



A Case Report of a Severe, Unusually Delayed Anaphylactoid Reaction to Intravenous N-Acetylcysteine During Treatment of Acute Acetaminophen Toxicity in an Adolescent

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Received: 30 March 2020 / Revised: 27 July 2020 / Accepted: 1 August 2020 / Published online: 21 August 2020
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Abstract

Introduction Anaphylactoid reactions are well-documented adverse events associated with the intravenous administration of N-acetylcysteine (NAC) in patients with acetaminophen overdose. Most reactions are mild, occurring within the first 1–5 hours of initiation. This report presents the case of an adolescent with a delayed, life-threatening anaphylactoid reaction 24.5 hours after starting NAC, where discontinuing NAC could have resulted in fulminant hepatic failure (FHF) and death.

Case Report A 17-year-old previously healthy female presented with nausea, vomiting, and abdominal pain 10 hours after an acute acetaminophen ingestion. Her 11-hour serum acetaminophen concentration was above the treatment line (149 µg/mL), and she had elevated transaminases (AST = 202 U/L, ALT = 284 U/L). She was treated with intravenous NAC, which was suspended for 3 hours after she developed an apparent life-threatening anaphylactoid reaction with angioedema and respiratory distress 24.5 hours after treatment initiation. Given her high risk of progression to FHF, NAC was resumed at double the previous rate along with scheduled corticosteroids and antihistamines after resolution of her symptoms. Her AST increased to 10,927 U/L, and INR peaked at 3.6, but she had no further anaphylactoid symptoms. She was discharged in her normal state of health after 6 days.

Discussion Discontinuing NAC in this case of severe, delayed anaphylactoid reaction could have resulted in FHF requiring liver transplant. The reason for her reaction is unclear but could be related to patient risk factors or medication error. Guidelines for reinitiation of NAC after development of delayed anaphylactoid reactions are not well-established. Close observation beyond the first 1–5 hours of NAC administration is warranted.

Keywords Acetaminophen · N-acetylcysteine · Anaphylactoid reaction

Supervising Editor: Mark B. Mycyk, MD

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s13181-020-00804-5>) contains supplementary material, which is available to authorized users.

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Introduction

Prompt initiation of N-acetylcysteine (NAC) prevents most cases of acute acetaminophen (APAP)-induced hepatotoxicity and reduces mortality in APAP overdose if initiated within the first 8–10 h following ingestion [1, 2]. Anaphylactoid reactions to NAC are well-documented adverse events [3, 4]. Symptoms can include rash, flushing, urticaria, vomiting, respiratory distress, bronchospasm, chest pain, angioedema, and hypotension [3, 5, 6]. In contrast to IgE-mediated anaphylaxis, anaphylactoid reactions are attributed to non-immunogenic histamine release from mast cells and basophils exposed to high NAC concentrations [3, 5, 6].

Anaphylactoid reactions to NAC are rate and dose-related, most commonly occurring within 1–5 hours of the rapidly infused loading phase, when the largest dose is administered over the shortest time [4–6]. Reported incidence varies widely from 3.7 to 56% depending on the methods used to ascertain

symptoms [4, 5, 7]. Most anaphylactoid reactions (> 75%) were found to be cutaneous in a cohort of patients treated with NAC, with ~2% of patients found to have severe systemic reactions such as respiratory distress [4, 6]. Approximately 2% of patients receiving NAC have treatment discontinued due to adverse reactions [2]. This is problematic because stopping NAC prematurely is associated with greater transaminase elevation and increased risk of liver transplant [4, 8].

We present the case of an adolescent with late-presenting acute APAP-induced hepatotoxicity and a course complicated by a suspected delayed, life-threatening anaphylactoid reaction to NAC and discuss the possible management of a severe anaphylactoid reaction in a setting where NAC could not be discontinued due to the significant risk of the patient developing fulminant hepatic failure (FHF) [2].

Case Report

A 17-year-old, 61 kg, previously healthy female presented to a community hospital for nausea, vomiting, and abdominal pain approximately 10 hours after an acute APAP ingestion. Upon presentation, she was well-appearing. She denied use of alcohol, illicit drugs, prescription medications, or other over-the-counter medications. She reported ingesting “four APAP tablets” of unknown strength for analgesia and denied any suicide attempt. The 11-hour serum APAP concentration was above the treatment line (149 µg/mL). The 21-hour Food and Drug Administration-approved three-bag intravenous (IV) NAC protocol was initiated with the first two bags administered at the community hospital. The patient was transferred to the intensive care unit of a quaternary care children’s hospital where the third bag of NAC was initiated at 6.25 mg/kg/h.

Ten hours later, the patient’s transaminases increase further (AST = 370 U/L, ALT = 316 U/L) with an elevated international normalized ratio (INR = 1.6, see Table 1). Because her transaminases continued to increase near the end of the 21-hour protocol (AST = 990 IU/L, ALT = 788 IU/L), IV NAC was continued at 6.25 mg/kg/h. Approximately 3.5 hour after starting the fourth bag of NAC (24.5 h into her continuous infusion), she reported throat itching and developed a low-grade fever with rhinorrhea, headache, and diarrhea. She then developed angioedema, bilateral wheezing, and subcostal retractions with respiratory distress. According to the primary team, she was lethargic, tachycardic, and tachypneic. NAC was stopped, and she was treated with solumedrol, intramuscular epinephrine, diphenhydramine, nebulized albuterol, and racemic epinephrine. Her respiratory symptoms improved, although she still had facial edema and swelling of the lips upon exam by the toxicology team an hour later.

The toxicology team had an extensive discussion with the patient, her parents, and the primary team regarding the risks and benefits of restarting NAC versus prematurely discontinuing treatment. Since the patient was at high risk of FHF due to her late hospital presentation, elevated transaminases, and elevated 11-hour presenting APAP concentration, the toxicology team recommended restarting IV NAC at double the previous rate with concurrent prophylaxis following resolution of the patient’s respiratory distress. All persons involved agreed to this plan. NAC was thus restarted after a 3-hour break at 12.5 mg/kg/h along with scheduled steroids and antihistamines (See Fig. 1).

Given the patient’s uncertain prognosis (AST = 10,927 U/L, ALT = 5671 U/L, INR = 3.6–44 h post-ingestion), the liver transplant service was consulted. NAC was continued at 12.5 mg/kg/h along with steroids and antihistamines without recurrence of anaphylactoid symptoms until her hepatic dysfunction improved. Although the patient consistently denied suicidal ideation, she was evaluated by psychiatry for suspected self-harm since her self-reported ingestion was inconsistent with her clinical course. She was discharged in her normal state of health after 6 days. Telephone follow-up 5 months after discharge confirmed that the patient continued to be clinically well.

Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Discussion

Administration of NAC demonstrably improves outcome for APAP overdose patients, while premature discontinuation of NAC risks clinical deterioration in patients with hepatic injury [9]. At least one case of FHF resulting in liver transplant after premature NAC discontinuation due to anaphylactoid reaction has been reported [8]. Given our patient’s high risk of progression to FHF and a presenting serum APAP level inconsistent with her history, we restarted NAC at double the pre-event rate after resolution of her severe anaphylactoid reaction. Our patient avoided liver transplant and made a full recovery.

Twenty-four hours after the initiation of IV NAC, she developed severe anaphylactoid symptoms. Her delayed symptom onset differs from the usual occurrence of anaphylactoid symptoms during the first or second NAC infusions, which are given at a faster rate [4–6]. A retrospective study examining incidence, severity, and timing of anaphylactoid reactions during the 21-hour IV NAC protocol found documented reactions in 8% of patients [4]. Seventy-five percent of these reactions were cutaneous. When reactions occurred, > 95% happened within the first 5 hours, with most in the first hour, and only ~4.5% occurred during administration of the third bag of

Table 1 Serum labs over time following APAP ingestion

	AST	ALT	INR	APAP	CO2	NH3	Na+	K+	BUN	Cr
Normal range	(1–50 U/L)	(5–30 U/L)	(0.9–1.2)	(mcg/ml)	(22–28 mEq/L)	(15–50 µmol/L)	(135–145 mmol/L)	(3.5–5 mmol/L)	(8–21 mg/dL)	(0.67–1.18 mg/dL)
Hours post-ingestion										
11	202	284	1.4	149						
21	370	316	1.6	34	15			3.5	8	0.9
33	990	788		Undetectable	19		139			
44	10,927	5671	3.6	Undetectable		59				
51	7724	5965	3.0*			32				
57	4495	4840	2.3			52				
66	2709	3790	2.0			34				
69	2143	3437	1.9			62				
Discharge										

*After vitamin K administration

NAC [4–6]. No severe anaphylactoid reaction was reported > 24 hours after NAC initiation.

The reason for the patient's sudden late development of a severe anaphylactoid reaction remains unclear, but multiple factors may have contributed. Risk factors associated with developing severe anaphylactoid reactions include female sex, younger age, asthma, atopy, drug allergies, family history of allergy, prior reaction to NAC, low serum APAP concentration, and a time interval > 8 hours from APAP ingestion to treatment with NAC [4–6]. Our patient had at least three of these predisposing risk factors, including female sex, late presentation, and an undetectable serum APAP concentration at the time of the event. Although the mechanism is unknown, higher serum APAP concentrations appear to be protective against anaphylactoid reactions [3, 5–7]. Incidence of anaphylactoid reaction was estimated to be between 3% and 5% with APAP concentrations > 200–300 mcg/mL and 20–25% with APAP < 150 mcg/mL [4, 7].

We also considered the possibility of an allergic reaction or iatrogenic error. However, no new medications were ordered or administered before the patient's anaphylactoid event, and she had no documented allergies, making an allergic medication reaction an unlikely explanation. The patient also ate her last meal > 3 hours prior to the event, making an unknown food allergy unlikely. Alternatively, several life-threatening reactions to NAC secondary to iatrogenic error have been reported in the literature [6]. Rare complications including cerebral edema, seizures, myocardial infarction, respiratory arrest, and death have been reported following iatrogenic overdose of IV NAC [6]. Since the remainder of the fourth bag of NAC was administered to the patient following resolution of her symptoms, we were unable to test the actual concentration of NAC in that bag. However, our patient remained asymptomatic for the first 3.5 hours after starting this bag of NAC, which makes this explanation seem less likely. An accidental increase in her infusion rate prior to the event is also possible, but no ordered rate increase or nursing administration error was documented.

Anaphylactoid reactions are usually mild and treatable with antihistamines if they occur [6]. Because life-threatening anaphylactoid reactions are rare, limited recommendations exist for their management in cases where discontinuing NAC could also be life-threatening. The seriousness of life-threatening hepatotoxicity after APAP overdose must be weighed against the risk of developing a life-threatening anaphylactoid reaction when considering whether to restart NAC after an anaphylactoid reaction. Administration of epinephrine with steroids and antihistamines effectively prevented further symptoms in our patient despite restarting IV NAC at double the previous rate. However, if this regimen had failed, our plan was to use oral NAC, which has a lower documented rate of adverse reactions other than nausea and vomiting [3, 6]. If life-threatening symptoms recurred with oral NAC, we planned to restart IV NAC with a concurrent epinephrine infusion (Table 2).

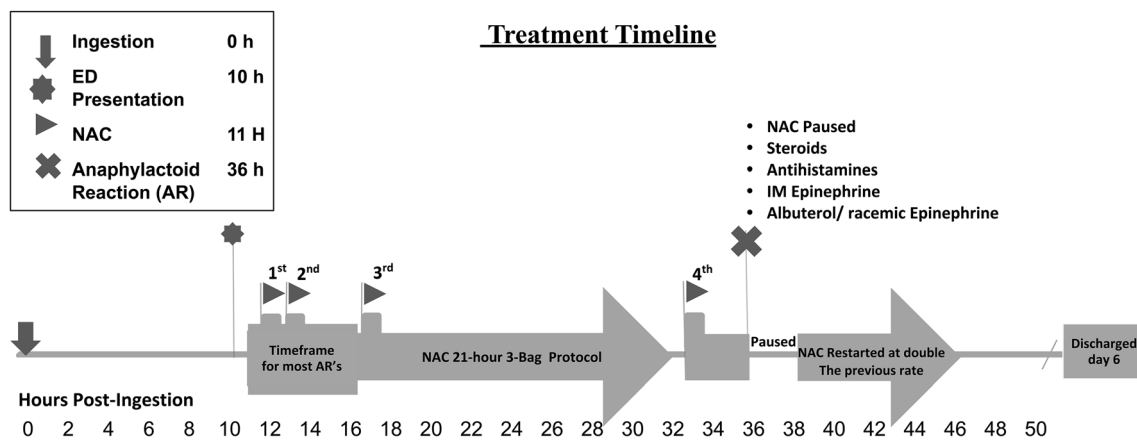


Fig. 1 Treatment timeline

Limitations

This is a single case report, which limits the generalizability of our treatment approach. The amount of the patient's APAP ingestion is also questionable given the mismatch between her report of taking four APAP tablets and the severity of her

clinical course. While several elements of the scoring system were not known, this case receives a Naranjo probability score of 4, suggesting a possible relationship for the adverse drug reaction ([Supplemental Figure](#)) [12]. Although the patient was rechallenged with NAC, this was not a true rechallenge test given that she was concurrently being treated with steroids

Table 2 Classification and management recommendations for anaphylactoid reactions to IV NAC

Reaction Severity	Symptoms	Treatment
Any	Any, including nausea and vomiting	1. Consider whether continuing NAC is necessary based on patient's serum APAP concentration and expected clinical course 2. Consider pretreating with antiemetics [5]. Nausea or vomiting alone does not constitute anaphylactoid reaction
Mild	Cutaneous (flushing)	1. Reactions confined to flushing without pruritus or urticaria require no treatment [4] 2. NAC infusion can be continued, unless more severe signs develop
Moderate	Cutaneous: urticaria, pruritus	1. Consider slowing the rate of infusion [5] 2. Provide supportive therapy with antihistamines [2] 3. NAC infusion can be restarted at prior rate once urticaria resolves 4. Meticulously monitor for systemic manifestations [3, 10]
Severe	Systemic: bronchospasm, angioedema, hypotension	1. Temporarily stop NAC and treat like anaphylaxis 2. Consider IM epinephrine, IV H1 & H2 antihistamines, steroids, and albuterol [10, 11]. Treat hypotension with rapid infusion of 1–2 l IV NS. After reaction resolves, reassess need for IV NAC 3. If still indicated, address risks vs. benefits [10] 1 h after epi- and antihistamines, carefully restart NAC at slower rate in absence of symptoms [7, 10] 4. Keep IM epinephrine and resuscitation equipment at bedside 5. Consider adding scheduled steroids and antihistamines 6. If reaction recurs, consider switching to PO NAC [3, 4] 7. If unable to tolerate PO NAC or reaction recurs in a patient with high risk of FHF, consider restarting IV NAC with simultaneous epinephrine infusion and scheduled steroids and antihistamines [11]
Medication dosing [10, 11]	• Diphenhydramine: 1 mg/kg IV (max 50 mg) • Famotidine 0.5 mg/kg IV (max 40 mg/day) • Methylprednisolone: 1 mg/kg IV • Epinephrine: 0.01 mg/kg (0.01 mL/kg of 1:1000 high concentration). Repeat q5–15 min PRN • Albuterol: 2.5 to 5 mg in 3 mL saline via nebulizer. Repeat PRN • Epinephrine infusion: begin if hypotension still persists despite fluids and IM epi. Start at 0.1 mcg/kg/min and titrate according to BP, HR, and oxygenation • Some patients may require a second vasopressor (in addition to epinephrine)	

†Slower NAC infusion rate does not necessarily prevent further anaphylactoid reaction [10]

and antihistamines to prevent symptoms from recurring. We did not test the concentration of NAC or obtain antibody or mast cell levels to rule out IgE-mediated allergic reaction.

Conclusion

Guidelines for reinitiation of NAC after development of delayed anaphylactoid reactions are not well-established. In this case, a risk-benefit analysis based upon the patient's expected clinical course and severity of symptoms guided management after a life-threatening anaphylactoid reaction. While severe, delayed anaphylactoid reactions to NAC are uncommon, anaphylactoid events > 24 hours after NAC initiation can occur, and close observation beyond the first 1–5 hours of NAC administration is warranted.

Acknowledgments The authors would like to thank Dr. Stacia Shipman for her help with editing the first draft of the case report.

Authors' Contribution All authors contributed to this case report. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Declaration Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

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