collect information on the patients that died in the cohort (whether their deaths were related to the ingestion, time of presentation, severity of disease, etc.).

Furthermore, as in all retrospective studies we are limited by the presence of missing or wrongly input data into the EMR. The generalizability of our study is also limited due to patient and hospital characteristics. We tried to improve this by analyzing two affiliated hospitals with identical protocols but different patient populations. We attempted to adjust for hospital specific factors by including the treating hospital into the logistic regression model. Another important factor that may limit generalizability is that, although treatment was guided generally by what is recommended in the NAC package insert and poison center guidelines, the decision to treat for acetaminophen is occasionally quite nuanced and may not be completely uniform from provider to provider (for example, a patient with a level of 148 micrograms/mL at 4 h may be treated with NAC or not, depending on the provider's belief in the accuracy of the ingestion timeline). Finally, the size of the cohorts, although similar to previously reported studies, remains quite small and was likely underpowered to show differences in NAAR and ALI. Further study is needed to prospectively collect data regarding NAAR and liver injury in this patient population in a manner that is appropriately powered to find a difference if one exists.

Conclusion

In this simplified NAC protocol for treating acetaminophen toxicity, we found that medication errors were less likely in the simplified two-bag approach. Minimizing medication errors and their downstream effects may represent an improvement in patient care. This adds to the literature that alternative two-bag NAC protocols may show benefits over the traditional approach.

Table 4 Outcomes of interest

Unadjusted outcomes	Total		3 bag		2 bag		OR* [95% CI]	*p* value
	(count)	(%)	(count)	(%)	(count)	(%)		
NAAR	11	2%	4*	2%	7*	3%	1.7 [0.49-6.8]	0.38
ALI	143	30%	79	33%	64	26%	0.72 [0.47-1.65]	0.10
Died	14	3%	8	3%	6	2%	0.73 [0.23-2.18]	0.56
Medication error	92	19%	65	27%	27	11%	0.33 [0.20-0.54]	<0.005
ICU	158	33%	73	31%	85	35%	1.21 [0.82-1.8]	0.31
Adjusted** outcomes							OR* [95% CI]	*p* value
NAAR							2.8 [0.77-12]	0.22
ALI							0.75 [0.41-1.48]	0.29
Mortality							0.67 [0.45-8.4]	0.79
Medication error							0.24 [0.15-0.40]	<0.005
ICU							0.88 [0.57-1.35]	0.61

*In the three bag group, 2 NAARs were determined to be severe in the 3 bag group, and 1 NAAR in the 2 bag group

*Relative to three-bag protocol

Abbrevations: NAAR, non-allergic anaphylactoid reaction; ALI, acute liver injury; ICU, intensive care unit

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Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

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