CASE REPORTS

Multiple Aminotransferase Peak Levels After Acute Acetaminophen Overdose in Three Patients

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After acetaminophen overdose, typical trends of aspartate and alanine aminotransferase (AST and ALT, respectively) levels consist of a single peak followed by a decrease to baseline. Based on this pattern, declining AST or ALT levels have been proposed as a criterion for when to discontinue *N*-acetylcysteine therapy in patients with acetaminophen overdose. We describe three patients who experienced multiple aminotransferase peak levels after acetaminophen overdose. In each case, an initial peak was followed by a 20% or greater decrease in AST or ALT level, then a second, higher peak exceeding 1000 U/L. In two cases, the second peak correlated with encephalopathy or coagulopathy. Two patients were treated with a continuous infusion of intravenous *N*-acetylcysteine, with treatment interrupted for 4 hours in one of them. As observed in the three patients, multiple aminotransferase peak levels can occur after acetaminophen overdose. Although declining levels typically coincide with clinical improvement, the presence of other markers of liver injury, such as coagulopathy or encephalopathy, should prompt continued *N*-acetylcysteine treatment.

Key Words: acetaminophen, overdose, *N*-acetylcysteine, aminotransferases, aspartate aminotransferase, alanine aminotransferase, AST, ALT.

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Typical trends of aspartate and alanine aminotransferase (AST and ALT, respectively) levels after acetaminophen overdose consist of a steady increase to a single peak, followed by a decrease to baseline.[1] This decrease usually corresponds with clinical recovery. Based on this pattern, some authors have proposed using declining AST or ALT levels as one of the criteria for when to discontinue *N*-acetylcysteine treatment.[2, 3] In this case report, however, we describe three patients with acetaminophen overdose who each experienced a decline in aminotransferase levels after an initial peak level, followed by a second, higher peak that correlated with evidence of hepatic failure.

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Case Reports

Patient No. 1

A 33-year-old woman was brought to the emergency department approximately 24 hours after acute ingestion of acetaminophen and quetiapine (doses unknown). Her mental status was normal. Her medical history was remarkable for schizoaffective disorder, epilepsy, Gilbert's

syndrome, and Kartagener's syndrome. Her initial laboratory results were AST 712 U/L (normal range 0–45 U/L), ALT 674 U/L (0–45 U/L), acetaminophen 30.7 µg/ml (therapeutic range 10–20 µg/ml), international normalized ratio (INR) 1.58 (normal range 0.8–1.2), and total bilirubin 4.0 mg/dl (0.3–1.2 mg/dl); her total bilirubin level was within her baseline range.

A loading dose of intravenous *N*-acetylcysteine 150 mg/kg, followed by a 50-mg/kg infusion over 4 hours, followed by a continuous infusion of 6.25 mg/kg/hour was started approximately 26 hours after acetaminophen ingestion. Eleven hours later (37 hrs after ingestion), her AST level peaked at 3467 U/L and ALT level at 3265 U/L; her acetaminophen level was 3.2 µg/ml and INR was 2.02. Eleven hours after that (48 hrs after ingestion), her AST level declined to 1958 U/L and ALT level to 2578 U/L. Her INR decreased to 1.92, but fresh frozen plasma had been given within the previous 8 hours, with no abnormal bleeding documented before its administration.

The patient's aminotransferase levels then increased, with AST peaking at 7518 U/L at 66 hours after ingestion and ALT peaking 8 hours later at 7554 U/L. She had now developed grade II encephalopathy and a peak INR of 3.44. Her condition began to consistently improve, and *N*-acetylcysteine was stopped 120 hours after acetaminophen ingestion. She did not develop any evidence of renal failure, rhabdomyolysis, or metabolic acidosis. Studies for human immunodeficiency virus and hepatitis B and C infection were negative.

Patient No. 2

A 23-year-old woman was brought to the emergency department 43 hours after consuming approximately 27.5 g acetaminophen (without any coingestants). Her medical history was remarkable for depression and hypothyroidism. Her initial laboratory results were AST 507 U/L (normal range 0–45 U/L), ALT 621 U/L (0–45 U/L), total bilirubin 2.3 mg/dl (0.3–1.2 mg/dl), and acetaminophen level was nondetectable. A loading dose of intravenous *N*-acetylcysteine 150 mg/kg, followed by a 50-mg/kg infusion over 4 hours, followed by a continuous infusion of 6.25 mg/kg/hour was started promptly. The next two consecutive measurements of her AST level showed decline, and *N*-acetylcysteine was stopped at 51 hours after acetaminophen ingestion (after 8 hrs of treatment); AST and ALT levels were 390 U/L and 505 U/L, respectively.

Four hours later, intravenous *N*-acetylcysteine 6.25 mg/kg/hour was restarted after the patient's AST level rose to 1488 U/L; 15 hours later, her ALT level peaked at 1542 U/L. The *N*-acetylcysteine infusion was continued until 92 hours after acetaminophen ingestion when her AST and ALT levels were declining over a 24-hour period. She did not develop encephalopathy or evidence of renal failure, rhabdomyolysis, or metabolic acidosis. Her peak INR was 1.50, and her serum acetaminophen level remained undetectable.

Patient No. 3

A 39-year-old woman was brought to the emergency department after acute ingestion of acetaminophen and tizanidine; doses and time of ingestion were both unknown. Her medical history was remarkable for chronic back pain, depression, gastroesophageal reflux disease, and Crohn's disease. On arrival, she was intubated due to depressed mental status. Significant initial laboratory results were an acetaminophen level of 336 µg/ml (therapeutic range 10–20 µg/ml), AST 1729 U/L (normal range 0–45 U/L), ALT 1204 U/L (0–45 U/L), prothrombin time 14.5 seconds (12–15 sec), INR 1.4 (0.8–1.2), serum creatinine 1.7 mg/dl (0.7–1.3 mg/dl); arterial blood gas measurements were pH 6.92 (7.35–7.45), partial pressure of carbon dioxide 13 mm Hg (35–45 mm Hg), partial pressure of oxygen 312 mm Hg (80–100 mm Hg), and base excess –29.0. A loading dose of intravenous *N*-acetylcysteine 150 mg/kg, followed by a 50-mg/kg infusion over 4 hours, followed by a continuous infusion at 6.25 mg/kg/hour was started 3 hours later. In addition, metronidazole 500 mg every 8 hours and piperacillin-tazobactam 2.25 g every 8 hours were started for empiric treatment of sepsis, and one dose of fomepizole 1000 mg was given for potential toxic alcohol ingestion.

Due to impending hepatic failure, the patient was transferred to a regional tertiary referral center. On arrival, approximately 24 hours after her initial presentation, her laboratory results revealed an AST level of 2667 U/L (normal range 0–45 U/L), ALT 2083 U/L (0–45 U/L), serum creatinine 2.4 mg/dl (0.7–1.3 mg/dl), and INR 5.2 (0.8–1.2). Her acidosis improved after resuscitation (pH 7.32 [(7.35–7.45], base excess –13.1), but the patient required a norepinephrine infusion to maintain adequate blood pressure. Her antibiotic therapy was also continued.

Twelve hours later (36 hrs after presentation

[hospital day 2]), the patient's mental status began to improve, and her AST and ALT levels decreased to 1807 U/L and 1666 U/L, respectively. Her INR was 3.9, but she had received fresh frozen plasma within the previous 8 hours, with no abnormal bleeding documented before its administration. Her serum acetaminophen level was 28.7 µg/ml. Continuous venovenous filtration was initiated due to declining urine output and an increasing serum creatinine level of 2.9 mg/dl.

Twenty-four hours later (hospital day 3), the patient's mental status had resolved and she was extubated; her depressed mental status was attributed to the tizanidine ingestion. However, her AST and ALT levels had increased to 7020 U/L and 5071 U/L, respectively, preceded by a peak INR of 7.1. Eight hours later, her ALT level peaked at 5452 U/L. The patient's clinical status and laboratory studies steadily improved except for her renal failure, but she did not develop rhabdomyolysis.

The patient's antibiotics were discontinued on hospital day 5, and *N*-acetylcysteine was discontinued on day 8. She still required hemodialysis at discharge on day 16. Studies for human immunodeficiency virus and hepatitis B and C infection were negative.

Discussion

The course of aminotransferase levels after acetaminophen overdose typically follows a single-peak elevation and a subsequent decline.[1] This observation led to the concept that declining aminotransferase levels be used as part of the criteria for when to discontinue *N*-acetylcysteine therapy in patients with acetaminophen overdose.[2, 3] We encountered three patients whose AST or ALT levels decreased by at least 20% after an initial peak before rebounding to a second, higher peak (Figure 1). Biphasic peaks in serum acetaminophen levels have been reported in patients after overdose,[4] but we were unable to find reports of multiple aminotransferase level peaks in the published literature. An elevation in aminotransferase levels serves as a consistent marker of acute liver injury; however, whereas peak levels correlate poorly with clinical outcome, an ALT level exceeding 1600 U/L has been associated with other evidence of hepatic dysfunction.[5] In our three patients, one developed encephalopathy whereas another developed concurrent coagulopathy (INR 7.1), demonstrating clinically significant hepatic damage.

We could not identify any distinctve characteristics shared by these patients to account for their biphasic increases in aminotransferase levels. Patient no. 1 reportedly coingested quetiapine, an antipsychotic agent possessing anticholinergic properties. However, her serum acetaminophen level consistently declined over time, making delayed absorption less likely. Gilbert's syndrome could have affected the metabolism of acetaminophen due to decreased glucuronidation. Patients with Gilbert's syndrome produce more oxidative acetaminophen metabolites compared with controls.[6, 7] In theory, this may increase the susceptibility to acetaminophen toxicity, but does not clearly relate to the fluctuations in aminotransferase levels. Gilbert's syndrome does not affect the bioavailability of acetaminophen or its clearance.[7, 8]

Patient no. 2 lacked any apparent factors that could alter acetaminophen absorption or metabolism. It is possible that the initial decline in her AST level would not have been detected with less frequent laboratory monitoring.

Patient no. 3 had Crohn's disease but no evidence of active inflammation. She also received fomepizole, which has been shown to reduce acetaminophen toxicity in animal and in vitro models.[9, 10] The first decline in her AST and ALT levels could have corresponded to a therapeutic effect of fomepizole. However, the overall increasing trend in INR values during this

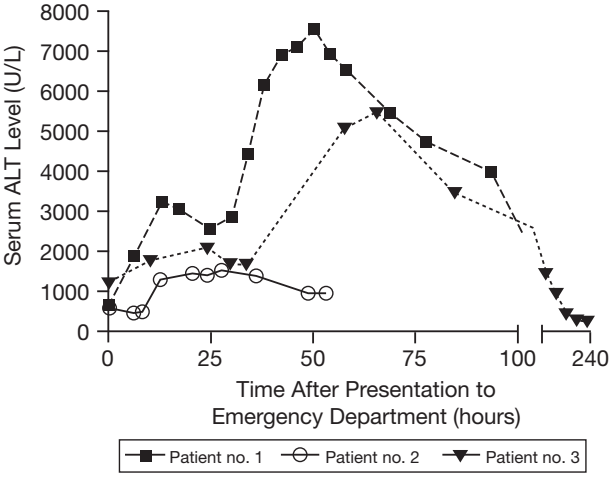

Figure 1. Time courses of serum alanine aminotransferase (ALT) levels for each patient during hospitalization after presenting to the emergency department with acetaminophen overdose (time 0). Patient no. 1 presented at 24 hours after overdose and patient no. 2 at 43 hours after overdose; time of acetaminophen overdose was unknown for patient no. 3.

time argues against a beneficial effect. Tizanidine, metronidazole, and piperacillin-tazobactam are not known to alter acetaminophen metabolism. This patient did experience hypotension severe enough to require norepinephrine infusion, and theoretically, ischemic liver injury could have contributed to either of the ALT peaks, depending on the time of acetaminophen ingestion. The actual effect is unclear, however, as ischemic hepatitis has been recently reported to occur primarily in the setting of simultaneous right-sided heart failure, and not with hypotension alone.[11]

The only common feature of all three patients is that they received *N*-acetylcysteine after developing aminotransferase elevations. Delayed treatment increases the risk of severe hepatotoxicity, as well as the degree of hepatic injury, after acute acetaminophen overdose.[1, 12, 13] Of interest, in patient nos. 1 and 2, the second ALT peak occurred approximately 72 hours after acetaminophen ingestion; this timing is similar to the timing of the single ALT peak found with typical acute overdoses.[1] In patient no. 3, the relationship of the peak ALT levels with time of acetaminophen ingestion could not be determined, as the time of ingestion was unknown. However, the patient's severe clinical condition is consistent with late presentation to the emergency department. Regardless, this feature suggests that delayed *N*-acetylcysteine treatment may be an etiology for the biphasic aminotransferase pattern, although the mechanism is unclear.

All three patients received intravenous *N*-acetylcysteine. A recent comparison of intravenous and oral treatment found that the risk of hepatotoxicity (AST or ALT level > 1000 U/L) was greater with intravenous *N*-acetylcysteine than with oral *N*-acetylcysteine in late-presenting patients.[14] However, that study used peak aminotransferase levels as an end point and did not analyze detailed trends in individual subjects. *N*-Acetylcysteine itself does not affect the initial metabolism of the parent acetaminophen molecule.[15] In a recent report, late administration of *N*-acetylcysteine worsened hepatic recovery after administration of a toxic dose of acetaminophen in mice.[16] If these data are applicable in humans, this could be a mechanism for our findings. This possibility is unlikely, however, as late dosing of *N*-acetylcysteine improves survival in patients with acetaminophen-induced liver failure.[17]

As with most self-poisonings, it is difficult to independently confirm the acetaminophen ingestion details in our three patients, specifically whether these ingestions were truly acute or represented repeated ingestions. Some reports suggest that patients taking repeated doses of acetaminophen in excess of 4 g/day may have worse clinical outcomes than those with acute ingestions[18]; we are unaware of data, however, that suggest that repetitive ingestion is more likely to produce the patterns of aminotransferase levels seen in our cases.

These cases are notable because declining aminotransferase levels may be used as a guide for when to stop *N*-acetylcysteine. Moreover, the optimal duration of therapy in patients with elevated aminotransferase levels, but without hepatic failure, is poorly defined. Published clinical guidelines have addressed when to initiate therapy, but not the duration of treatment.[19] In such cases, continuing *N*-acetylcysteine until "all liver abnormalities resolve," defined as a decreasing AST level to less than 1000 U/L, has been advised.[3] One study reported that a shorter duration of oral *N*-acetylcysteine therapy could be safely used under the following circumstances: minimum of 20 hours of treatment, AST and ALT levels of 60 U/L or lower, serum acetaminophen level of 10 μg/ml or lower, and an INR value of 1.3 or less.[20] However, that study excluded patients with elevated aminotransferase levels at baseline. Other authors have recommended a "normal or improving" ALT level (e.g., a decrease from 1500 to 500 U/L) as one criterion for ending therapy.[2] Other criteria they recommend include an undetectable acetaminophen concentration and improving clinical measures; they specifically argue against using strict, time-based protocols.[2] This approach appears to be well suited to our patient nos. 1 and 3. During the initial declines in their aminotransferase levels, both patients demonstrated worsening renal failure and coagulopathy; patient no. 1 also experienced encephalopathy. Patient no. 2 did not show signs of ongoing acetaminophen toxicity during the initial decreases in serum aminotransferase levels.

We should note that our findings are limited by the fact that these cases were collected from referrals to our consultation service. Hence, we cannot comment on the overall frequency of patients with multiple aminotransferase peak levels after acetaminophen overdose. For most of the three patients' laboratory results, we were unable to compare them with their baseline values, but the resolution of laboratory abnor-

malities in all three patients is more consistent with acute hepatic injury than baseline hepatic disease. As is the case with any patient's clinical history in an overdose, an exhaustive evaluation of all possible etiologies for hepatic injury was not performed as part of typical clinical care. Therefore we cannot completely exclude occult hepatotoxicant exposure or idiosyncratic reactions to known coingestants. Given the predictable hepatotoxicity of acetaminophen, however, it remains the most likely cause of the aminotransferase level elevations in our three patients.

Conclusion

This case series emphasizes that declining aminotransferase levels should not be the sole criterion for when to discontinue *N*-acetylcysteine therapy in patients with acetaminophen-induced hepatic injury. Although declining aminotransferase levels often coincide with clinical improvement, our patients experienced a rebound in aminotransferase levels, which was associated with hepatic failure, specifically, coagulopathy and encephalopathy. As others have recommended, the presence of these markers of liver injury should prompt the continuation of *N*-acetylcysteine treatment despite decreasing aminotransferase levels.

References

1. **Rumack BH, Peterson RC, Koch GG, Amara IA**. Acetaminophen overdose—662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med 1981;141:380–5.
2. **Dart RC, Rumack BH**. Patient-tailored acetylcysteine administration. Ann Emerg Med 2007;50:280–1.
3. **Hendrickson RG, Bizovi KE**. Acetaminophen. In: Flomenbaum NE, Goldfrank LR, Howland MA, Lewin NA, Nelson LS, eds. Goldfrank's toxicologic emergencies, 8th ed. New York: McGraw-Hill, 2006:523–43.
4. **Smith SW, Howland MA, Hoffman RS, Nelson LS**. Acetaminophen overdose with altered acetaminophen pharmacokinetics and hepatotoxicity associated with premature cessation of intravenous *N*-acetylcysteine therapy. Ann Pharmacother 2008;42:1333–9.
5. **Heard K, Green JL, Bogdan GM, et al**. At what AST and ALT does hepatic dysfunction occur following acetaminophen poisoning [abstract]? J Toxicol Clin Toxicol 2006;44:713.
6. **Esteban A, Perez-Mateo M**. Heterogeneity of paracetamol metabolism in Gilbert's syndrome. Eur J Drug Metab Pharmacokinet 1999;24:9–13.
7. **DeMorais SMF, Uetrecht JP, Wells PG**. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. Gastroenterology 1992;102:577–86.
8. **Douglas AP, Savage RL, Rawlins MD**. Paracetamol (acetaminophen) kinetics in patients with Gilbert's syndrome. Eur J Clin Pharmacol 1978;13:209–12.
9. **Hazai E, Vereczkey L, Monostory K**. Reduction of toxic metabolite formation of acetaminophen. Biochem Biophys Res Commun 2002;291:1089–94.
10. **Brennan RJ, Mankes RF, Lefevre R, et al**. 4-Methylpyrazole blocks acetaminophen toxicity in the rat. Ann Emerg Med 1994;23:487–94.
11. **Seeto RK, Fenn B, Rockey DC**. Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 2000;109:109–13.
12. **Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH**. Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose. N Engl J Med 1988;319:1557–62.
13. **Smilkstein MJ, Bronstein AC, Linden C, et al**. Acetaminophen overdose: a 48-hour intravenous *N*-acetylcysteine treatment protocol. Ann Emerg Med 1991;20:1058–63.
14. **Yarema MC, Johnson DW, Berlin RJ, et al**. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med 2009;54:606–14.
15. **Corcoran GB, Todd EL, Racz WJ, et al**. Effect of *N*-acetylcysteine on the disposition and metabolism of acetaminophen in mice. J Pharmacol Exp Ther 1985;232:857–63.
16. **Yang R, Miki K, He X, Killeen ME, Fink MP**. Prolonged treatment with *N*-acetylcysteine delays liver recovery from acetaminophen toxicity. Critical Care 2009;13:R55.
17. **Keays R, Harrison PM, Wendon JA, et al**. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. Br Med J 1991;303:1026–9.
18. **Schiødt FV, Rochling FA, Casey DL, Lee WM**. Acetaminophen toxicity in an urban hospital. N Engl J Med 1997;337:1112–17.
19. **Wolf SJ, Heard K, Sloan EP, Jagoda AS**. Clinical policy: critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. Ann Emerg Med 2007;50:292–313.
20. **Betten DP, Cantrell FL, Thomas SC, Williams SR, Clark RF**. A prospective evaluation of shortened course oral *N*-acetylcysteine for the treatment of acute acetaminophen poisoning. Ann Emerg Med 2007;50:272–9.