Can AST/ALT ratio indicate recovery after acute paracetamol poisoning?

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Context. Paracetamol (acetaminophen or APAP) is the most common pharmaceutical exposure in the US. Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels indicate hepatic toxicity. AST and ALT levels rise in similar proportions but later decline at different rates, with AST falling more rapidly than ALT. Objective. To determine whether the AST/ALT ratio can indicate that a patient has passed the time of peak AST concentration. Methods. We retrospectively identified cases of patients hospitalized for acute APAP poisoning by querying the pharmacy database of all patients treated with acetylcysteine (NAC) from January 1, 2001 to March 19, 2013. We included all patients with severe APAP poisoning, defined as AST or ALT greater than 1000 IU/L. Patients who were given NAC for other indications, those without APAP poisoning, and those receiving liver transplantation were excluded. We then recorded paired AST and ALT concentrations from each patient’s hospital course. We classified each pair as clearly post-peak or not, and calculated the AST/ALT ratio for each pair of values. We compared different thresholds of AST/ALT ratio in increments of 0.1 to find the optimal value that reliably indicated resolving transaminases. Results. We identified 1820 patients who received NAC during the study period. Of these, 333 received NAC for suspected poisoning by APAP. After excluding patients without severe APAP poisoning, other diagnoses explaining transaminase elevations, and patients who underwent liver transplantation, we had 37 evaluable patients with 343 evaluable pairs of AST and ALT concentrations. An AST/ALT ratio less than or equal to 0.4 was 99% sensitive for identifying patients with resolving transaminases. Conclusion. An AST/ALT ratio less than or equal to 0.4 following severe hepatic toxicity from paracetamol poisoning appears to be highly predictive of recovery in patients treated with NAC. This has potential to be an indicator of safe discontinuation of NAC treatment.

Keywords Hepatotoxicity; Transaminases; Prognostic factors

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We recorded serial paired AST and ALT concentrations from each patient’s hospital course. Concentrations were measured at the same time from the same specimen. Each pair was classified as clearly post-peak or not. We classified pairs as not clearly post-peak if they were before the observed peak AST, they were at the observed peak AST, or the relation to the peak AST was indeterminate (for example, if two successive AST values were similar in magnitude). For late presenters with elevated AST and ALT concentrations, we classified the first pair as being not post-peak regardless of the ratio and even if all subsequent AST values were lower.

We calculated AST/ALT ratios for each pair. All patient ratio data were pooled, and different values of ratio thresholds were compared in increments of 0.1 to find the optimal value that reliably indicated resolving transaminases. We computed sensitivity and specificity of incremental thresholds after determining true negative, true positive, false negative, and false positive values for each threshold. We constructed a receiver operating characteristic (ROC) curve to illustrate the trade-off of sensitivity and specificity of AST/ALT ratio in identifying whether or not the paired specimen occurred after the observed highest AST value.

The duration of antidotal therapy with NAC was determined in each case by the treating physicians and consulting toxicologists at the time. The AST/ALT ratio was not explicitly used in treatment decisions.

The Institutional Review Board at Washington University in St. Louis reviewed and approved this study.
Results

During the study period, we identified 1820 patients who were treated with NAC. Of these patients, 333 received NAC for suspected poisoning by APAP. After excluding patients without severe APAP poisoning, other diagnosis explaining transaminase elevations, and those who received liver transplantation, we had 37 evaluable patients. After defining and pooling the AST/ALT ratios of all patients, we had 343 evaluable pairs of simultaneous AST and ALT concentrations.

An AST/ALT ratio $< 0.4$ resulted in $99\%$ sensitivity for identifying a given specimen as occurring after the peak observed AST. A ratio $< 0.5$ had a sensitivity of over $97\%$ in identifying a post-peak pair of transaminases. The area under the ROC curve (Fig. 2) was 0.92, which suggests that this ratio has a fairly good ability to distinguish between post-peak and other pairs of transaminases. The ratio with the greatest diagnostic accuracy was 0.6 (84\% accuracy), but the sensitivity was only $93\%$ with a specificity of $71\%$.

The highest ratio to achieve $100\%$ sensitivity was 0.2. However, this had a high false positive rate with a positive predictive value of 42\%.

Discussion

Initiation of antidotal therapy after an acute overdose is based on plotting a timed APAP concentration above the treatment line on the Rumack–Matthew nomogram. However, once AST and ALT levels are elevated, there is no clear consensus on when it is safe to stop NAC administration in patients without fulminant hepatic failure. Toxicologists generally recommend stopping NAC administration when transaminase concentrations are improving with normal mental status and near-normal International Normalized Ratio (INR), but there is no consensus on what comprises sufficient improvement in transaminases to support discontinuing NAC.

Another problem which is often confronted by toxicologists is the patient who presents 2–3 days after APAP overdose with elevated AST and ALT concentrations at the time of presentation. Generally, these patients receive antidotal therapy with NAC regardless of mental status or INR until further laboratory data become available. We speculate that some of these patients have passed their peak AST and ALT concentrations and are already improving prior to receiving the antidote. Currently, there is no consensus on which, if any, of these patients may be medically cleared and do not require antidotal therapy. However, our study did not include late-presenting patients who did not receive NAC.

Our findings indicate that the AST/ALT ratio may be a reliable indicator that a patient has passed the peak AST concentration. An AST/ALT ratio $< 0.4$ achieves $99\%$ sensitivity in identifying a given pair as occurring after the peak AST in patients who do not meet the KCH criteria.

We excluded patients who met KCH criteria (acidosis, elevated creatinine, hyperbilirubinemia, coagulopathy, and encephalopathy), because the presence of these indicators of poor prognosis compel further treatment with IV NAC regardless of the transaminase concentrations. We also excluded patients with preexisting liver disease or other causes of transaminase elevations. Our results only apply to previously healthy patients who have transaminase elevations without meeting KCH criteria.

Since the consequences of missed diagnosis and undertreatment with the antidote may be severe (possibly including preventable death or liver transplant), and the risks and cost of antidotal treatment are low, a more sensitive ratio is clearly preferable.

Our study is limited because all patients, including late presenters, received NAC regardless of AST/ALT ratio. It is possible that the results may vary if a patient is not treated with NAC or if NAC is discontinued earlier based on AST/ALT ratio. Some patients in the study were transferred from outlying hospitals. Laboratory values obtained at referring hospitals were included if that hospital was in the same hospital system sharing the same electronic medical record system. We excluded AST and ALT values obtained at other hospitals outside that system. There were some patients in the study who were late presenters—some of them received NAC at an outside hospital prior to transfer.

Additionally, our hospital uses a “one-bag” IV NAC protocol with a different dosing schedule than that described in the package insert for Acetadote\textsuperscript{10}. We have medical toxicologists and hepatologists on site to consult on APAP-poisoned patients. The results might vary if applied in a smaller hospital with less specialty support.

Conclusion

In paracetamol-poisoned patients with hepatotoxicity treated using NAC, an AST/ALT ratio less than or equal to 0.4 had $99\%$ sensitivity for identifying patients with resolving transaminases. In a patient with no other indicators of hepatic failure (such as elevated INR and encephalopathy), the AST/ALT ratio may indicate that NAC may be safely discontinued. This finding warrants validation using a larger data set of APAP-poisoned patients. Future research might also explore whether this applies to late-presenting patients with untreated hepatotoxicity.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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