

Assessing the Influence of *Acetadote* on Use of Intravenous *N*-acetylcysteine for Acetaminophen Poisonings

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Abstract

Background: Until recently in the United States, the intravenous (IV) administration of *N*-acetylcysteine (NAC) in acetaminophen (APAP) poisonings was reserved for patients unable to take or tolerate oral NAC. Aside from these situations, oral administration of NAC was preferred. In February 2004 an IV formulation of NAC, *Acetadote*, was approved by the US Food and Drug Administration. This study was designed to examine the influence of *Acetadote* availability on the use of IV NAC in the treatment of APAP poisonings.

Methods: A retrospective review of poison center records was performed for cases reported to a poison control system 6 months before (PRE) and 6 months after (POST) the release of *Acetadote*. Extracted variables included patient age and sex, reason for exposure, type of APAP product involved, exposure duration, rationale for use of IV NAC, reported adverse reactions, medical outcomes, and source of IV. Also, the average wholesale price for *Acetadote*, *Mucomyst*, and generic NAC were obtained.

Results: IV NAC was administered to 50 (2.9%) patients in the PRE group and to 183 (9.6%) patients in the POST group. Demographic data were similar for both groups. Adverse reactions to IV NAC included 2 allergic-type reactions and 1 complaint of chest tightness in the POST group and 1 allergic-type reaction in the PRE group.

Discussion: The release of *Acetadote* was associated with a 266% (2.9% to 9.6%) increase in IV NAC use. This change occurred despite a higher risk of serious adverse events with the IV route, an increase in cost when using *Acetadote* with equivalent treatment durations, and a lack of convincing data demonstrating that the IV route is superior in efficacy to the oral route.

Conclusion: The change in IV NAC usage without published rationale may be the result of effective promotional campaigns by the manufacturer of *Acetadote* or the assumption that newly approved products are superior to existing products.

Key Words—*Acetadote*, acetaminophen, *N*-acetylcysteine

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For over 3 decades, acetylcysteine (*N*-acetylcysteine; NAC) has been administered to patients with acetaminophen (APAP) poisoning.^{1,2} The intravenous (IV) route has been preferred throughout Europe, Canada, and Aus-

tralia,³ whereas in the United States the IV route has been reserved for patients unable to take or tolerate oral NAC.⁴ Until recently, whenever IV NAC was administered in the United States, the oral formulation was used. In February 2004 an IV

formulation of NAC, *Acetadote* (Cumberland Pharmaceuticals Inc; Nashville, TN), was released after receiving approval by the US Food and Drug Administration (FDA) for use as a first-line agent in mild-to-moderate APAP poisonings. It is

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a sterile solution of 20% w/v acetylcysteine. This study was designed to examine the impact of *Acetadote* availability on the use of IV NAC in the treatment of APAP poisonings.

METHODS

A retrospective review of poison center records was performed for all cases reported to the California Poison Control System (CPCS) 6 months before and 6 months after the June 2004 release of *Acetadote* in which NAC was coded as a treatment in CPCS records. Exclusion criteria included non-APAP exposures and cases in which treatment with IV NAC was coded but not received by the patient. Data were extracted from *Visual Dotlab Enterprise* (WBM Software; Fresno, CA) using a standardized *Microsoft Excel* (Microsoft Corp; Redmond, WA) spreadsheet. Extracted variables included patient age and sex, reason for exposure, type of APAP product involved, exposure duration, the presence of coingestants, reason or rationale for use of IV NAC, reported adverse reactions associated with NAC administration, source of IV NAC (*Acetadote* or an oral formulation given IV), and final patient dispositions. Final patient dispositions were defined as follows:

No effect: no symptoms as a result of the exposure

Minor effects: symptoms of minimal clinical significance (eg, drowsiness, mild gastrointestinal symptoms)

Moderate effects: symptoms that are more pronounced or more prolonged than minor symptoms (eg, hypotension/hypertension, hepatic injury without encephalopathy)

Major effects: symptoms that are life threatening or that result in significant residual disability or disfigurement (eg, hepatic encephalopathy, renal failure) and death

In addition, the average whole-

sale prices (AWPs) for *Acetadote*, *Mucomyst*, and generic NAC were obtained from a hospital pharmacy through verbal communication with Philip Anderson, PharmD (March 2006).

Statistical analysis between the before *Acetadote* marketing (PRE) and after *Acetadote* marketing (POST) groups was performed by calculating the odds ratio (OR) and 95% confidence intervals using the calculator by DJR Hutchon.⁵

RESULTS

The total number of cases in which any form of NAC was administered totaled 1,697 in the PRE group and 1,909 in the POST group. Of these, IV NAC in some amount was given to 50 (2.9%) patients in the PRE group and to 183 (9.6%) patients in the POST group. Demographic data such as age, sex, product type ingested, and number of cases involving coingestants was similar for both groups (see Table 1). IV NAC only (no oral) was administered to 20 (40%) patients in the PRE group and to 117 (64%) patients in the POST group. IV NAC was started and then switched to oral NAC in 8 (16%) PRE cases and 28 (15%) POST cases. Oral NAC was started and then switched to IV NAC in 12 (24%) PRE cases and in 32 (17%) POST cases. Of patients receiving oral NAC whose therapy was switched to IV NAC and then back to oral NAC, there were 10 (20%) in the PRE group and 6 (3%) in the POST group. Only 1 patient (POST group) began taking IV NAC, switched to oral NAC, and then switched back to IV NAC. These data are summarized in Figures 1 and 2.

Although the formulation of IV NAC used was not documented in 47 of 183 (26%) cases in the POST group, *Acetadote* was the formula-

tion used in 73 (40%) cases and the oral NAC formulation was given IV 63 (34%) times.

Documented adverse reactions to IV NAC included 2 allergic-type reactions (1 with *Acetadote*, 1 with oral formulation) and 1 complaint of chest tightness (formulation not documented) in the POST group and 1 allergic-type reaction in the PRE group.

Odds ratio values demonstrated that after the introduction of *Acetadote*, APAP poisoning cases had a significantly higher likelihood of receiving IV NAC (OR = 3.49). The PRE and POST groups were similar with respect to gender, product type ingested, coingestants, time to first NAC dose, and allergic reactions to NAC. The POST group, however, had less significant risk of developing major clinical effects (OR = 0.367).

Of the total cases, 168 (72%) had a documented reason for IV NAC use. In this subset, the primary reasons documented for giving IV NAC in both the PRE and POST groups were protracted vomiting, "nothing by mouth" orders, and decreased level of patient consciousness. Notably, IV NAC was the physician's first choice in only 1 case (3%) in the PRE group and in 16 (12%) cases in the POST group (OR = 0.242).

DISCUSSION

In this study, the release of *Acetadote* was associated with a 266% (2.9% to 9.6%) increase in IV NAC use. This change occurred despite a higher risk of serious adverse events with the IV route,³ a substantial increase in cost when using the FDA-approved form with equivalent treatment durations, and a lack of convincing data demonstrating that the IV route is superior in efficacy to the oral route. The AWP of the available

Table 1. Extracted PRE- and POST-*Acetadote* Case Information

	<i>PRE</i> - <i>Acetadote</i> Release	<i>POST</i> - <i>Acetadote</i> Release	<i>Odds Ratio</i> (95% <i>CI</i>)
Number of NAC Cases	1,697	1,909	
Number of IV NAC Cases	50 (2.9%)	183 (9.6%)	3.49 (2.53 to 4.80) ^a
Reason for IV NAC^a			
Physician first choice	1 (3%)	16 (12%)	0.242 (0.031 to 1.90)
Patient NPO	6 (19%)	15 (11%)	
Protracted vomiting	15 (47%)	81 (60%)	
Decreased LOC	2 (6%)	6 (4%)	
Poison center recommendation	5 (16%)	10 (7%)	
Other	3 (9%)	8 (6%)	
Source of IV NAC			
<i>Acetadote</i>	Not applicable	73 (40%)	
Oral NAC given IV	50 (100%)	63 (34%)	
Undeterminable	0 (0%)	47 (26%)	
Average Age	32 y; SD, 16 (range, 13 to 66 y)	29 y; SD, 15 (range, 2 to 84 y)	
Sex			
Men	11 (22%)	50 (27%)	1.33 (0.633 to 2.80)
Women	39 (78%)	131 (72%)	
Pregnant	0 (0%)	2 (1%)	
Product Type			
APAP alone	21 (42%)	69 (38%)	0.480 (0.216 to 1.07)
Combination product	11 (22%)	75 (41%)	
Unknown	18 (36%)	39 (21%)	
Number of Cases With Coingestants	11 (22%)	51 (28%)	1.36 (0.651 to 2.87)
Adverse Reactions to IV NAC			
Allergic reaction	1 (2%)	2 (1%)	0.816 (0.83 to 8.02)
Chest tightness	0 (0%)	1 (0.5%)	
Final Patient Disposition			
No effect	2 (4%)	4 (2%)	
Minor effects	9 (18%)	94 (51%)	
Moderate effects	18 (36%)	46 (25%)	
Major effects	9 (18%)	26 (14%)	0.367 (0.179 to 0.749) ^b
Death	8 (16%)	5 (3%)	
Unknown	4 (8%)	6 (3%)	
Unrelated effects	0 (0%)	2 (1%)	

^aBased on those cases with documented reason for intravenous *N*-acetylcysteine (IV NAC); ^bSignificant differences; APAP = acetaminophen; CI = confidence interval; LOC = level of consciousness; NPO = nothing by mouth; SD = standard deviation.

NAC 90 mL vial formulations are as follows: *Acetadote*, \$428; *Mucomyst*, \$53; and generic NAC, \$18.

Decades of literature support that both routes of NAC administration with the oral formulation are effective in decreasing the morbidity and mortality associated with APAP poisonings. The prima-

ry arguments in favor of oral NAC use are that it is noninvasive and that reported adverse effects caused by therapy tend to be relatively mild in nature. The oral product also has a considerably lower purchase cost than *Acetadote*.

With respect to the IV route, arguments in favor of using it as a first-line agent include ease of ad-

ministration, improved patient tolerance, and a shorter treatment duration resulting in decreased hospital stay. A continuous IV infusion prevents dosing every 4 hours, as well as a noxious odor that can cause vomiting of the doses and subsequently require larger amounts of antiemetics.⁶ A recent study found that in 221 patients treated with IV

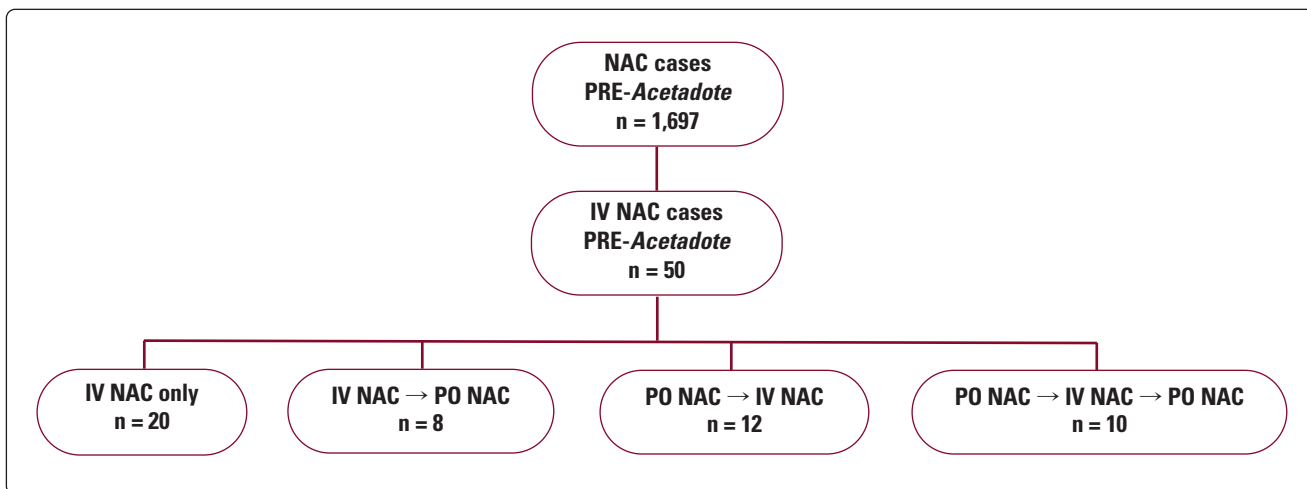


Figure 1. PRE-*Acetadote* algorithm. IV = intravenous; NAC = *N*-acetylcysteine; PO = oral; PRE = before *Acetadote* marketing.

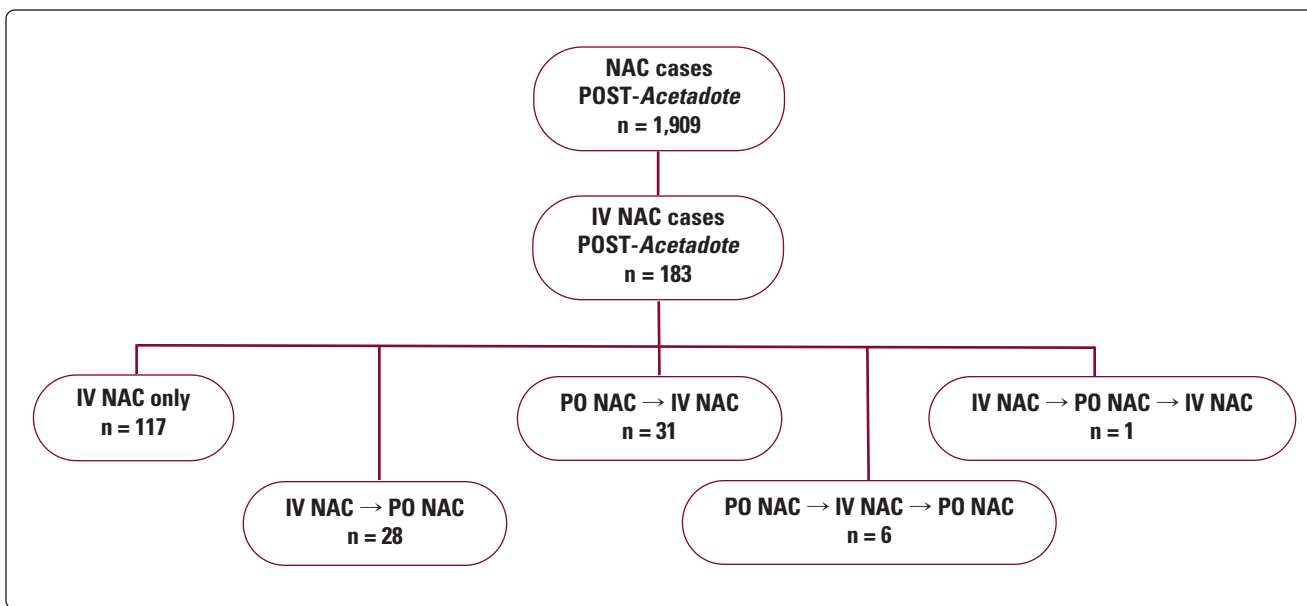


Figure 2. POST-*Acetadote* algorithm. IV = intravenous; NAC = *N*-acetylcysteine; PO = oral; POST = after *Acetadote* marketing.

NAC, 33% experienced at least 1 medication error during therapy.⁷ To date there are no similar studies published involving oral NAC administration, so the comparative relevance of this seemingly high error rate cannot be determined. With respect to the shorter duration of treatment, published data suggest that the duration of oral NAC therapy can be safely shortened to minimize length of thera-

py,⁸⁻¹⁰ thereby nullifying this proposed benefit.

Adverse reactions related to oral NAC are usually mild and limited to gastrointestinal disturbances. In contrast, IV NAC has been associated with potential life-threatening anaphylactic or anaphylactoid reactions in up to 17% of patients.¹⁰ Although slower infusion rates may reduce the frequency of these occurrences, they remain a concern. Re-

ported adverse reactions were uncommon in this study's data set, but the sample size might have been too small for detection of any changes in adverse reaction reports. In addition, adverse reactions might not have been captured by poison specialists if they were mild in nature and, subsequently, not reported by health care providers.

In this study, the source of IV NAC could be determined in 136

POST cases. In this subset, 73 (54%) involved the use of *Acetadote*. A possible explanation for this high rate of use may be the perception that *Acetadote* is safer than the oral product given IV. No studies exist that directly compare the safety profiles of different IV NAC formulations; however, a comparison of published reports on adverse reactions related to IV NAC administration found that the FDA-approved IV formulation of *Acetadote* is no safer than the IV administration of the oral solution.¹¹

Another reason that clinicians might have chosen an FDA-approved product over IV administration of the oral solution is the fear of legal liability. Although there is a substantial amount of literature supporting the IV administration of oral or inhalational NAC solution products,^{12,13} changing the route of administration of a sterile solution to an IV preparation when a commercial sterile and pyrogen-free product is available may not be attractive to some practitioners. Furthermore, federal and state laws¹⁴ regarding the compounding of extemporaneous solutions from oral or inhalational formulations for IV use may influence the decision process.

Only 40% of the PRE group and 64% of the POST group received IV NAC exclusively. Because of the retrospective nature of the data collection, drawing concrete conclusions as to why this occurred is difficult. This may reflect clinician or poison specialist biases with respect to one route over another. Alternatively, it may reflect a patient's ability to tolerate one route over another. Many patients were initially prescribed oral NAC and experienced protracted vomiting; their therapy was subsequently changed to IV NAC. Conversely, one patient who developed a rash

soon after the initiation of IV NAC therapy was switched to oral NAC and subsequently finished the course of therapy without additional problems.

This study had some limitations. The relatively small number of cases involving the administration of IV NAC might reflect underreporting of such cases to poison centers by clinicians. Because the data were not collected prospectively, there was a relatively small proportion of cases describing the rationale for administering IV NAC and this might have negatively affected the statistical analysis. The actual cost of the various NAC products may vary from hospital to hospital, although *Acetadote* is likely more expensive than generic oral NAC for all hospitals. Furthermore, outcome data varied somewhat between the PRE and POST groups, but because of the retrospective nature of the study and the inability to control the collection of specific data points (eg, the amount ingested and the latency to onset of NAC therapy), accurately determining the relevance of this finding is difficult. Lastly, the study period of 6 months was arbitrarily chosen. A lengthier study may yield different findings.

CONCLUSION

The availability of *Acetadote* was associated with an increase in IV NAC use for APAP poisonings. Once *Acetadote* was released in the US market, more than half of all IV NAC cases reported to the system involved this product. This occurred despite a lack of any additional published evidence of improved efficacy, change in indication for use, or safety over the existing products. If administered for equal durations, *Acetadote* was associated with a higher acquisition cost than an oral/inhalational solu-

tion given orally or IV. Based on this study's findings, the change in IV NAC usage and the subsequent disproportionate use of *Acetadote* without published rationale may be the result of effective promotional campaigns by the manufacturer of *Acetadote* or the mistaken assumption that newly approved products are always superior to existing products.

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