Acute Versus Chronic Alcohol Consumption in Acetaminophen-Induced Hepatotoxicity

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The aim of this study was to determine by multivariate analysis how alcohol and other factors affect the clinical course and outcome in patients with acetaminophen (paracetamol) poisoning. A total of 645 consecutive patients admitted from 1994 to 2000 with single-dose acetaminophen poisoning were studied, giving special attention to alcohol history, time between overdose and intravenous N-acetylcysteine (NAC) treatment ("time to NAC"), and other data available at the time of admittance. Up until 72 hours after ingestion, time to NAC was the single most important independent risk factor. With a time to NAC less than 12 hours, the mortality rate was 0.42% (95% CI, 0.05-2.7). When time to NAC exceeded 12, 24, and 48 hours, the mortality rate increased to 6.1%, 13%, and 19%, respectively. Chronic alcohol abuse was an independent risk factor of mortality (odds ratio [OR], 3.52; 95% CI, 1.78-6.97). Acute alcohol ingestion was an independent protective factor regarding mortality in alcoholic patients (OR, 0.08; 95% CI, 0.01-0.66) but not in nonalcoholic patients (OR, 0.21; 95% CI, 0.03-1.67). Patient age and quantity of acetaminophen were independent risk factors. In conclusion, time to NAC was confirmed as the major risk factor in acetaminophen-induced hepatotoxicity and mortality. Chronic alcohol abuse was an independent risk factor that could be counteracted by concomitant acute alcohol ingestion. We suggest that patients with chronic alcoholism and suspected acetaminophen poisoning due to an increased risk of developing hepatotoxicity should be treated with NAC regardless of risk estimation. (Hepatology 2002;35:876-882.)

Acetaminophen (paracetamol) poisoning is the most common cause of acute liver failure in Denmark and the United Kingdom and is occurring with increasing frequency in the United States and Australia.¹ ² ³ Effective antidote treatment with N-acetylcysteine (NAC) is well established even with late presentation.² ³ The overall mortality is less than 1%.⁴ ⁵ ⁶ A delay in presentation with consequent late or withheld treatment may result in severe cases of hepatotoxicity.² ³ ⁴ ⁷ ⁸

The most important prognostic factor is the time from overdose to treatment ("time to NAC").² ³ ⁴ ⁹ ¹² A long time to NAC results in a low survival rate, which is even lower if NAC is withheld.² Patients with chronic alcoholism are widely considered to be at an increased risk of acetaminophen hepatotoxicity from overdose as well as from therapeutic misadventure.¹ ³ ⁷ ¹³ ¹⁷ Experimental studies have suggested that the underlying mechanisms are related to the induction of CYP2E1 in combination with depletion of liver glutathione.¹⁴ ¹¹ ¹² However, in most large-scale studies of acetaminophen poisoning, the prognosis was not adversely affected by prior ingestion of alcohol.¹ ² ³ ⁴ ³ ⁵ ¹³ ¹⁴ It has therefore been suggested that patients with chronic alcoholism only seem more susceptible to acetaminophen hepatotoxicity because they often present late and thereby have a long time to NAC. ³ ¹³ ¹⁴ Acute alcohol ingestion inhibits microsomal acetaminophen oxidation by CYP2E1 in animals, leading to a reduced synthesis of N-acetyl-p-benzoquinone imine, the reactive metabolite of acetaminophen.¹ ³ ⁴ ⁶ ⁷ ¹³ ¹⁴ ¹⁷ However, a protective effect of acute alcohol ingestion in humans has only been indicated in a few clinical studies.² ⁶ ¹⁴ ¹⁷

In the present study, the most important prognostic factors that are available at the time of decision to treat were identified in a large series of single-dose acetaminophen overdose cases. Multivariate analyses were performed to establish if alcohol abuse was a risk factor independently from other known and possible risk factors in acetaminophen-induced hepatotoxicity.
Patients and Methods

All patients admitted to Rigshospitalet (Copenhagen, Denmark) with acetaminophen poisoning during a 7-year period from 1994 to 2000 were identified. Patients admitted until 1998 were studied retrospectively and those thereafter prospectively. In Denmark, all residents are issued a central personal registration number that is used in all registers for exclusive identification. All patients admitted to the Department of Hepatology are registered with the central personal registration number and diagnosis at admittance. In addition, all patients are registered at discharge with the central personal registration number and discharge diagnosis code in the central hospital computer. For each case, the following data were recorded: age, sex, transfer from other hospitals, quantity of acetaminophen ingested ("dose"), time to NAC, ingestion of other drugs on an acute or regular basis, ingestion of alcohol on an acute or regular basis, nadir prothrombin index, peak bilirubin level, alanine transaminase level, creatinine level, serum acetaminophen level, hepatic encephalopathy (HE) grade II to IV, orthotopic liver transplantation, and death/survival. 31

Regular abuse of alcohol was defined as an excess of 14 units weekly for women and 21 units for men (1 unit equaling 10 g ethanol). Acute alcohol ingestion was defined as ingestion of alcohol as part of the intoxication in excess of the patient's regular daily consumption. Consequently, a patient could be registered with both acute and chronic ("combined") ingestion of alcohol.

In accordance with the Danish recommendations, all patients with suspected acetaminophen overdose regardless of severity were immediately treated with NAC. 32 The standard regimen consisted of infusion of 150 mg/kg NAC intravenously as a bolus and then 50 mg/kg over 4 hours followed by repeated infusions of 100 mg/kg over 16 hours until 3 consecutive recovering values of the prothrombin index were obtained. Some patients were admitted directly from the locality in Copenhagen. Most were transferred from other hospitals based on the criteria of prothrombin index less than 0.40, creatinine level greater than 300 μmol/L, platelets less than 100 × 10^9/L, arterial pH less than 7.30, or the development of HE. Mechanical ventilation, hemodialysis, and plasmapheresis were instituted when indicated by the clinical condition of the patients. Patients fulfilling the "King's College criteria" were considered for orthotopic liver transplantation. 33

Statistics. The statistical significance between any 2 variables was tested by the Mann-Whitney test, and the χ² test was used for comparison of frequencies. Survival rates were compared using the Kaplan-Meier method and Cox's F test. For the multivariate analyses, a backward, stepwise multiple regression analysis or a logistic regression analysis (STATISTICA, version 5.1, 1997 Edition; StatSoft Inc., Tulsa, OK) was applied where appropriate. The analyses were performed using mean substitution of missing data. Because of the low degree of missing data, analyses using case-wise deletion produced similar findings (not shown). Odds ratios (OR) with 95% CIs were determined from the logistic regression analysis. The level of significance was set to P < .05.

Results

A total of 672 patients were admitted with acetaminophen intoxication (101 in 1994, 90 in 1995, 74 in 1996, 99 in 1997, 109 in 1998, 108 in 1999, and 91 in 2000). The registration of patients at admittance versus discharge showed more than 95% concordance, which statistically makes the identification of the patients studied retrospectively more than 99% complete. The charts of all patients identified were retrieved using the central personal registration number. In 27 cases, a time to NAC could not be established, either because the information was unobtainable or because of multiple overdosing. The remaining 645 patients with single-dose acetaminophen poisoning were included in the study. Information on medication, alcohol, biochemical variables, and outcome variables were available in all cases. Information on the ingested acetaminophen dose was available in 611 cases (95%) and was otherwise stated as unobtainable. All registration of data was performed by the principal author (L.E.S.), and no differences in the consistency or quality of data recorded retrospectively or prospectively were apparent.

The median age was 31 years (range, 12-86 years). There were 427 women (66%) and 218 men. A total of 474 patients (73%) were transferred from other hospitals. The remaining 171 patients from the local region all survived. All patients received immediate NAC treatment.

Multivariate Analysis. A multivariate analysis was performed using age, sex, time to NAC, dose of acetaminophen, acute alcohol ingestion, regular alcohol abuse, acute ingestion of other drugs, and regular ingestion of other drugs as independent variables. The dependent variables were prothrombin index, alanine transaminase level, bilirubin level, and creatinine level in the multiple regression analysis and HE and death or orthotopic liver transplantation in the logistic regression analysis. The results from the analyses are given in Table 1. In the analyses, the examined variables only accounted for approximately half of the variation in the dependent variables.

Time to NAC. The multivariate analyses showed that time to NAC was the most important risk factor. With a time to NAC less than 12 hours, the mortality rate was
Table 1. Results of Multivariate Analyses Using Age, Sex, Time to NAC, Dose, Alcohol, and Other Medication as Independent Variables in 645 Cases of Single-Dose Acetaminophen Poisoning Showing Risk Factors and Protective Factors for Variables Associated With Clinical Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Factors</th>
<th>Protective Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin index</td>
<td>T-NAC (−0.43) &gt; close (0.22), NAC (−0.09)</td>
<td>AUA (0.12)</td>
</tr>
<tr>
<td>Alkaline transaminase</td>
<td>T-NAC (0.30) &gt; close (0.22)</td>
<td>AUA (0.11)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>T-NAC (0.33), NAC (0.19) &gt; age (0.12)</td>
<td>AUA (0.08)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>T-NAC (0.27), NAC (0.21)</td>
<td>AUA (0.11)</td>
</tr>
<tr>
<td>Hist</td>
<td>T-NAC, NAC, age, 90%</td>
<td>AUA</td>
</tr>
<tr>
<td>Death or liver</td>
<td>Age, NAC, NAC</td>
<td>AUA</td>
</tr>
</tbody>
</table>

NOTE: Standardized regression coefficients from the multiple regression analyses are given in parentheses. >, the first variable contributes significantly more to the risk than the second variable.

Abbreviations: T-NAC, time to NAC; CAA, chronic alcohol abuse; AUA, acute alcohol use.

22% (95% CI, 0.05-2.7). When time to NAC exceeded 24, and 48 hours, the mortality rate increased to 1%, 13%, and 19%, respectively. The corresponding rates for development of HE were 13%, 12%, 25%, and 38%, respectively. More correctly, the impairment of prognosis with increasing time to NAC should be conceived as a continuum as shown in Fig. 1. The risk increased for at least 72 hours, and no initial time lag was observed.

**Acute and Chronic Alcohol Use.** By their use of alcohol (≤ acute and ≥ chronic), the patients were divided into 4 subgroups, hereafter referred to as the none, acute, chronic, and combined subgroups. When the data for each subgroup (Table 2) were compared, the chronic subgroup showed a significantly higher severity of disease but also showed a significantly longer time to NAC. The other 3 subgroups seemed more similar.

In the multivariate analysis (Table 1), chronic alcohol abuse was an independent risk factor of HE (OR, 4.21; 95% CI, 2.42-7.32) and mortality (OR, 3.52; 95% CI, 1.78-6.97). Acute alcohol ingestion was an independent protective factor regarding HE (OR, 0.40; 95% CI, 0.19-0.83) and mortality (OR, 0.12; 95% CI, 0.03-0.53). To further show that the risk associated with alcohol was independent from that of time to NAC, a Kaplan-Meier plot was constructed showing the cumulative survival rates for every time to NAC for each alcohol subgroup (Fig. 2). The survival rate in the chronic subgroup was significantly lower (Cox’s F test; P < .0001) compared with any of the other 3 subgroups. Exclusion of the 171 patients from the local region did not alter the results of the analysis (data not given). The 157 patients with chronic alcohol abuse could semiquantitatively be divided into 85 with severe abuse (10 or more units daily) and 72 with moderate abuse (less than 10 units daily). No excess risk could be shown from severe abuse when compared with moderate abuse.

The severity of hepatotoxicity was markedly lower in the combined subgroup compared with the chronic subgroup, whereas the none and acute subgroups scored very similar. Consequently, the protective effect of acute alcohol ingestion seemed limited to those with prior chronic alcohol consumption. This was evaluated by multivariate analyses performed separately for patients with and without regular abuse of alcohol (Table 3). In abusers of alcohol, acute alcohol ingestion was an important protective factor regarding HE (OR, 0.18; 95% CI, 0.06-0.58) and mortality (OR, 0.08; 95% CI, 0.01-0.66). In nonabusers, only a nonsignificant trend toward a protective effect of acute alcohol ingestion could be shown (mortality OR, 0.21; 95% CI, 0.03-1.67).

**Dose, Age, and Other Prognostic Factors.** In the multivariate analysis, dose of acetaminophen was a risk factor, especially in nonalcoholic patients (Table 3). Doses resulting in death ranged from 15 to 125 g. However, 28 cases of severe hepatotoxicity (alanine transaminase level greater than 1,000 U/L) resulted from ingestion of a single dose of less than 12 g. Twenty-one of these 28 cases were associated with regular alcohol abuse. Age was a risk factor for HE and for death or orthotopic liver transplantation, particularly in alcoholic patients. No sex-specific differences were shown. Regular medication or coinfection with other drugs did not emerge as prognostic factors.

Using a nomogram with the standard 200-mg/L and 300-mg/L treatment lines, patients presenting within 16 hours can be placed into low-, intermediate-, and high-risk groups. Of 303 patients presenting within 16 hours,
Table 2. Biochemical and Clinical Data in 645 Patients With Single-Dose Acetaminophen Poisoning Divided into 4 Subgroups by Their Use of Alcohol

<table>
<thead>
<tr>
<th></th>
<th>N cute (n = 395)</th>
<th>Chronic (n = 108)</th>
<th>Acute (n = 53)</th>
<th>Combined (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>26 (20-36)</td>
<td>45 (38-55)*</td>
<td>30 (22-40)*</td>
<td>42 (30-50)*</td>
</tr>
<tr>
<td>Female (%)</td>
<td>73%</td>
<td>49%*</td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td>Dose (g)</td>
<td>25 (18-50)</td>
<td>25 (12-50)*</td>
<td>39 (16-50)</td>
<td>33 (20-50)</td>
</tr>
<tr>
<td>I-NAC (hr)</td>
<td>16 (6-30)</td>
<td>28 (17-48)*</td>
<td>12 (4-24)*</td>
<td>6 (4-21)*</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>0.27 (0.15-0.48)</td>
<td>0.13 (0.09-0.18)*</td>
<td>0.32 (0.14-0.57)</td>
<td>0.38 (0.26-0.66)*</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>3,620 (26.980)</td>
<td>6,711 (3,077-10,148)*</td>
<td>1,588 (21.920)*</td>
<td>63 (25-2,000)*</td>
</tr>
<tr>
<td>Bilirubin (µmol/L)</td>
<td>30 (13-60)</td>
<td>118 (56-269)*</td>
<td>24 (13-55)</td>
<td>16 (11-31)*</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>85 (75-109)</td>
<td>248 (107-529)*</td>
<td>85 (74-104)</td>
<td>85 (76-103)</td>
</tr>
<tr>
<td>HE (mo.)</td>
<td>38 (9.5%)</td>
<td>51 (46%)*</td>
<td>7 (7.5%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Death/OIT (no.)</td>
<td>37 (5.3%)</td>
<td>28 (28%)*</td>
<td>1 (1.1%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

NOTE: Values are given as median (1st quartile to 3rd quartile).
Abbreviations: I-NAC, time to NAC; ALT, alanine transaminase; OIT, liver transplant.
*P < .05 (Mann-Whitney or χ² test) compared with the none subgroup.

115 patients were assessed as low risk, 54 as intermediate risk, and 134 as high risk. None of the low- or intermediate-risk patients died, compared with 6 (4.5%) of the high-risk patients (not signficant). However, 8 (7.2%) of the low-risk patients developed signs of severe hepatotoxicity (alanine transaminase level greater than 1,000 U/L).

Discussion

From the information available at the time of admission, time to NAC, quantity of acetaminophen, chronic alcohol abuse, and age were independent risk factors in the development of hepatotoxicity in patients with acetaminophen poisoning. Acute ingestion of alcohol eliminated the excess risk associated with chronic alcohol abuse but was not protective in nonalcoholic patients.

This study confirmed time to NAC as the most important prognostic factor. The risk of developing hepatotoxicity increased with time to NAC up to at least 72 hours (Table 1 and Fig. 1). The apparent absence of a time lag from the time of ingestion contrasts with the notion that it is safe to await the determination of plasma acetaminophen level before deciding whether or not to treat. Mechanistically, the major conversion of acetaminophen to N-acetyl-p-benzoquinone imine takes place within the first few hours after dose, stressing the importance of initiating NAC treatment without delay and without awaiting blood test results. With early treatment, most N-acetyl-p-benzoquinone imine can be scavenged by glutathione.

Although time to NAC is already established as the most important prognostic factor, existing data from large-scale studies regarding the prognostic significance of alcohol consumption are at best ambiguous. Numerous uncontrolled case reports have suggested that the hepatotoxicity of acetaminophen is increased in patients with chronic alcoholism, and the collective weight has even been generally accepted as proof. In a recent review, Prescott holds this claim to be anecdotal and explains the apparent susceptibility of alcoholic patients to acetaminophen-induced hepatotoxicity by their late presentation. The present study provides the first systematic evidence obtained in humans that chronic alcohol abuse is an independent risk factor (Table 1 and Fig. 2). Thus, we have refuted the argument that the susceptibility of alcoholic patients to acetaminophen-induced hepatotoxicity may be entirely explained by their late presentation. However, patients with chronic alcoholism did indeed often present late and thereby added the independent risk of late presentation to that associated with alcohol abuse.

Acute ingestion of alcohol is believed to protect against the hepatotoxicity of acetaminophen and is suggested to eliminate the effect of chronic alcohol abuse. In the present study, acute alcohol ingestion in alcoholic patients was a significant protective factor that eliminated the risk associated with regular alcohol abuse. However,
we could not show any protective effect of cointoxication with alcohol in nonalcoholic patients (Table 3). The protective effect of acute alcohol ingestion is apparently limited to alcoholic patients. Because the protective effect of acute alcohol ingestion is believed to be due to inhibition of CYP2E1, the increased risk associated with chronic alcohol abuse is likely to result from the induction of CYP2E1 rather than from other mechanisms such as depletion of glutathione. 1,18–21,38,36 Because acute alcohol ingestion was not protective in nonalcoholic patients, it suggests that CYP2E1 plays a major role in acetaminophen toxicity in humans only when induced.

Age has not previously been suggested as an independent risk factor in acetaminophen-induced hepatotoxicity (Table 1) with the exception of the relative resistance of younger children. 30,37,38 In general, young patients are more likely to overcome the complications of hepatic failure. 49 A larger hepatic cell mass before hepatic damage, a greater capacity for regeneration, and perhaps a higher capacity for nontoxic metabolism of acetaminophen could contribute, but these factors remain to be investigated. Regular medication or cointoxication without specification of drug group did not emerge as risk factors. Possible risk associated with individual drug groups requires further investigation. 40

The influence of genetic variation in resistance to acetaminophen poisoning is difficult to evaluate but could be significant because the independent variables only explained approximately half of the total variation in the multivariate analyses. Genetic variation in cytochrome P450 and acetaminophen metabolism is described, and it is well known that some patients, even including alcoholic patients, may show considerable resistance to acetaminophen intoxication. 41,45 In addition, animals with certain genetic defects may be highly resistant to acetaminophen-induced hepatotoxicity. 46

In most countries, the decision to treat with NAC is based on modifications of the plasma concentration versus time since overdose nomograms originally suggested by Prescott as well as Rumack and Matthew. 47,48 However, the use of nomograms is not without problems. The information from the patient regarding the time of the overdose needs to be accurate to estimate the risk correctly. Misinterpretation of the nomogram may cause NAC to be withheld in patients meeting the treatment requirements. In one study, this was the case in 142 of 560 patients. 49 Another study describes 11 fatal cases in which NAC was mistakenly withheld. 9 Even with correct use of the nomogram, deaths have occurred in low-risk patients because NAC was "correctly" withheld. 49 In the present study, all patients received NAC and no deaths occurred in low-risk patients. Eight low-risk patients developed signs of severe hepatotoxicity despite immediate treatment with NAC. If NAC had been withheld or delayed in those 8 patients, liver failure or even death may have resulted. In Denmark, it has been decided to treat all patients regardless of risk estimation to secure a maximum risk reduction. Treatment with NAC is simple and safe, and the costs involved are small when compared with the morbidity and costs of treating patients with acute liver failure. 50

The partly retrospective design may be considered a weakness of the study. However, with the Danish registration system, patients and charts can be identified with great accuracy. Acetaminophen poisoning is a routine diagnosis in the Department of Hepatology, and a detailed history regarding alcohol and medication is mandatory. If patients were unable to cooperate, then data would be obtained from the transferring hospital or from next of kin when possible. This probably explains the high consistency and low degree of missing data in the study.

### Table 3. Results of Multivariate Analyses Using Age, Sex, Time to NAC, Dose, Alcohol, and Other Medication as Independent Variables in 157 Patients With and 488 Patients Without Regular Abuse of Alcohol Showing Risk Factors and Protective Factors for Variables Associated With Clinical Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Regular Alcohol Abuse</th>
<th>Without Regular Alcohol Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Factors</td>
<td>Protective Factors</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>T: NAC (−0.31), dose (−0.17)</td>
<td>Acute alcohol use (0.46)</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>Dose (0.19)</td>
<td>Acute alcohol use (−0.49)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>T: NAC (0.33)</td>
<td>Acute alcohol use (−0.26)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>T: NAC (0.23)</td>
<td>Acute alcohol use (−0.31)</td>
</tr>
<tr>
<td>HE</td>
<td>T: NAC, age</td>
<td>Acute alcohol use</td>
</tr>
<tr>
<td>Death or DLT</td>
<td>Age, T: NAC</td>
<td>Acute alcohol use</td>
</tr>
</tbody>
</table>

Note: Standardized regression coefficients from the multiple regression analysis are given in parentheses. >, the first variable contributes significantly more to the risk than the second variable.

Abbreviations: T: NAC, time to NAC; DLT, liver transplant.
In conclusion, we find that time to NAC, chronic alcohol abuse, quantity of acetaminophen, and age are independent risk factors in the development of severe hepatotoxicity in patients with acetaminophen poisoning. The acute ingestion of alcohol was shown to eliminate the excess risk of chronic alcohol abuse but did not protect against hepatotoxicity in nonalcoholic patients. We suggest that patients with chronic alcoholism and suspected acetaminophen poisoning should be treated with NAC regardless of risk estimation, particularly older alcoholic patients and those with recent alcohol withdrawal.

References