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Predicting risk in patients with acetaminophen overdose

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Abstract

Acetaminophen (APAP) overdose is a very common cause of drug overdose and acute liver failure in the US and Europe. Mechanism-based biomarkers of APAP toxicity have the potential to improve the clinical management of patients with large dose ingestions of APAP. The current approach to the management of APAP toxicity is limited by imprecise and time-constrained risk assessments and late-stage markers of liver injury. A recent study of “low-risk” APAP overdose patients who all received treatment with N-acetylcysteine, found that cell-death biomarkers were more sensitive than alanine aminotransferase (ALT) and APAP concentrations in predicting the development of acute liver injury. The data suggest a potential role for new biomarkers to identify “low risk” patients following APAP overdose. However, a practical and ethical consideration that complicates predictive biomarker research in this area is the clinical need to deliver antidote treatment within 10 hours of APAP overdose. The treatment effect and time-dependent nature of N-acetylcysteine treatment must be considered in future “predictive” toxicology studies of APAP-induced liver injury.

Keywords

acetaminophen; miRNA122; HMGB1; K18; necrosis; biomarker; Rumack nomogram; acute liver injury

Methods and Results

This study addresses the question of predictive toxicology using recently described, liver-based biomarkers of acetaminophen (APAP) toxicity.[1] Performed in the United Kingdom (UK), the study examined the ability of selected biomarkers to predict the development of acute liver injury to APAP. The biomarkers under study were selected based upon recently published data concerning the potential mechanistic significance of these biomarkers as indicators of hepatocyte, mitochondrial, or cell death mechanisms. They regulate a number of diverse pathways involved with gene regulation, cellular immune response, cell stress, apoptosis and necrosis, cytokine signaling and humoral response. Biomarkers included were microRNA-122 (miR-122), high-mobility group box-1 protein (HMGB1), full-length and caspase cleaved Keratin 18 (K18, indicators of necrosis and apoptosis, respectively) and glutamate dehydrogenase (GLDH).

Antoine *et al* examined APAP-induced acute liver injury among 129 patients presenting to emergency departments in the early stages of APAP toxicity.[1] Seventy five percent (97 of 129) of the patient samples were obtained from subjects participating in a study designed to evaluate the efficacy of the anti-emetic ondansetron in the management of nausea and vomiting associated with APAP toxicity. All patients received a full course of treatment with IV N-acetylcysteine (NAC) per a standard protocol.[2] Biomarkers were tested for their ability to identify patients that would develop acute liver injury (defined as an ALT > 150 IU/L, a more than threefold elevation of the upper limit of normal). Blood samples for analysis of biomarkers were obtained at a median (interquartile range) time of 8 (6-15 hours) from the time of the ingestion, and prior to the start of NAC treatment. Biomarker performance was compared to currently available clinical assays including plasma serum alanine aminotransferase (ALT) and APAP concentration using receiver operator curve analysis (ROC) and Pearson's correlation test.

Consistent with the known demographic profile of acute APAP overdose, a high percentage of the study cohort (60%) was female and the population had a median age of 34 years. All biomarkers were found to significantly correlate with the peak measured ALT value. Of the four biomarkers, HMGB1 had the highest correlation coefficient (0.67) and the highest Pearson R value (0.82). In addition, HMGB1 had the best performance of the four biomarkers compared to the peak international normalized ratio (INR) prothrombin time.

In further analysis of 98 of the 129 patients who had a normal ALT at the time of hospital presentation, all biomarkers were higher in the patients that subsequently developed acute liver injury, as compared to those that did not. The biomarker with the highest area under the curve (AUC) values on the ROC analysis was HMGB1. For patients whose initial blood sample was obtained within 8 h of the APAP overdose, the ROC-AUC (95% C.I.) was good, 0.83 (0.69-1.0). The ROC-AUC increased to excellent, 0.99 (0.96-1.0) for patients whose blood sample was obtained beyond 8 hours of the APAP overdose. Interestingly, positive and negative predictive values for all biomarkers were greater in patients that were evaluated 8 h *after* the APAP ingestion, compared to those evaluated within the initial 8 h of the ingestion. For example, the positive predictive value for HMGB1 increased from 90.7 to 100% (low false positives) , while the negative predictive values increased from 86.5 to 90.4% (relatively low false negatives).

Discussion

The data by Antoine *et al.* are important because they suggest that novel, mechanism-based liver biomarkers may be more informative than the current diagnostic approach in the early stages of APAP toxicity. As stated by the authors, identifying patients that do *not* require treatment with the antidote NAC could ultimately lead to a personalized medicine approach for the management of APAP poisoning, which has the potential to be resource sparing. The diagnostic approach to the clinical problem of APAP poisoning has not changed significantly in the last four decades.[3] The current clinical approach is based upon measurement of the APAP concentration in a patient blood sample during the initial 24 hours following excess dosing of APAP (i.e., Rumack nomogram[4]) and serves as a risk assessment tool for physicians to make treatment decisions regarding the need for NAC.[5]

Limitations of the nomogram include its restriction to patients that present to medical facilities early (i.e., initial 24 hours of the overdose) following acute ingestions and its dependence upon accurate histories concerning the dose and timing of the drug exposure.[6] In the later stages of toxicity, APAP concentrations may be low to undetectable and thus fail to provide the physician with useful information concerning the recent drug exposure. Serum ALT levels may be normal in the early stages of toxicity and slowly rise over a 48 to 96 hour period to peak levels that may be as high as 20,000 IU/L.[7] Thus, the current approach among most practicing physicians for patients that present later in the toxicity is to treat patients who have a history of APAP ingestion, regardless of the APAP levels, particularly if the patient has elevated hepatic transaminases. The diagnostic criteria for initiating treatment with NAC in other patients that chronically consume excess doses of APAP are less defined. These patients include those with multiple time point ingestions; chronic, “excessive dose” exposures; and/or patients with underlying medical conditions or concurrent medications that would alter the metabolism of APAP. Serum ALT levels, though entrenched in the clinical approach to the recognition of liver injury, are not tissue or drug specific and are not predictive of the severity of the injury, or the potential need for liver transplantation.

Despite the intriguing nature of the results, a number of issues must be addressed in future studies in this area. Additional studies are needed to more clearly define particular clinical scenarios for which new biomarkers of APAP toxicity could serve as adjunctive tests or replace existing approaches. Further, the predictive values of these identified biomarkers needs to be further examined using a separate sample (for validation) and the possibility of raising the sensitivity by taking a combination of markers needs to be further investigated. Additional considerations in the design of future research in this area must address a number of clinical questions that reflect clinical nuances and the many challenges of biomarker research in the field of drug induced liver injury.

Five Year Review

One premise of the study by Antoine *et al.* is that the identification of highly sensitive biomarkers of liver injury will allow for the development of personalized medicine approaches for the management of APAP overdose. From the cohort of patients that had normal ALT's with the first collected blood sample, the authors observed that patients that ultimately developed ALT elevations (n=11) had higher levels of the new biomarkers at presentation. Conversely, patients that had did *not* develop ALT elevations had lower levels of the new biomarkers. However, all patients, including those with “low” and “high” biomarker values, received prompt treatment with NAC (median time of treatment, 10 hours) soon after the study blood sample was obtained, and thus the ability of the novel biomarkers to “predict toxicity” at a later point in time is obscured by therapeutic impact of prompt treatment with NAC. Unfortunately, the data were not analyzed in greater detail relative to the time of NAC treatment, which may have provided additional useful information on the performance of the biomarkers in patients that were treated later in the course of the toxicity, a large segment of the patient population, particularly in the United States.[7] Whether or not toxicity would develop without NAC treatment cannot be ethically evaluated in future clinical studies. However, it is possible that meaningful data can be

generated by examining biomarker profiles in other groups of APAP overdose patients, particularly those at high risk, such as patients that present late (24 h and beyond) following the APAP ingestion and/or those receiving concomitant therapy with drugs that could alter the metabolism of APAP. In addition, the predictive nature of these biomarkers in patients with preexisting disease, such as non-alcoholic fatty liver disease (NAFLD) is relevant, as K18 has been shown to be increased in multiple liver disease processes, including NAFLD.[8]

Despite limitations in the present approach to the evaluation and management of APAP toxicity, this approach is built upon solid data for which any new and future biomarker must be compared. Smilkstein's landmark study performed in 2540 patients who received treatment with oral NAC following APAP overdose found that the risk of developing hepatotoxicity (defined as an ALT > 1000 IU/L) rose from 6.1 to 26.4% in patients treated within 10 hours compared to those treated 10 hours beyond the time of the APAP overdose.[5] Nine of the 11 deaths among the 2540 patients occurred in patients that had an ALT elevation at the time of presentation to the medical facility. No deaths occurred in those that were treated within 16 h of the overdose. Thus, prompt treatment with NAC – ideally within 10 h of the stated time of the APAP overdose – became and remains the standard treatment approach for the management of APAP toxicity in patients with elevated APAP levels obtained 4 h (reflecting post-absorption) to 24 h following the overdose.[5] Of note, the negative predictive value of APAP levels (92.8%) in Antoine's study for patients presenting beyond 8 h of the APAP overdose slightly exceeded that of HMGB1 (90.4%). The ideal biomarker for the treating physician would be a negative predictive value of 100%. Thus, from the “risk-benefit” mindset of emergency department physicians, “over-treating” patients with NAC will continue to outweigh the potential economic benefits of identifying a subset of patients that may not need hospitalization for treatment with the antidote. It is unlikely that the current initial approach will change, until extensive, new data can be generated to accurately distinguish the “low” from the “high risk” toxicity patient.

While biomarkers with enhanced sensitivity and specificity are clearly needed in the assessment of drug induced liver injury, a review of existing knowledge gaps in the clinical arena is important. Biomarkers that determine the resolution of injury and/or the initiation of hepatocyte repair may help guide future physicians on decisions concerning the need for continuing and/or discontinuing NAC treatment, as well as the need for a liver transplant. Data demonstrating the elimination profile of new biomarkers may have relevance to these questions. For example, in an earlier report, the same authors reported that miR-122 normalized more rapidly than ALT in a subset of 11 patients in which serial assays were performed.[9] Moreover, miR-122 had the highest negative predictive value of the new biomarkers in patients whose blood sample was collected beyond 8 hours of the overdose (95.2%). In contrast, ALT may remain elevated for 10-12 days following large APAP overdoses.[10]

It is highly likely that particular biomarkers for APAP toxicity will be more useful in certain clinical scenarios than in others. Examining the effect of co-morbidity including the impact of obesity and fatty liver is essential in future research. Identifying the effect of chronic APAP exposure on biomarker panel profiles is also of interest due to the widespread

prevalence of APAP in over-the-counter products and the lack of recognition of toxicity of APAP by many consumers, particularly those in the US. Finally, future studies of APAP biomarkers should examine the full dynamic profile of biomarkers as potential early indicators of toxicity, as well as signals of recovery and/or response to antidotal therapy.

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Reference

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**of considerable interest

1. Antoine DJ, Dear JW, Starkey-Lewis P, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. Hepatology. 2013

2. Acetadote, Package insert. Cumberland Pharmaceuticals; Nashville, TN:

*3. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002; 40:3–20. [PubMed: 11990202] [Historical and scientific overview of the development of the Rumack nomogam.]

4. Rumack BH. Acetaminophen overdose in children and adolescents. Pediatr Clin North Am. 1986; 33:691–701. [PubMed: 3714342]

5. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med. 1988; 319:1557–62. [PubMed: 3059186] [Landmark study of NAC use in APAP toxicity.]

**6. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med. 2008; 359:285–92. [PubMed: 18635433] [Highlights clinical approaches and challenges in the management of APAP toxicity.]

7. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am. 2008; 92:761–94. viii. [PubMed: 18570942]

8. Wieckowska A, Zein NN, Yerian LM, et al. In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease. Hepatology. 2006; 44:27–33. [PubMed: 16799979]

**9. Starkey Lewis PJ, Dear J, Platt V, et al. Circulating microRNAs as potential markers of human drug-induced liver injury. Hepatology. 2011; 54:1767–76. [PubMed: 22045675] [First report of microRNA in APAP mediated liver injury in humans.]

10. James LP, Simon MT, Capparelli EV, Hinson JA, Dalvern TJ, Lee WM. Pharmacokinetic analysis of acetaminophen protein adducts in adults with acute liver failure. Clinical Pharmacology & Therapeutics. 2007; 81:2.

Key Points

1. The existing approach for determining risk of developing hepatotoxicity following large dose ingestion of APAP relies upon measurement of APAP levels in plasma within the initial 24 hours of the overdose.
2. The cell death biomarker panel was compared to plasma APAP concentrations and ALT values in patients that presented to emergency departments that met criteria for treatment with the antidote NAC. All patients received treatment with NAC after the initial blood sample was obtained.
3. In patients with low ALT values in the initial blood sample, all four biomarkers were higher in the initial blood sample (obtained at a median time of 8 hours after the overdose) in the patients that eventually developed acute liver injury, defined as an ALT elevation of more than 3 fold the upper limit of normal (or 150 IU/L).
4. Of the four biomarkers, HMGB1 had the best performance with an ROC AUC of 0.83 for those patients whose blood sample was obtained within 8 h of the overdose, which improved in patients that presented 8 h beyond APAP overdose to 0.99.
5. In patients presenting 8 h beyond the APAP overdose, the negative predictive value (which increases as the false negative rate drops) of APAP levels at presentation (92.8%) was slightly greater than that of HMGB1 (90.4%). Of the three indicators, miR-122 had the highest negative predictive value (95.2%), compared to APAP levels and
6. The clinical and ethical need for prompt treatment with NAC in patients deemed to be at risk for the development of acute liver injury following APAP overdose is a confounding factor in APAP toxicity biomarker research.
7. Larger studies of cell death biomarkers are needed to better define select clinical scenarios for their potential clinical application in the assessment and management of APAP toxicity.