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ARTICLE

When do the aminotransferases rise after acute acetaminophen overdose?

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Context. Rising aminotransferases (ATs) [either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are one of the first signs of hepatotoxicity following acetaminophen (APAP)] overdose (OD). However, the timing and speed of such rises are not well characterized, hampering early risk prediction. *Objective.* To describe the kinetics of AT release in acute APAP OD patients who develop hepatotoxicity despite treatment. *Methods*. A descriptive study of acute APAP OD patients with peak AT >1,000 IU/L taken from the derivation subset of the Canadian Acetaminophen Overdose Study (CAOS), a large, multicenter retrospective cohort of patients hospitalized for APAP poisoning. *Results.* Of 2,488 hospital admissions for acute APAP OD, 94 met inclusion criteria. Treatment with acetylcysteine, mostly intravenously, was begun in all cases within 24 h of ingestion. The initial AT concentration was already elevated in most patients at presentation [median 211 (IQR 77–511) IU/L obtained at 15.3 (12.1–19.2) h postingestion], and exceeded 100 IU/L in almost all patients within 24 h of ingestion. Serum AT concentrations rose rapidly [doubling time 9.5 h (95% CI: 8.7–10.4 h)], especially in patients who developed AT >1,000 IU/L within 48 h of ingestion. Coagulopathy was worse in these patients and in those with an AT >250 IU/L during the first 12 h of treatment with acetylcysteine. *Discussion and conclusions.* An abnormal and rapidly doubling AT at presentation is more typical in severely poisoned patients, as judged by the effects on clotting. These data suggest that risk prediction instruments may be improved by incorporating both the serum AT concentration at initiation of antidotal therapy and its rate of change. Further studies using such an approach are warranted.

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

Introduction

Acetaminophen (APAP) is the most common medication taken in overdose (OD) and is a leading cause of hospital admissions, fulminant liver failure, and deaths following OD in most Western countries.[1–4] Although early treatment with acetylcysteine prevents hepatotoxicity, its effectiveness declines rapidly when initiated more than 8 h after acute OD.[5,6] Moreover, important questions surround the optimal duration, route, and dosing intensity of the antidote.[7] This has led to suggestions of individualized patient-based treatment predicated on early risk assessment.[8] This approach increases the importance of early risk prediction to decide when to stop and when to continue antidote therapy. Unfortunately, the clinical and biochemical signs of hepatotoxicity are classically thought to be nonspecific until at least 24 h postingestion.[9–13] Among the available biochemical markers of hepatotoxicity, serum aminotransferase (AT) concentrations (i.e., aspartate aminotransferases (ASTs) and alanine aminotransferases (ALTs) or transaminases) are among the first parameters to change following OD.[9,14] Yet when and how quickly ATs rise after OD has not been well characterized.[9]

We sought to describe the time course of AT changes in patients who developed hepatotoxicity following acute OD. We chose to study acute OD patients in part because the time of ingestion represents a natural time zero. By better characterizing AT release in this relatively homogenous population, we hoped to make progress toward the ultimate goal of more accurate risk assessment for all cases of APAP OD, including chronic and time unknown.

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Methods

Study design

This study was a secondary analysis of the Canadian Acetaminophen Overdose Study (CAOS), a large multicenter

retrospective medical record review of patients hospitalized for APAP poisoning.[6,7] Research ethics board approval for the parent study was granted at each participating institution. We analyzed only the data from the first one-third of patients entered into the database, which represent the derivation subset for this and other analyses.[6,15] For this study, we selected only those patients presenting within 1 day of a single, acute APAP OD and who developed hepatotoxicity.

Study setting and population

The CAOS identified all patients hospitalized for APAP OD in 34 Canadian hospitals between 1980 and 2005 based on electronic search of discharge diagnoses.[6,7] Subjects were included in this study if they developed hepatotoxicity, defined as having a peak serum AST or ALT greater than 1,000 IU/L at any point.[3,11,16] We excluded the subjects with any of the following: uncertainty regarding ingestion time or multiple ingestions over >6 h, no serum APAP concentration measured ≤24 h postingestion, no serum AST or ALT concentration measured >24 h postingestion, preexisting hepatic injury, or delayed presentation (as defined previously).[6]

Measurements and definitions

We recorded every measured serum APAP, AST, ALT, prothrombin time, and international normalized ratio (INR) into the CAOS dataset. The time of ingestion was ascertained by careful review of all pre-hospital, emergency department, and in-patient records. When either a time interval or multiple single times were recorded, the earliest time was taken as the time of ingestion. Because some patients had only AST or only ALT concentrations measured, the term AT is used throughout this article. For patients in whom both AST and ALT were measured, the greater of the two values was used. All AT concentrations measured after the criterion of AT >1,000 IU/L had been attained were not considered further in this analysis.

Data analysis

Serum AT kinetics were first characterized by the predicted time, postingestion, to reach 1,000 IU/L. This time was estimated for each subject using the two consecutive AT concentrations spanning 1,000 IU/L, assuming first-order kinetics. Patients were then grouped according to the time interval postingestion needed for the AT to reach 1,000 IU/L (≤24, 24–48, 48–72, and >72 h postingestion). This grouping was established *a priori* and was based on the hypothesis that earlier rises in AT are associated with less favorable clinical outcomes.

We then characterized the doubling velocity (i.e., the first-order rate constant) when AT crossed 1,000 IU/L. To combine the individual rate estimates into a population rate, a pooled approach was used rather than simply taking the unweighted average of the individual rates.[17,18] This technique allows for the nonexperimental nature of the data and is designed to limit the influence of outliers. The timed consecutive AT concentrations spanning 1,000 IU/L for each subject were laterally translated to cross the time = 0 axis at a predicted AT of 1,000 IU/L. A single least squares regression line was then fitted through all the available data points to estimate the population doubling velocity.[18] Because each subject contributed two data points to the analysis, the influence of clustering within the dataset was considered to be minor. Rates of doubling and the 95% confidence intervals are expressed as the equivalent doubling times throughout. In cases where the first AT above 1,000 was reported to be, for example, ">1,200" and further dilutions were not performed, the AT concentration was assigned to this lower limit. Summary statistics are reported throughout, as there was no *a priori* null hypothesis to be tested.

Results

Subjects were selected from the derivation subset of the first 3,202 admissions in the CAOS database as of February 2003. Of these, 2,488 resulted from 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 beyond 24 h following ingestion. Of the remaining 1,280 acute APAP ODs with sufficient laboratory data for consideration, 10 were excluded because of preexisting hepatic injury [initial AT>100 IU/L, APAP concentration more than 70% below the 1,000 μmol/L (150 mg/L) line, and peak AT less than two times the initial value] or delayed presentation (undetectable APAP at presentation and AT>1,000 IU/L regardless of reported time of ingestion). The characteristics of these patients have been reported previously.[6] For this analysis, we retained only the 94 patients (7.4%) who developed hepatotoxicity (peak serum AST or ALT ≥1,000 IU/L) (Table 1). All of these 94 patients were treated with acetylcysteine, initiated a median of 15.5 h [interquartile range (IQR) 12.3, 18.4] postingestion. The 20-h Prescott intravenous protocol[16] was initiated in all but three cases and extended beyond 24 h in one-third of cases. The first post-4 h APAP concentration exceeded the 1,000 μmol/L (150 μg/mL) at 4 h treatment line of the Rumack–Matthew nomogram in all cases (Fig. 1). None of these patients, all of whom were treated with acetylcysteine within 24 h of acute OD, died and only one underwent liver transplant.

AT concentrations were measured at 707 different time points [median 73 h (IQR 34–118 h)] postingestion, up to and including the first AT >1,000 IU/L. Both AST and ALT were measured at 413 of these time points [median ratio 1.32 (IQR 1.19–1.52)]. The first measured AT concentration averaged 211 IU/L (median, IQR 77–511 IU/L; range 8 to >5,200 IU/L) and collected at a median of 15.3 h (IQR 12.1–19.2 h)

Table 1. Characteristics of acute overdose patients with hepatotoxicity (study group) compared with those without hepatotoxicity

Median (IQR) or count (percentage)	Hepatotoxicity (n = 94)	No hepatotoxicity (n = 1176)
Age (year)	23.7 (18.4, 36.3)	21.9 (17.1, 31.8)
Female (%)	57 (60.6)	819 (69.6%)
Ethanol coingested (%)	19 (20.2)	347 (29.5%)
Alcoholic (%)	19 (20.2)	191 (16.2%)
Initial serum aminotransferase (IU/L)	211 (77, 511)	19 (14, 27)
4-h serum acetaminophen equivalent[a] (μmol/L)	4,030 (2,340, 6,250)	1,350 (961, 1,960)
Time to first measured acetaminophen (h)	14.9 (11.2, 17.3)	5.1 (3.7, 9.3)
Time to acetylcysteine postingestion (h)	15.5 (12.3, 18.4)	7.8 (5.9, 11.6)

Only acute overdose patients with serum acetaminophen measured within 24 h of overdose and with serum AT measured at least 24-h postoverdose are included. Hepatotoxicity is defined as a peak AT >1,000 IU/L.
[a]The "4-h serum acetaminophen equivalent" measures the vertical distance of the first measured acetaminophen concentration above the treatment line of the Rumack–Matthew nomogram.

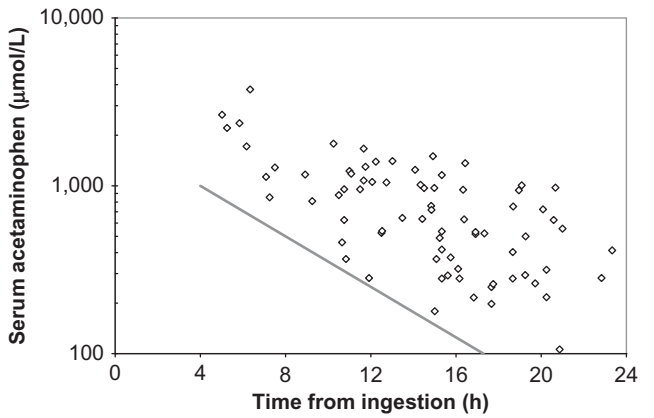

Fig. 1. Initial serum acetaminophen concentration following acute overdose in subjects who developed aminotransferase concentrations over 1,000 IU/L despite treatment. The gray line denotes the 1,000 μmol/L (150 μg/mL) at 4 h treatment line of the Rumack–Matthew nomogram.

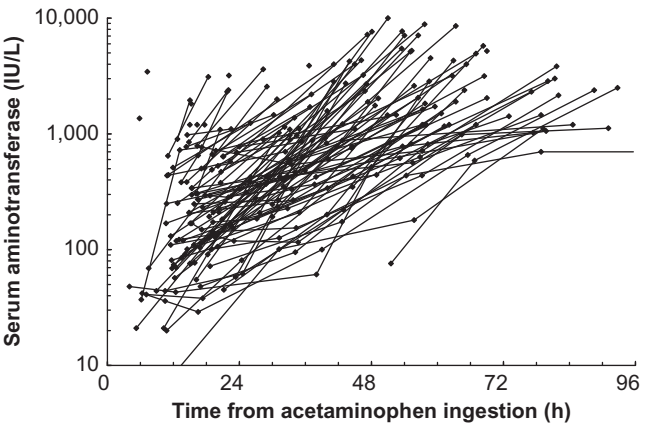

Fig. 2. Serum aminotransferase concentrations following acute overdose in patients who develop hepatotoxicity despite treatment with acetylcysteine. Timed serum aminotransferase concentrations up to and including the first concentration >1,000 IU/L are shown for individual subjects.

postingestion. Almost all AT concentrations measured 12 or more hours postingestion exceeded 50 IU/L and exceeded 100 IU/L when measured more than 24 h postingestion (Fig. 2). When considered relative to the start of acetylcysteine, serum AT concentrations were usually much higher than 100 IU/L at the start of treatment and rose above 100 IU/L in all but three cases during the first 20 h of antidotal therapy (Fig. 3).

The predicted time to reach 1,000 IU/L could be established in 93 subjects. This traditional criterion for hepatotoxicity was attained by 24 h postingestion in 19 subjects (20%), by 48 h in 62 (67%), and by 72 h in 87 (94%). The AT doubling times grouped by the time interval for AT to reach 1,000 IU/L are shown in Table 2. The serum AT doubling time was substantially shorter, averaging less than 8 h among subjects attaining an AT concentration of 1,000 IU/L within 48 h of ingestion. Coagulopathy, as measured by peak INR, was also more common and severe in these patients (Fig. 4). Patients who

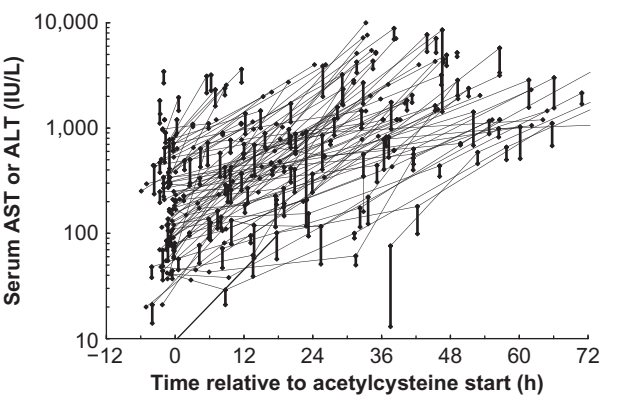

Fig. 3. Serum AST and ALT concentrations expressed relative to the initiation of treatment with acetylcysteine. Timed serum AST and ALT concentrations are shown relative to the initiation of antidotal therapy. In cases where both AST and ALT are measured simultaneously, both values are shown joined by a thick vertical line.

Table 2. Kinetics of aminotransferase release and peak INR based on estimated time to meeting criterion for hepatotoxicity

Time to AT = 1,000 IU/L (h)	n	Serum aminotransferase Doubling time (h) (95% CI)	R^2	Peak INR median (IQR)
≤24	12	7.7 (6.3, 10.1)	0.76	4.7 (3.5, 5.9)
24–48	41	7.4 (6.7, 8.1)	0.85	2.5 (1.7, 4.5)
48–72	24	12.6 (10.7, 15.1)	0.74	1.8 (1.6, 2.2)
>72	6	18.1 (11.8, 39.0)	0.63	1.7 (1.7, 1.9)
Overall	83	9.5 (8.7, 10.4)	0.74	2.3 (1.7, 4.1)

Shown are the pooled serum AT doubling times and peak INR, grouped by the time needed for serum AT to reach 1,000 IU/L. The R^2 estimates the variation of individual subjects' data pairs from the group pooled least squares regression line. Ten subjects were excluded because the initial serum AT was above 1,000 IU/L.

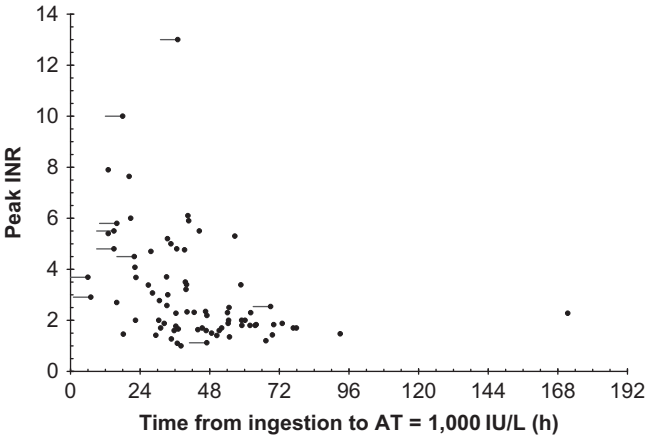

Fig. 4. Peak INR is much higher in overdose patients whose serum AT concentration reaches 1,000 IU/L within 48 h of acute ingestion. Horizontal error bars indicate the 10 patients in whom the first measured AT was already over 1,000 IU/L. Note that the INR usually peaked many hours after the AT reached 1,000 IU/L (time of peak not shown on this graph). INR, international normalized ratio; AT, aminotransferase.

developed prolonged INR generally had an AT>250 IU/L within the first 12 h of *N*-acetylcysteine treatment (Fig. 5).

Discussion

Whether to initiate antidotal therapy following acute OD has been guided by the Rumack–Matthew nomogram for three decades.[19] Yet the questions of when to discontinue acetylcysteine therapy and by which route or at what dose to administer it remain unclear. At the root of these controversies is the imprecise risk prediction during the first 24 h of treatment, partly limited by our understanding of the timing of changes in serum markers shortly after OD. We have shown that an initially abnormal AT that doubles roughly

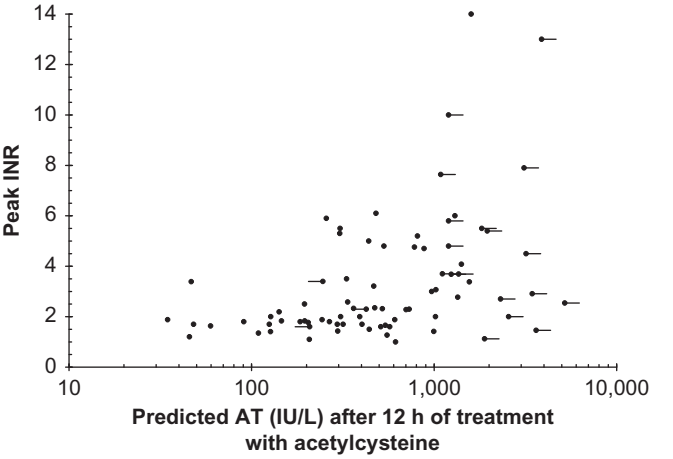

Fig. 5. Severe coagulopathy is unlikely when the serum AT is relatively low after 12 h of acetylcysteine therapy. Horizontal error bars are shown when either no AT was measured (open to left) or the AT was already over 1,000 IU/L (open to right) during the first 12 h of acetylcysteine therapy. INR, international normalized ratio; AT, aminotransferase.

every 8 h is typical for patients who eventually meet the AT criteria for hepatotoxicity within 48 h of acute ingestion and also develop severe coagulation disturbances. This is important as AT alone is a poor predictor of mortality in APAP poisoning.[20,21]

Our study is the most detailed analysis of AT kinetics in the early postingestion stage of hepatotoxicity. Singer et al. described 19 patients, only 8 of whom met the traditional definition of hepatotoxicity (AT > 1,000 IU/L).[9] Six of these had abnormal AST values within 24 h of ingestion. We have characterized the time course of serum AT rise in terms of both the predicted time to reach 1,000 IU/L and the estimated doubling rate at that moment. AT concentrations peak a variable number of days after acute APAP OD, but they attain 1,000 IU/L within 48 h of ingestion in two-thirds of cases destined to do so. The correlation with peak INR corroborates clinical experience suggesting that patients reaching this threshold sooner have more severe hepatic injury. Indeed, abnormalities of serum AT developing 2 or more days after ingestion are of little consequence and treatment of late, isolated AT elevation is generally not warranted.[22,23] Not surprisingly perhaps, the rate at which AT concentrations increase is slower in such patients. By calculating doubling time only during the interval crossing 1,000 IU/L, we attempted to reduce some of the circularity of this observation. We postulate that two distinct processes contribute to the rise of serum AT: an early leak from severely injured zone 3 hepatocytes and a late spike as healing and turnover occurs. This paradigm is consistent with recent observations[24] and may explain why the height of the AT peak *per se* is not predictive of encephalopathy and death.[25,26] More work is needed to clarify both AT release and clearance as well as differences between the time profiles of AST and ALT.

Our data can be used to inform evolving practice guidelines regarding the duration of treatment with acetylcysteine. Nearly all our patients developed elevated AT by 12–24 h after acute APAP ingestion, and thus during the first day of treatment. Severe coagulopathy developed only in patients with AT concentrations reaching 1,000 IU/L during or shortly after the first 20 h of treatment. This suggests patients with undetectable APAP and more modest AT concentration abnormalities (i.e., 100–1,000 IU/L) but nearly normal INR may not benefit from extending antidotal treatment. Further work is needed to clarify this issue. At present our findings should not alter the established practice of initiating antidotal therapy in patients deemed to be at some risk of hepatotoxicity based on the Rumack–Matthew nomogram. All patients in this study were above the usual treatment line and were appropriately treated with antidote.

We recognize that the occasional patient will develop isolated rises in AST or ALT several days after stopping acetylcysteine. These patients are usually alert and have relatively normal pH and INR, which excludes hepatic failure.[22,25,27,28] Because the 20-h Prescott protocol is widely used in Canada and testing ATs after discontinuation of acetylcysteine is not universally recommended here, such patients are likely underrepresented in this dataset. Repeat blood tests after acetylcysteine therapy are routine in other countries.[22,29] Nevertheless, the study collected data from regional tertiary care and referral hospitals and would have identified any patient returning to hospital with hepatic failure following discharge. Our observations are intended to describe the typical pattern of serum AT changes relative to the serum APAP in at-risk patients, rather than fully characterizing the outliers.

We also recognize that serum APAP concentrations can remain elevated because of decreased hepatic clearance, massive ingestion, and delayed gastric emptying due to coingestants, and agree that acetylcysteine should be continued until the serum APAP is undetectable.[8,23,30–32] We believe that risk prediction involves comparing both the (falling) serum APAP and the (rising) serum AT and have proposed a simple method for doing so.[33]

This study is purely a descriptive analysis, and not a comparative study. We did not analyze the rate of AT changes in patients with peak concentrations below 1,000 IU/L. Using existing health records, we were also obliged to make several assumptions to accommodate the vagaries of real-world data. For example, the frequency, timing, and completeness of laboratory testing were inconsistent. Nevertheless, we believe the assumptions used were both conservative and practical, and a reasonable compromise against the equally concerning practice of excluding many patients from the analysis. There is likely substantial interassay variability of AT among hospitals over the two decades of laboratory data collected. Moreover, we recoded both ATs into a single parameter for the purposes of this analysis because some hospitals measured only ALT or only AST. These sources of variability were mitigated by examining the intrasubject rate of change of the AT.

Conclusions

In conclusion, most patients with acute APAP OD who develop hepatotoxicity (an AT >1,000) despite treatment have abnormal AT at presentation. Moreover, the AT rises more quickly during the first day of antidotal therapy in patients with earlier onset hepatotoxicity and more severe coagulopathy. Risk prediction instruments may therefore benefit from incorporating this information, and formal prospective studies of this approach are warranted.

Declaration of interest

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