Multiplying the serum aminotransferase by the acetaminophen concentration to predict toxicity following overdose

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Context. The first available predictors of hepatic injury following acetaminophen (APAP) overdose are the serum APAP and aminotransferases [AT, i.e., aspartate (AST) aminotransferase or alanine (ALT) aminotransferase]. Objective. We describe the initial value, rate of change, and interrelationship between these biomarkers in patients who develop hepatotoxicity despite treatment following acute overdose. A new parameter, the APAP × AT multiplication product, is proposed for early risk stratification. Methods. We conducted a descriptive study of individuals selected from a multicenter retrospective cohort of patients hospitalized for APAP poisoning. We selected those acute APAP overdose patients who subsequently developed AT > 1,000 IU/L. Rising serum AT values were compared to simultaneously measured (or estimated) falling serum APAP. The APAP × AT was expressed relative to initiation of acetylcysteine therapy and grouped by time to meeting hepatotoxicity criteria. Results. In the 94 cases studied, serum APAP concentrations were still appreciable at the time of the first measured AT [211 (77–511) IU/L at 15.3 (12.1–19.2) h post-ingestion], yielding an initial APAP × AT of 99,000 (52,000–240,000) μmol × IU/L2. Because serum AT rose rapidly (doubling time 9.5 h) and APAP fell slowly (half-life 4.8 h), the multiplication product remained elevated during the first 12–24 h of antidotal therapy, especially among patients who developed earlier hepatotoxicity (AT > 1,000 IU/L). Discussion and conclusions. The APAP × AT multiplication product, calculated at the time of presentation and after several h of antidotal therapy, holds promise as a new risk predictor following APAP overdose. It requires neither graphical interpretation nor accurate time of ingestion, two limitations to current risk stratification.

Keywords Acetaminophen; N-Acetylcysteine; Transaminase; Aspartate aminotransferase; Alanine aminotransferase

Introduction

Despite the frequency of acetaminophen (APAP) overdose and the emerging emphasis on patient-tailored therapy, risk stratification remains relatively crude resulting in both over- and undertreatment.1–7 Risk prediction is especially uncertain in patients with delayed presentation, chronic ingestions, or unknown time of ingestion, because the Rumack–Matthew nomogram cannot be used to interpret serum APAP concentrations in these cases.8–11 Yet these very patients are at greatest risk of serious outcomes, including fulminant liver failure and death.12–14

The serum APAP concentration and serum aminotransferase concentrations [i.e., aspartate (AST) and alanine (ALT) aminotransferases or transaminases] are routinely measured, and are the first parameters to change following overdose.15,16 Yet the significance and interpretation of such changes have not been well characterized, even after acute overdose.15

Using a cohort of patients who developed hepatotoxicity following acute overdose, we sought to develop a risk prediction tool that would be independent of a single, known time of ingestion. The need for such a tool was evident in our planned analysis of the larger cohort of all APAP overdose cases, including chronic and time unknown ingestions. We hoped that such a tool might ultimately be used to inform management decisions, such as when to discontinue or when to intensify treatment following APAP overdose.
Materials and methods

Study design

This study was a secondary analysis of the Canadian Acetaminophen Overdose Study (CAOS), a large multicenter retrospective cohort study of patients hospitalized for APAP poisoning.\textsuperscript{17,18} Research ethics board approval for the parent study was granted at each participating institution.

Study setting and population

The CAOS identified all patients hospitalized for APAP overdose in eight large Canadian cities between 1980 and 2005 based on electronic search of discharge diagnoses.\textsuperscript{17,18} For this study we selected from the derivation subset only single, acute APAP overdose patients who developed hepatotoxicity,\textsuperscript{17,19} defined as having a peak serum AST or ALT greater than 1,000 IU/L.\textsuperscript{10,20,21} We excluded subjects with uncertain ingestion time or multiple ingestions over >6 h, no serum APAP concentration measured >24 h post-ingestion, no serum AST or ALT concentration measured >24 h post-ingestion, pre-existing hepatic injury, or delayed presentation (as defined previously).\textsuperscript{17,22}

Measures and definitions

Only APAP concentrations obtained at least 4 h post-ingestion were included. The time of ingestion was ascertained by careful review of all pre-hospital, emergency department, and in-patient records. When both AST and ALT were measured, the greater value was used and is denoted aminotransferase (AT) throughout this article. Subjects were grouped by the predicted time post-ingestion to attain an AT of 1,000 IU/L based on the two consecutive concentrations spanning 1,000 IU/L, as described previously.\textsuperscript{22} This a priori grouping was chosen as a surrogate of overdose severity.

Data analysis

Acetaminophen elimination kinetics

APAP elimination rate was determined using least squares regression, assuming first-order elimination kinetics for each patient with at least two post-peak serum APAP concentrations. The first APAP concentration below the local laboratory limit of assay sensitivity [range 7–66 μmol/L (1–10 μg/mL)] was recoded to half this limit unless this value was obtained more than 16 h after the prior level, in which case it was recoded as missing. Individual rate constants and their 95% confidence intervals are reported as the equivalent half-lives for clarity.

Serum acetaminophen and aminotransferase interrelationship

To explore the interrelationship between serum APAP and AT concentrations, we plotted serum APAP against simultaneously measured serum AT on a logarithmic scale using the first two [log(AT), log(APAP)] data pairs for each subject. In cases with no APAP concentration measured at the time of the AT, the missing value was imputed by interpolation using the available APAP concentrations or extrapolated from the previous detectable APAP concentration using the individual APAP elimination rate (or mean subgroup rate when necessary). Such assumptions were prespecified and based on current understanding of the kinetics of APAP following overdose. When the second APAP concentration was below the limit of detection, it was recoded to 10 μmol/L for modeling purposes. To avoid making assumptions about the shape of the AT versus time curve, no missing AT values were imputed.

Finally, we defined a new parameter APAP × AT as the multiplication product of the two simultaneous serum concentrations. We selected this transformation to capture and compare the opposing kinetic phenomena being studied: an exponentially rising serum AT and falling serum APAP. We calculated the value of this product at the time of each measured AT concentration, up to and including the first AT value greater than 1,000 IU/L. Serum APAP concentrations were used when available, or imputed as described above. This product was then plotted relative to the time of initiation of N-acetylcysteine (N-AC), as this time can be known with certainty, in contrast to the reported time of ingestion.

Summary statistics are reported throughout, as there was no a priori null hypothesis to be tested.

Results

Of 3,202 patients in the derivation subset of the CAOS dataset, 2,488 were the result of a single, acute APAP ingestion. We excluded 196 subjects because no serum APAP was measured within 24 h of ingestion, and excluded 1,012 because no serum AT was measured >24 h following ingestion. Of the remaining 1,280 acute APAP overdoses with sufficient laboratory data for consideration, 10 were excluded because of pre-existing hepatic injury or delayed presentation. The characteristics of these patients have been reported previously.\textsuperscript{17,22} For this analysis, we retained only the 94 (7.4%) who developed hepatotoxicity (serum AST or ALT ≥ 1,000 IU/L) during hospitalization, all of whom were treated with N-AC, initiated a median of 15.5 h [interquartile range (IQR) 12.3, 18.4] post-ingestion. The 20-h Prescott intravenous protocol\textsuperscript{23} was initiated in all but three cases, and extended beyond 24 h in one-third of the cases.

Acetaminophen kinetics

The serum APAP elimination rate could be estimated in 70 (74%) subjects. Twenty-four subjects were excluded because...
only a single serum APAP concentration was obtained (n = 17), because the second serum APAP concentration was undetectable and taken >16 h after the first (n = 5), or because the calculated half-life seemed implausible (1.0 h and 17 h, respectively) and were assumed to represent either a data entry error or ongoing absorption (n = 2). All initial APAP concentrations exceeded 1,000 μmol/L (150 mg/L) at 4-h treatment line of the Rumack–Matthew nomogram, and its slope corresponds to a 4-h elimination half-life.

**Acetaminophen versus aminotransferase**

Figure 2 displays the first measured serum AT concentrations plotted against the simultaneously measured (n = 132) or estimated (n = 32) serum APAP concentration. In general, these acute overdose patients presented with abnormal serum AT, and the abnormalities were present while serum APAP concentrations were still appreciable (median serum APAP at time of initial AT 570 μmol/L; IQR 314–983 μmol/L). All data pairs but one lay above a straight line joining (10 IU/L, 1,000 μmol/L) and (1,000 IU/L, 10 μmol/L). Because such diagonals join inversely proportional APAP and AT values, this observation is equivalent to stating that the initial APAP \times AT multiplication product exceeded 10,000 μmol \times IU/L^2 in all but one case (or 1,500 μg/mL \times IU/L in non-SI units). In fact, the initial APAP \times AT product was usually an order of magnitude higher [median 99,000 μmol \times IU/L^2 (IQR 52,000–240,000)].

When grouped according to the time to serum AT over 1,000 IU/L, the APAP \times AT product was substantially higher...
(i.e., farther above the diagonal) in patients with earlier onset hepatotoxicity. Furthermore, the line joining serially measured data pairs in such individuals was less steep (i.e., more parallel to the diagonal) in these patients, indicating the APAP × AT product fell less quickly. When plotted relative to the time of initiation of antidotal therapy with N-acetylcysteine (N-AC), rather than reported time of ingestion, and summarized based on 12-h blocks. The multiplication product falls more slowly during the first 12 h of antidotal treatment in higher risk patients.

Excluded patients
Of the 10 patients excluded for pre-existing hepatic injury or late presentation, all had declining AT values from presentation and all survived to discharge. AT values exceeded 1,000 IU/L in only four of these patients, with an initial measured AT ranging from >5,000 to 15,219 IU/L. These four patients all had undetectable serum APAP at presentation and were thus deemed to have concealed a late presentation (initial APAP likely obtained more than 24 h post-ingestion). Four of the remaining six patients had detectable APAP (range 84–206 μmol/L) at the same time as the elevated initial AT (range 170–563 IU/L).

Among the 196 patients excluded for lack of a measured APAP within 24 h of ingestion, there were four deaths, all deemed because of hepatotoxicity. In the three fatalities with sufficient available data, the measured APAP ranged from 70 to 1,018 μmol/L at the time of the initial AT that ranged from >2,600 to >8,000 IU/L. There was one death, not because of hepatotoxicity, among the 1,012 patients excluded for no measured AT more than 24 h post-ingestion. The 32
remaining deaths occurred in patients not meeting the definition of single, acute APAP overdose.

Discussion

Individualizing therapy is predicated upon accurate risk prediction. We propose and describe a new risk predictor during the first day of treatment in patients who subsequently meet traditional criteria for hepatotoxicity following acute APAP overdose.

The APAP elimination half-life itself has long been suggested as an early risk predictor. Because APAP is metabolized primarily by the liver, its rate of elimination reflects hepatic function. There has been surprisingly little published information on this rate in treated patients since Prescott’s initial observations, which antedate the use of N-AC.

Our data represent the largest study of APAP elimination kinetics in patients with hepatotoxicity. All of our patients were treated with N-AC. The APAP elimination half-life is normally 2–2.5 h, but was greater than 4 h in 16 of 17 untreated patients who developed hepatotoxicity. An elimination half-life greater than 4 h was observed in 56 of 64 patients with an ALT > 1,000 IU/L despite treatment with N-AC. Our findings corroborate the imperfect sensitivity of this single kinetic parameter for the identification of patients who will develop hepatotoxicity. Despite the APAP elimination half-life being, on average, longer in patients with earlier rises in AT, the sensitivity was only moderately better in this subgroup. Other concerns with using this parameter have also been raised. To estimate the elimination half-life accurately, it is important to ensure that ongoing absorption of APAP is negligible, that levels are obtained at least 4 h after last oral intake of APAP, and that the sampling interval is sufficiently long to provide a stable kinetic estimate.

In an accompanying report, we characterize the time course of AT appearance in the serum in this same subset of acute overdose patients. We observed that earlier and faster rises in AT were typical of patients with more severe hepatotoxicity.

We propose the use of a new composite predictor of toxicity, defined as the multiplication product of the simultaneously measured serum APAP and AT concentrations. When serum APAP elimination and AT release both follow first-order kinetics, so will their multiplication product, with a rate constant equal to the algebraic sum of the APAP elimination rate (a negative number) and the AT release rate (a positive number). This can be easily shown graphically when plotted on a semilogarithmic scale, because both of these first-order processes will be straight lines. Moreover, the APAP × AT product at each time point is the vertical sum of the two multiplicands (a property of logarithms), and thus also a straight line. Moreover, after collapsing along the time dimension, serial serum AT and APAP concentration pairs will lie along another straight line when plotted on a log APAP versus log AT scale. The slope of this diagonal is the ratio of the respective first-order rate constants, or the ratio of AT doubling time to APAP elimination half-life. A low-risk patient with rapid APAP elimination and slow rise in AT will follow a more vertical line, and the APAP × AT value will decline rapidly. When the APAP elimination half-life approaches the AT doubling time (a poor prognostic sign), this line more closely follows the main diagonal, and the APAP × AT product remains constant over time.

This APAP × AT multiplication product has several properties that render it useful for risk prediction. It is based on readily available tests and can be easily calculated at the bedside. It requires neither graphing nor logarithmic calculations. It is elevated by virtue of either a high serum APAP or AT, or both. It decreases less rapidly in patients developing early hepatotoxicity, and thus remains relatively stable over time in these patients. Importantly, it can be calculated even when the overdose is taken over many h or days, or when the time of ingestion is uncertain, instances in which the Rumack–Matthew nomogram cannot be applied. If acute overdose patients who develop hepatotoxicity have an elevated APAP × AT product, one would expect patients with repeated supratherapeutic ingestions of APAP who develop hepatotoxicity to have an even higher product, given the potential effect of additional doses on the serum APAP concentration. Finally, the APAP × AT multiplication product can be ascertained with accuracy in research studies involving medical record review. Despite these properties, the discriminatory power of this new prediction parameter following chronic APAP overdose is
unknown. We intend to describe this parameter further in the larger set of all patients enrolled in CAOS, especially those who experience significant toxicity and death.

We further propose that this multiplication product be expressed relative to the time of initiation of N-AC. This event is biologically relevant as it estimates the extinction of the toxic metabolite N-acetyl-p-benzo-quinone imine (NAPQI), is under direct medical control, and can be reliably ascertained from the medical record. We also believe that the relative change in the multiplication product after a short period of treatment may convey more information than any single absolute value or threshold. The product may be elevated at presentation by virtue of a high serum APAP concentration alone. However, a low-risk patient who eliminates APAP with a half-life of less than 3.6 h and has no change in AST will have a multiplication product that falls at least 10-fold (>3.3 half-lives) during the first 12 h of N-AC therapy, a reassuring sign.

Our study has three limitations that merit emphasis. First, the convention of recoding undetectable APAP concentrations as 10 μmol/L was arbitrary, yet also conservative, practical, and preferable to using the value 0 or “missing.” Such recoding was only necessary for a few measurements obtained during the first 20 h of N-AC therapy, suggesting that complete elimination of APAP within this interval is itself a good prognostic sign. Conversely, many of the late rises in the multiplication product were based on such recoding (data not shown). Nevertheless, no patient who developed hepatotoxicity had a normal AT and undetectable APAP. Second, the shape of the APAP × AT product versus time curve has been presented assuming that first-order kinetics prevails for both markers, an assumption consistent with previous research. However, this constraint is not necessary for the product to be informative. Third, we did not distinguish between AST and ALT, and their release kinetics may well differ following acute APAP overdose.

Conclusions

A slowly declining serum APAP concentration combined with a rapidly rising AT is associated with earlier onset hepatotoxicity and more severe coagulopathy. To help interpret these laboratory values, we propose multiplying the serum APAP concentration with a rapidly rising AT is associated with earlier onset hepatotoxicity and more severe coagulopathy. To help interpret these laboratory values, we propose multiplying the serum APAP concentration with a rapidly rising AT is associated with earlier onset hepatotoxicity and more severe coagulopathy. To help interpret these laboratory values, we propose multiplying the serum APAP concentration by the AT, both at presentation and again after several h of N-AC to help estimate risk following APAP overdose. Because this parameter does not require knowledge of time of ingestion or graphical interpretation, it may prove useful for early risk stratification in all patients treated with antidote, including the many patients to whom the Rumack–Matthew nomogram cannot be applied.

Declaration of interest

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