The hepatoprotective effect of *N*-acetylcysteine with repeated toxic acetaminophen ingestions: a case report

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**ABSTRACT**

We present a patient who presented 37 times after large acute acetaminophen ingestions without residual signs of liver dysfunction. The presentations were all very similar: witnessed ingestions of 25 g of acetaminophen presenting within 1 h. Due to a potentially toxic serum acetaminophen concentration, she received *N*-acetylcysteine 16 times within a 12-month period and 21 times overall. This case is an extreme real-life example regarding the absence of subsequent hepatic injury with repeated potentially toxic acetaminophen ingestions requiring repeated treatments with *N*-acetylcysteine despite a theoretical vulnerable time period immediately after acetaminophen overdose.

**KEYWORDS**

Toxicology; acetaminophen; paracetamol; *N*-acetylcysteine; antidotes

**Introduction**

Acetaminophen (APAP) overdose is one of the most common causes of acute hepatic failure worldwide and the most common in the United States [1–4]. A widely held belief suggest that a patient surviving to stage IV, or the recovery phase, of a hepatotoxic APAP overdose will have complete hepatic regeneration [1, 2]. The same assumption exists for APAP-induced hepatotoxicity successfully treated with *N*-acetylcysteine (NAC) [1].

There are no reported cases of chronic hepatic dysfunction after recovery from APAP overdose [1]. Even without liver failure, there have been studies demonstrating formation of acetaminophen-cysteine adducts and changes in hepatic protein regulation even when there is no elevation of serum transaminases and no progression to cirrhosis [5–8]. We present an unusual case of repeated APAP ingestions successfully treated with NAC.

The patient provided verbal and signed informed consent to have her case published.

**Case**

A woman in her 30s presented 37 times after potentially toxic acute APAP ingestions and 26 times within a 12-month period. We reviewed her electronic medical record (EPIC\(^\text{®}\) Verona, WI) at her preferred hospital site as well as the Minnesota Poison Control System (Toxicall\(^\text{®}\), Computer Automation Systems, Inc. Aurora, CO) to identify total number of ingestions.

All presentations were very similar: witnessed ingestion and presentation within 1 h after ingestion of 25 g of immediate-release APAP. The patient resided in a long-term care facility but had independence to overcome obstacles in order to obtain an unopened bottle of extra strength (500 mg) acetaminophen containing 50 tablets. The reason for this specific formulation and bottle size is unknown, but employees at her group home consistently state this is the amount ingested throughout her overdose attempts.

The patient received NAC 21 times over a 10-year period due to serum APAP concentrations above the Rumack–Matthew nomogram treatment line (150 mcg/mL at 4 h post-ingestion) and 16 times in a 12-month period. The NAC dosing was based on the standard Prescott intravenous dosing regimen (150 mg/kg for 1 h followed by 50 mg/kg over four hours followed by 100 mg/kg over 16 h). Table 1 provides a timeframe of ingestion, four-hour serum APAP concentrations, transaminase concentrations and International Normalized Ratio (INR) during this period.
12-month period in addition to all prior overdoses at our institution.

She had no laboratory evidence for significant hepatic dysfunction during the year. Her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) each exceeded 40 IU/L once during the 12-month period. She had elevated transaminases during a single encounter during the year. Following a 4-h [APAP] greater than 337 mcg/mL, her peak AST and ALT were 140 and 158 IU/L, respectively. There was no trend of rising transaminases or INR to suggest residual or unrecognized hepatic injury in consecutive visits.

Her INR never exceeded 1.2 during this 12-month period. During one hospitalization three years prior, her INR reached 2.3 thirteen hours after a 1-h serum APAP concentration of 355.5 mcg/mL with normal transaminases. She did not have a four-hour concentration during this encounter.

We calculated apparent half-lives included for the overdoses with at least two measurable APAP concentrations in Table 1. Calculations based upon only two concentrations and times limit reliable estimation elimination half-lives. However, there was no apparent trend toward shorter half-lives to suggest increased APAP metabolism in later encounters.

**Discussion**

The patient in this case had no hepatic dysfunction after repeated APAP overdoses adequately treated with NAC. In this case, repeated toxic ingestions did not appear to have a cumulative effect despite multiple overdoses in close succession.

In one large, multicenter study, 35% of patients who ingested a median of 24 g of APAP either died or underwent liver transplant if not treated with NAC [4]. Our patient ingested 25 g of APAP at least 37 times without developing liver failure. Each of these episodes represents a potentially lethal overdose.

Animal evidence suggests adaptation in APAP metabolism with repeated and increasing APAP dosing in mice [9]. We considered the possibility that this patient may have an upregulation of the hepatic P450

**Table 1.** All serum APAP concentrations from overdose encounters to authors’ institution appear in chronologic order with “Day 0” representing the beginning of a twelve-month period with an increased frequency of overdoses. Time_1 is four hours post-ingestion, unless otherwise noted. Repeat measured APAP serum concentrations appear as [APAP]_2 or [APAP]_3 with the corresponding time post-ingestion. A “+” indicates NAC administration. AST, ALT, and INR represent the highest observed values for each encounter.

| Day | [APAP]_1 (mcg/mL) | Time_1 (h) | [APAP]_2 (mcg/mL) | Time_2 h | [APAP]_3 (mcg/mL) | Time_3 h | NAC | AST (IU/L) | ALT (IU/L) | INR | Apparent \( t_{1/2} \) (h) |
|-----|------------------|------------|------------------|----------|------------------|----------|-----|------------|------------|-----|---------------------|
| −2681 | 12.6 | | | | | | | 25 | 42 | 1.0 |
| −2540 | 153.1 | <10 | 34 | + | 21 | 11 | 1.0 |
| −1754 | 87.8 | | | | | | | 46 | 21 |
| −973 | 355.5 | 1 | <10 | 16.5 | + | 24 | 25 | 2.3 |
| −84 | 162 | <3 | 22.5 | + | 28 | 14 | 1.1 |
| 0 | 96 | | | | | | | 11 | 12 | 0.9 |
| 30 | 249 | 6.5 | <3 | 25 | + | 10 | 15 | 1.0 |
| 43 | 162 | <3 | 26 | + | 7 | 12 | 1.0 |
| 52 | 55 | 45 | 14 | <3 | 37.5 | + | 23 | 13 | 1.0 |
| *64 | 152 | | | | | | | 13 | 1.0 |
| 71 | 234 | <3 | 27 | + | 15 | 13 | 1.0 |
| 76 | 78 | | | | | | | 11 | 14 | 0.9 |
| 78 | 154 | <3 | 24 | + | 7 | 14 | 1.0 |
| 85 | 218 | <3 | 24 | + | 8 | 19 | 1.2 |
| 90 | 119 | | | | | | | 11 | 16 |
| 100 | 142 | | | | | | | 12 | 1.0 |
| 106 | 257 | <3 | 25 | + | 9 | 15 | 1.0 |
| 109 | 201 | <3 | 25 | + | 8 | 11 |
| 113 | 38 | | | | | | | 8 | 12 | 0.9 |
| 119 | 48 | | | | | | | 8 | 12 | 0.9 |
| 125 | 197 | 22 | 8 | <3 | 14 | + | 8 | 12 | 1.1 | 1.3 |
| 132 | 67 | | | | | | | 11 | 13 |
| 160 | 224 | 42 | 12.5 | <3 | 27.5 | + | 5 | <10 | 1.2 | 3.5 |
| 163 | 25 | <3 | 15 | + | 11 | 14 | 1.0 |
| 170 | 113 | | | | | | | 13 | 14 |
| 192 | 284 | | | | | | | 8 | <10 | 1.1 |
| 198 | >337 | <3 | 25 | + | 140 | 158 | 1.0 |
| 205 | 27 | | | | | | | 10 | 21 | 1.0 |
| 249 | 152 | 16 | 11.5 | <3 | 27 | + | 10 | 12 | 1.2 | 2.3 |
| 267 | 308 | 16 | 18 | 3 | 23 | + | 10 | <10 | 1.1 | 3.3 |
| 349 | 234 | <3 | 36.5 | + | 12 | 11 | 1.1 |

*This encounter was at another hospital. Data are from Toxicall®.

**This apparent half-life was implausible (>31 h) and likely reflects continued absorption after four hours.
enzymes, specifically CYP2E1, which may change the risk of subsequent hepatic injury. Despite theoretical CYP2E1 induction due to repeated acetaminophen metabolism, our patient did not show evidence for this. The limitations in our attempt to calculate half-lives include attempting to calculate a half-life on two measurements and limited data points. We were unable to identify any metabolic upregulation.

**Conclusion**

This is an unusual case of repeated APAP ingestions with serum concentrations above the treatment line on the Rumack–Matthew nomogram, successfully treated with NAC with no apparent cumulative effect.

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