Acetaminophen Dose Does Not Predict Outcome in Acetaminophen-Induced Acute Liver Failure

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Background: Acetaminophen is a dose-dependent toxin. Prognosis in severe acute liver injury is related presumably in part to the dose ingested. We sought to assess the value of acetaminophen dosing information in patients with acute liver failure (ALF) due to acetaminophen toxicity to determine the role of dose as a prognostic indicator.

Methods: Prospective data from 113 patients with ALF having single-time-point ingestions of acetaminophen were analyzed. Multivariate and χ^2 tests were used to determine the relationship of dose to clinical outcome. We also used the Mann-Whitney *U* test to compare prognosis and survival in ALF with acetaminophen dose ingested.

Results: Multivariate and χ^2 analyses failed to show any relationship between acetaminophen dose and spontaneous survival. A separate analysis showed no correlation between acetaminophen dose and clinical prognostic indicators.

Conclusions: Dose of acetaminophen ingested did not seem to play a role in prognosis. The most important prognostic factor was coma grade on admission to study. Acetaminophen dosing information is not always obtainable. When it is, it adds little to the clinical assessment. Severity of encephalopathy is a more reliable indicator of prognosis in these critically ill patients.

Key Words: acetaminophen, acute liver failure, *N*-acetylcysteine

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Acetaminophen is a highly popular analgesic that exists in both over-the-counter and combination prescription formulations. It is estimated that 36% of Americans consume an acetaminophen-containing preparation at least once a month.[1] Although it is generally safe when used within the recommended limit of 4 g/d,[2] doses exceeding 4 g/d may be associated with dose-dependent hepatotoxicity and acute liver failure (ALF).[3] Acetaminophen overdose is the leading cause of ALF in the United States[4,5] and the United Kingdom[6] and accounts for nearly half of all ALF cases annually. Acute liver failure is defined as the onset of coagulopathy and hepatic encephalopathy occurring within 26 weeks of illness in patients without preexisting liver disease.[7] It carries a high mortality rate and often afflicts the young and previously healthy.

Many variables influence the extent of liver injury and prognosis in acetaminophen-induced ALF. Factors negatively impacting outcome include excessive dosing, concomitant medications, alcohol use, starvation, advanced age,[8,9] and delay in seeking medical attention. A highly effective antidote, *N*-acetylcysteine (NAC),[10–14] protects against liver injury if given within 12 hours of ingestion but is less effective thereafter. Liver transplantation is utilized in a small fraction of cases and can be lifesaving in suitable patients.[15,16]

Determination of prognosis in acetaminophen overdose is vitally important; therefore, several criteria have been developed to predict outcome. Unfortunately, these have relatively low sensitivity and specificity.[17–20] Multiple indicators in isolation, however, are known to affect outcome. Advanced hepatic encephalopathy (coma grades 3 or 4) is associated with poor prognosis,[21] and some authors recommend that all patients with coma grade 3 or higher be considered for liver transplantation.[22] Another factor influencing prognosis is delay in receiving NAC, which has been correlated with an increased risk of hepatotoxicity. Studies by Schiødt et al.[23] suggest that receipt of NAC at 48 hours or more from time of ingestion resulted in hepatic injury with prolongation of acetaminophen half-life, a surrogate for impaired hepatic metabolic function.

Despite being recognized as a dose-dependent toxin, the quantity of acetaminophen ingested has never been incorporated into any prognostic criteria. Authors have stressed the unreliability of dosing information reported by patients on admission, either due to encephalopathy, inaccurate recall, or purposeful deception.[24] Information from next of kin is even less reliable because family members typically are unaware of dosing details.

Acetaminophen dosing information might prove valuable to clinicians managing patients with ALF. We sought to assess the reliability of acetaminophen dosing information in determining prognosis by correlating this information with patient outcomes. We selected a group of patients with acetaminophen-induced ALF who had an overdose at a single time point from the large, prospectively collected database of the US Acute Liver Failure Study Group, which contains detailed clinical information on more than 1400 patients. We used multivariate and χ^2 analyses to determine the influence of reported acetaminophen dose on survival. We also divided patients into groups based on admission coma grade, time from overdose to hospital admission, outcome, and reported ingestion amounts to determine whether information on acetaminophen ingestion could help in predicting outcome.

MATERIALS AND METHODS

Between January 1998 and May 2007, 527 patients with ALF presumed to be due to acetaminophen toxicity were prospectively identified and enrolled in the ALF study by the 22 participating US tertiary-care centers. All but one of these were a liver transplant center. All centers were in compliance with their local institutional review board requirements. A certificate of confidentiality was obtained from the National Institute of Mental Health for the entire study. Enrollment required fulfillment of the criteria for ALF,[25] defined as the presence of coagulopathy (international normalized ratio ≥1.5) and hepatic

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TABLE 1. Multivariate Analysis Comparing the Variables Sex, Age, Ethnicity, Acetaminophen Dose, ALT, and Ratio of Dose to Body Weight With Outcome Measure Spontaneous Survival

	β Coefficient	SE	Wald χ^2	*df*	*P*	OR
Female sex	0.197	0.466	0.178	1	0.673	1.217
Age, y	−0.013	0.020	0.385	1	0.535	0.987
White ethnicity	−1.255	0.975	1.657	1	0.198	0.285
Dose, g	0.000	0.000	2.134	1	0.144	1.000
ALT, IU/L	0.000	0.000	2.402	1	0.121	1.000
Dose/body weight, g/kg (n = 106)	0.001	0.001	3.297	1	0.069	1.001

encephalopathy within 26 weeks of the development of symptoms in the absence of previous liver disease. To establish a diagnosis, a detailed history of acetaminophen ingestion was collected, including total amount taken, type of acetaminophen compound consumed, and duration of use. For the purpose of this study, 414 of the 527 patients were excluded either because the patient had ingested acetaminophen chronically rather than at a single time point (n = 310) or because historical data (dosing information or date of overdose, n = 92) or detailed laboratory data (alanine aminotransferase [ALT], coma grade, or acetaminophen level, n = 12) were lacking. The remaining 113 patients comprised the study group.

Statistical Analysis

We used multivariate analysis to determine the influence of patient-reported acetaminophen dose, sex, age, ethnicity, admission ALT, and ratio of dose to body weight on spontaneous survival. A χ^2 analysis was used to identify differences in survival among patients ingesting greater than or less than/equal to 10 g (n = 92 and 23 patients, respectively), 20 g (n = 70 and 45), 30 g (n = 69 and 46), 40 g (n = 85 and 30), and 50 g (n = 102 and 13) of acetaminophen. We also stratified patients based on whether 48 hours had elapsed between overdose and admission. Patients within these two groups were subdivided by severity of hepatic encephalopathy on admission into either low (grades 1–2) or high grade (grades 3–4). We compared survival in low versus high-coma-grade patients using the χ^2 test. We also compared acetaminophen dose in low- versus high-coma-grade patients using the Mann-Whitney *U* test to determine whether there was any difference in the distribution of reported doses among these groups. Possible outcomes were spontaneous survival (defined as survival without liver transplantation)[4] or death (this group included transplanted patients). Statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL).

TABLE 2. χ^2 Analysis of Patients Divided Into Groups Based on Cutoff Values of 10, 20, 30, 40, and 50 g of Acetaminophen and Compared for Differences in Spontaneous Survival

Acetaminophen Dose Cutoff, g	No. Patients With ≤Dose Cutoff	No. Patients With >Dose Cutoff	*P*
10	22	91	0.605
20	44	69	0.142
30	68	45	0.150
40	84	29	0.245
50	100	13	0.388

TABLE 3. Demographic Features of Low- Versus High-Coma-Grade Patients

	Coma Grades 1–2 (n = 78)	Coma Grades 3–4 (n = 35)	*P*
Female sex, n (%)	51 (65)	25 (71)	0.304
Median age (range), y	30 (17–62)	31 (18–54)	0.499
White race, n (%)	69 (88)	33 (97)	0.437
Median overdose (range), mg	27,000 (300–158,000)	25,000 (6500–125,000)	0.264
Median body mass index (range), kg/m^2	24 (17–38)	27 (18–44)	0.102
Recent positive opiate ingestion, n (%)	11 (14)	7 (20)	0.193

All analyses were 2-tailed. $P < 0.05$ was considered statistically significant.

RESULTS

Multivariate analysis (Table 1) showed that acetaminophen dose did not predict the probability of spontaneous survival to any significant degree ($P = 0.146$; odds ratio [OR], 1.000). Spontaneous survival was also not significantly affected by admission ALT ($P = 0.121$; OR,1.000), sex ($P = 0.673$; OR, 1.217), age ($P = 0.535$; OR,0.987), ethnicity ($P = 0.198$; OR,0.285), or ratio of dose to body weight ($P = 0.069$; OR,1.001).

The χ^2 analysis (Table 2) failed to identify any difference in survival among patients ingesting greater or less than 10 g ($P = 0.605$), 20 g ($P = 0.142$), 30 g ($P = 0.150$), 40 g ($P = 0.245$), or 50 g ($P = 0.388$) of acetaminophen.

The low- and high-grade encephalopathy groups are described in Table 3. The groups were similar in demographic features and in median acetaminophen dosing. Both low- and high-coma-grade groups were predominantly female ($P = 0.304$) and white ($P = 0.437$). There was similarly no significant difference between the groups in age, acetaminophen dose, body mass index, and ingestion of any opiates.

Spontaneous survival rates in coma grades 1 to 2 versus 3 to 4 are compared in Table 4. The low-coma-grade group (n = 78) had a much higher survival rate than the patients (n = 35) comprising the high-coma-grade group (83% vs 40%; $P = <0.0001$).

Spontaneous survival rates in early-presenting (<48 hours) patients with coma grades 1 to 2 versus 3 to 4 are shown in Table 5. Survival in the early-presenting group with low coma grade was significantly higher than survival in high-coma-grade patients (83% vs 39%; $P < 0.0001$). Similarly, low-coma-grade patients in the late-presenting (≥48 hours) group tended to have a much more favorable survival rate than those with more advanced coma grades (83% vs 42%; $P < 0.0001$) (Table 6).

In a separate analysis, we examined median acetaminophen dose among subgroups divided by coma grade (Table 7). There was no significant difference in dose ingested between the

TABLE 4. Overall Spontaneous Survival

	Coma Grades 1–2 (n = 78)	Coma Grades 3–4 (n = 35)	*P*
Spontaneous survival, n (%)	65 (83)	14 (40)	<0.0001

TABLE 5. Spontaneous Survival in Early-Presenting Patients

	Coma Grades 1–2 (n = 60)	Coma Grades 3–4 (n = 23)	*P*
Spontaneous survival, n (%)	50 (83)	9 (39)	<0.0001

early-presenting low- and high-coma-grade patients (30,000 vs 25,000 mg; $P = 0.461$). Nor was there a difference in reported dose between the late-presenting low- and high-coma-grade groups (24,000 vs 18,750 mg; $P = 0.298$).

DISCUSSION

We sought to correlate acetaminophen ingestion data with outcome using multiple analytic approaches. Our multivariate analysis suggested that none of the variables surveyed (sex, age, ethnicity, dose, admission ALT, ratio of dose to body weight) significantly influenced outcome. Thus, increasing acetaminophen dose did not seem to affect mortality in our set of patients. This finding could result from inherent inaccuracy in data that were gathered largely from patients with hepatic encephalopathy. Of note, these findings are generalizable only to this population of patients with ALF where altered mental status is a criterion for study entry. Our results may not apply to acetaminophen ingestions in the absence of encephalopathy and ALF.

An alternative explanation as to why acetaminophen dose does not seem to affect mortality may relate to a plateau effect, in which acetaminophen doses above a certain threshold do not result in additional liver injury. The possibility of a plateau effect of acetaminophen toxicity is suggested by our analysis of serial acetaminophen doses. In this analysis, we compared survival outcomes at various cutoff doses. We found no significant difference in mortality among patients taking greater or less than multiple fixed doses of acetaminophen. This suggests that mortality does not increase with increasing dose. Indeed, there seems to be no distinct dose at which mortality is clearly greater. Rather, it is possible that once a patient has taken a quantity of acetaminophen sufficient to induce ALF, the effect on mortality with increasing dose is minimal. Hepatic injury may be so extensive once the threshold of ALF has been reached that acetaminophen toxicity ceases to be additive.

In a separate analysis, we attempted to correlate outcome in acetaminophen overdose with anticipated prognosis based on admission coma grade. Coma grade repeatedly has been shown to correlate with survival in patients with ALF, and this was also borne out by our data. Regardless of whether they presented early or late, patients with grades 3 to 4 encephalopathy had much lower spontaneous survival rates than patients with grades 1 to 2. If dose were both accurate and an independent outcome determinant, we would expect to find higher doses reported in patients with a higher coma grade.

Although time from overdose to administration of NAC has previously been suggested to influence the degree of hepatic injury, we could not demonstrate a difference in survival for early- versus late-presenting patients with the same initial coma grade (Tables 5 and 6). The reasons for this result are unclear but may be related to genotypic differences in acetaminophen metabolism[26,27] or the fact that most patients surpassing the threshold of ALF fall into the "severe" category. Nevertheless, these data suggest that coma grade remains a stronger determinant of survival than dose of acetaminophen ingested or time to presentation.

TABLE 6. Spontaneous Survival in Late-Presenting Patients

	Coma Grades 1–2 (n = 18)	Coma Grades 3–4 (n = 12)	*P*
Spontaneous survival, n (%)	15 (83)	5 (42)	<0.0001

TABLE 7. Median Acetaminophen Dose in Patients Stratified by Coma Grade and Time of Presentation

	Coma Grades 1–2	Coma Grades 3–4	*P*
Early presentation: <48 h, dose (n)	30,000 mg (n = 60)	25,000 mg (n = 23)	0.461
Dose range	3500–158,000 mg	6500–125,000 mg	
Late presentation: >48 h (range)	24,000 mg (n = 18)	18,750 mg (n = 12)	0.298
Dose range	300–75,000 mg	6500–65,000 mg	

After dividing patients into subcategories based on prognosis, we calculated the median acetaminophen dose reported by patients in each group. Mild hepatic encephalopathy would be predicted to result in a better prognosis, whereas grades 3 to 4 would indicate a worse prognosis, and this assumption was supported by the differences in survival observed. Provided that acetaminophen dosing information is accurate, we presumed that higher doses of acetaminophen would be associated with a poorer prognosis. However, our analysis revealed no significant difference in reported acetaminophen dose between the prognostic groups (Table 7). In other words, patients with a better prognosis (ie, lower grade of encephalopathy) did not report ingesting lower quantities of acetaminophen. Indeed, both subgroups with coma grades 1 to 2 reported taking higher median doses of acetaminophen than their grades 3 to 4 counterparts, although this difference was not significant.

These results suggest either that the acetaminophen dosing information obtained is inaccurate or that the quantity of acetaminophen ingested is not, in and of itself, a consistent determinant of outcome. Although acetaminophen is inarguably hepatotoxic in a dose-dependent fashion, reported dose does not seem to correspond directly to mortality. The poor correlation between dose and outcome may be related to the multifactorial nature of acetaminophen metabolism, which varies from patient to patient and is influenced by genetic factors, coingested substances, and alcohol use. We also cannot rule out the possibility of a plateau phenomenon in the setting of massive acetaminophen overdose. The hepatotoxic effects of acetaminophen may not be linear when doses are so high and liver injury is so extensive. Interestingly, admission ALT levels also did not seem to predict survival. This may be because liver injury in acetaminophen-induced ALF is massive, and ALT levels tend to be orders of magnitude outside the range of normal. Differences in ALT may not be meaningful in the setting of such extensive damage. Another possibility is that mortality is not related to the degree of liver injury but to the complications thereof. Indeed, secondary complications such as infection or bleeding have been closely linked to outcome in ALF.[28]

Our study had several limitations. We were unable to obtain dosing information in a large percentage of patients enrolled by the Acute Liver Failure Study Group. In some cases, this information may have been less available in those with advanced encephalopathy, thereby skewing the data collection away from the sickest patients. Data regarding time from overdose to admission was similarly difficult to collect, and we could obtain

a complete history of alcohol ingestion only in a small fraction of patients. Our data failed to reproduce a correlation between increasing age and mortality found by previous authors.[17] It should be kept in mind, however, that our data set included only patients who had an overdose at a single time point, often in an attempt at suicide. Our patients tended to be younger on average than patients in other studies and in many cases were considerably younger than 40 years. Thus, the results of prior studies may not pertain to our patient set. Lastly, this is a retrospective, descriptive analysis that may not impact the management of patients with ALF greatly as reported acetaminophen dose is not a component of overdose management protocols.

Acetaminophen dosing information, taken in isolation, is an unreliable predictor of survival in patients with ALF. Our data suggest that other factors alone or in combination affect prognosis more strongly than the acetaminophen dose itself. Groups of patients ingesting similar amounts of acetaminophen seem to experience different outcomes, depending on the degree of encephalopathy on admission. Thus, patients presenting with massive overdoses of acetaminophen (40 or 50 g) do not necessarily have a grim prognosis, but more importantly, patients with relatively smaller ingestions (10 or 20 g) may experience rapidly fatal deterioration if lifesaving measures are not anticipated. Clinicians should consider reported acetaminophen dose in the context of the patient's overall clinical picture, with particular attention to mental status when predicting prognosis in ALF.

REFERENCES

1. US Department of Health and Human Services (DHHS). *Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III Second Laboratory Data File* [CD-ROM, series 11, no. 2A]. Hyattsville, MD: Centers for Disease Control and Prevention; 1998.
2. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA*. 2006;296:87–93.
3. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med*. 1995;333: 1118–1127.
4. Schiødt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg*. 1999;5:29–34.
5. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137:947–954.
6. Bernal W. Changing patterns of causation and the use of transplantation in the United Kingdom. *Semin Liver Dis*. 2003;23:227–237.
7. O'Grady JG. Acute liver failure. *Postgrad Med J*. 2005;81:148–154.
8. Schiødt FV, Lee WM, Bondesen S, et al. Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose. *Aliment Pharmacol Ther*. 2002;16:707–715.
9. Van Thiel DH, Stauber R, Gavaler JS, et al. Hepatic regeneration. Effects of age, sex hormone status, prolactin, and cyclosporine. *Dig Dis Sci*. 1991;36:1309–1312.
10. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med*. 2003;349: 474–485.
11. Prescott LF, Illingworth RN, Critchley JAJH, et al. Intravenous *N*-acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ*. 1979;2:1097–1100.
12. Douglas AP, Hamlyn AN, James O. Controlled trial of cysteamine in treatment of acute paracetamol (acetaminophen) poisoning. *Lancet*. 1976;1:111–115.
13. Prescott LF, Sutherland GR, Park J, et al. Cysteamine, methionine and penicillamine in the treatment of paracetamol poisoning. *Lancet*. 1976;2:109–113.
14. Keays R, Harrison PM, Wendon JA, et al. A prospective controlled trial of intravenous *N*-acetylcysteine in paracetamol-induced fulminant hepatic failure. *BMJ*. 1991;303:1024–1029.
15. Pauwels A, Mostefa-Kara N, Florent C, et al. Emergency liver transplantation for acute liver failure. Evaluation of London and Clichy criteria. *J Hepatol*. 1993;17:124–127.
16. Schiødt FV, Bondesen S, Tygstrup N, et al. Prediction of hepatic encephalopathy in paracetamol overdose: a prospective and validated study. *Scand J Gastroenterol*. 1999;34:723–728.
17. Donaldson BW, Gopinath R, Wanless IR, et al. The role of transjugular liver biopsy in fulminant hepatic failure: relation to other prognostic indicators. *Hepatology*. 1993;18:1370–1374.
18. Lake J, Sussman N. Determining prognosis in patients with fulminant hepatic failure: when you absolutely, positively have to know the answer. *Hepatology*. 1995;21:879–882.
19. Shakil AO, Kramer D, Mazariegos GV, et al. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transpl*. 2000;6:163–169.
20. Mitchell I, Bihari D, Chang R, et al. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. *Crit Care Med*. 1998;26:279–284.
21. Takahashi Y, Kumada H, Shimuzu M, et al. A multicenter study on the prognosis of fulminant viral hepatitis: early prediction for liver transplantation. *Hepatology*. 1994;19:1065–1071.
22. Anand AC, Nightingale P, Neuberger JM. Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria. *J Hepatol*. 1997;26:62–68.
23. Schiødt FV, Ott P, Christensen E, et al. The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage. *Clin Pharmacol Ther*. 2002;71:221–225.
24. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005;42:1364–1372.
25. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179–1197.
26. Court MH, Duan SX, Von Moltke LL, et al. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: identification of relevant acetaminophen UDP glucuronosyltransferase isoforms. *J Pharmacol Exp Ther*. 2001;299:998–1006.
27. Ueshima, Tsutsumi M, Takase S, et al. Acetaminophen metabolism in patients with different cytochrome P4502E1 genotypes. *Alcohol Clin Exp Res*. 1996;20(suppl 1):25A–28A.
28. Vaquero J, Polson J, Chung C, et al. Infection and the progression to deep hepatic encephalopathy in early fulminant hepatic failure. *Gastroenterology*. 2003;125:755–764.